Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
February 12, 2014

Table of Contents

Helpful Hints/Reference Document..... 2

External Criteria
Skin and Mucous Membrane Agents..... 4

Agenda 5

Pharmacotherapy Class Re-Reviews
Pharmacotherapy Review of Skin and Mucous Membrane Antibacterials 6
Pharmacotherapy Review of Skin and Mucous Membrane Antivirals..... 46
Pharmacotherapy Review of Skin and Mucous Membrane Antifungals..... 69
Pharmacotherapy Review of Skin and Mucous Membrane Scabicides and Pediculicides 150
Pharmacotherapy Review of Skin and Mucous Membrane Local Anti-infectives, Miscellaneous 182
Pharmacotherapy Review of Skin and Mucous Membrane Anti-inflammatory Agents 208
Pharmacotherapy Review of Skin and Mucous Membrane Antipruritics and Local Anesthetics..... 288
Pharmacotherapy Review of Skin and Mucous Membrane Astringents 334
Pharmacotherapy Review of Skin and Mucous Membrane Keratolytic Agents 343
Pharmacotherapy Review of Skin and Mucous Membrane Keratoplastic Agents 355
Pharmacotherapy Review of Skin and Mucous Membrane Agents, Miscellaneous 356

Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document

P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Benzodiazepines and barbiturates with the exception of those specified by the Alabama Medicaid Agency
- Agents used to promote smoking cessation, unless authorized for pregnant females or plan first recipients
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are in Non-preferred status or if they required PA prior to the PDL

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Skin and Mucous Membrane Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trial

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred skin and mucous membrane agents in this class, either generic, OTC or brand, within the past 6 months, or one failed treatment trial when appropriate based on PDL preferred agents, or have a documented allergy or contraindication to all preferred agents in this class.

- For scabicides and pediculicides, the patient must have failed 14-day treatment trials with at least two prescribed and preferred skin and mucous membrane agents in this class, either generic, OTC or brand within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- To meet prior usage requirements, drugs within this specific classification must be judged against others in the same class (AHFS specific).

    - For example, to qualify for a non-preferred topical anti-inflammatory agent, the patient must have met prior usage requirements of 30-day treatment trials with two other topical anti-inflammatory agents, either generic or brand.

Stable Therapy

- Approval may be given for children age 18 years and under who have been stable on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Skin and mucous membrane agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

February 12, 2014
9:00 a.m. – 12:00 p.m.

---

1. Opening remarks…….……..……Chair
2. Approval of November 13, 2013 P&T Committee Meeting minutes…..……Chair
3. Pharmacy program update.....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews…….…….University of Massachusetts Clinical Pharmacy Services
    - Skin and Mucous Membrane Antibacterials – AHFS 840404
    - Skin and Mucous Membrane Antivirals – AHFS 840406
    - Skin and Mucous Membrane Antifungals – AHFS 840408
    - Skin and Mucous Membrane Scabicides and Pediculicides – AHFS 840412
    - Skin and Mucous Membrane Local Anti-infectives, Miscellaneous – AHFS 840492
    - Skin and Mucous Membrane Anti-inflammatory Agents – AHFS 840600
    - Skin and Mucous Membrane Antipruritics and Local Anesthetics – AHFS 840800
    - Skin and Mucous Membrane Astringents – AHFS 841200
    - Skin and Mucous Membrane Keratolytic Agents – AHFS 842800
    - Skin and Mucous Membrane Keratoplastic Agents – AHFS 843200
    - Skin and Mucous Membrane Agents, Miscellaneous – AHFS 849200
6. Results of voting announced…….....……...……..Chair
7. Next meeting date
    - May 14, 2014
8. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antibacterials
AHFS Class 840404
February 12, 2014

I. Overview

The skin and mucous membrane antibacterials are approved for the treatment and/or prevention of various skin infections and bacterial vaginosis.[1-15] Humans are natural hosts for many microorganisms that colonize the skin as normal flora.[16,17] Bacterial infections of the skin are classified as either primary or secondary. Primary infections usually involve previously healthy skin and are typically caused by a single pathogen. Secondary infections occur in areas of previously damaged skin and are frequently polymicrobic.[16]

Bacterial vaginosis results from replacement of the normal hydrogen peroxide-producing *Lactobacillus* species in the vagina with anaerobic bacteria. Untreated vaginitis is associated with numerous health risks, such as pelvic inflammatory disease, cervicitis, postoperative infection, preterm delivery, postpartum endometritis, posthysterectomy infections, intrauterine infections and other sexually transmitted infections.[18,19]

Impetigo is a contagious superficial skin infection seen predominantly in children. The most common causative organisms include *Staphylococcus aureus* and *Streptococcus pyogenes*. The goals of therapy are to relieve local symptoms, improve cosmetic appearance, as well as prevent spread and recurrence. Although impetigo usually heals spontaneously within two weeks without scarring, treatment may speed the time to resolution.[20]

Peritonitis is a complication that can occur in patients treated with peritoneal dialysis, which may result in sepsis and death. Peritoneal dialysis catheter-related infections are frequently related to direct contamination of the tubing or connection devices during exchanges. Exit-site infections predispose patients to peritonitis and the most common pathogens are *S. aureus* and *P. aeruginosa*. Prevention of catheter infections is the primary goal of therapy, and antibiotic protocols have been developed to prevent exit-site infections.[21]

The skin and mucous membrane antibacterials that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Products solely indicated for the treatment of acne and/or rosacea are not covered by Alabama Medicaid. Therefore, these products are not included in this review. Most of the agents within this class are available in a generic formulation. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Antibacterials Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Clindamycin	vaginal cream, vaginal suppository	Cleocin®*, Clindesse®	clindamycin
Gentamicin	cream, ointment	N/A	gentamicin
Metronidazole	vaginal gel	MetroGel-Vaginal®*, Vandazole®*	metronidazole
Mupirocin	cream, ointment	Bactroban®*, Centany®*, Centany AT®	mupirocin
Retapamulin	ointment	Altabax®	none
Combination Products			
Neomycin, bacitracin, polymyxin B, and hydrocortisone	ointment	Cortisporin®	none
Neomycin and polymyxin B	irrigation solution	Neosporin G.U. Irrigant®*^	neomycin and polymyxin B
Neomycin, polymyxin B, and hydrocortisone	cream	Cortisporin®	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antibacterials are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antibacterials

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines[18] (2010)**	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir 200 mg orally five times daily for seven to 10 days, famciclovir 250 mg orally three times daily for seven to 10 days or valacyclovir 1,000 mg orally twice daily for seven to 10 days. Treatment can be extended if healing is incomplete after 10 days of therapy. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • The safety and efficacy of suppressive therapy have been documented among patients receiving daily therapy with acyclovir for as long as six years and with famciclovir or valacyclovir for one year. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy. • Recommended regimens for suppressive therapy of genital herpes include acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily, valacyclovir 500 mg orally once daily or valacyclovir 1,000 mg orally once daily. • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Effective episodic treatment of recurrent herpes requires initiation of therapy

Clinical Guideline	Recommendation(s)

	within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms being.
	• Recommended regimens for episodic treatment of genital herpes include acyclovir 400 mg orally three times daily for five days, acyclovir 800 mg orally twice daily for five days, acyclovir 800 mg orally three times daily for two days, famciclovir 125 mg orally twice daily for five days, famciclovir 1,000 mg orally twice daily for one day, famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days, valacyclovir 500 mg orally twice daily for three days or valacyclovir 1,000 mg orally once daily for five days.
	• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.
	• The sex partners of patients who have genital herpes can benefit from evaluation and counseling.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with human immunodeficiency virus (HIV) include acyclovir 400 to 800 mg orally twice daily, famciclovir 500 mg orally twice daily or valacyclovir 500 mg orally twice daily.
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV include acyclovir 400 mg orally three times daily for five to 10 days, famciclovir 500 mg orally twice daily for five to 10 days or valacyclovir 1,000 mg orally twice daily for five to 10 days.
	• The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established.
	• Infants exposed to HSV during birth should be followed carefully in consultation with a pediatric infectious disease specialist.
	
	<u>Pediculosis pubis (pubic lice infestation)</u>
	• Recommended regimens:
	  ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  ○ Ivermectin 250 µg/kg orally and repeated in two weeks.
	
	<u>Scabies</u>
	• Recommended regimens:
	  ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  ○ Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Alternative regimens:
	  ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	
	<u>Bacterial vaginosis</u>
	• Recommended regimens for nonpregnant women include:
	  ○ Metronidazole 500 mg orally twice a day for seven days.
	  ○ Metronidazole 0.75% gel 5 g intravaginally for five days.
	  ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.

Clinical Guideline	Recommendation(s)

	• Alternative regimens for nonpregnant women include:
	  ○ Tinidazole 2 g orally once daily for two days.
	  ○ Tinidazole 1 g orally once daily for five days.
	  ○ Clindamycin 300 mg orally twice daily for seven days.
	  ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days.
	• Additional regimens include metronidazole (750 mg extended-release tablets once daily for seven days), or a single dose of clindamycin intravaginal cream, although data on these alternative regimens are limited.
	
	<u>Uncomplicated vulvovaginal candidiasis</u>
	• Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women.
	• Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis.
	• The topically applied azole drugs are more effective than nystatin.
	• Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy.
	• Recommended regimens include:
	  ○ Butoconazole 2% cream 5 g intravaginally for three days.
	  ○ Butoconazole 2% cream 5 g single intravaginal application.
	  ○ Clotrimazole 1% cream 5 g intravaginally for seven to 14 days.
	  ○ Clotrimazole 2% cream 5 g intravaginally for three days.
	  Miconazole 2% cream 5 g intravaginally for seven days.
	  ○ Miconazole 4% cream 5 g intravaginally for three days.
	  ○ Miconazole 100 mg vaginal suppository for seven days.
	  ○ Miconazole 200 mg vaginal suppository for three days.
	  ○ Miconazole 1,200 mg vaginal suppository, for one day.
	  ○ Nystatin 100,000-unit vaginal tablet, one tablet for 14 days.
	  ○ Tioconazole 6.5% ointment 5 g single intravaginal application.
	  ○ Terconazole 0.4% cream 5 g intravaginally for seven days.
	  ○ Terconazole 0.8% cream 5 g intravaginally for three days.
	  ○ Terconazole 80 mg vaginal suppository for three days.
	  ○ Fluconazole 150 mg oral tablet in single dose.
	
	<u>Complicated vulvovaginal candidiasis</u>
	• Complicated vulvovaginal candidiasis is defined as recurrent (four or more episodes in one year) or severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with uncontrolled diabetes, debilitation or immunosuppression.
	• Treatment: Each individual episode of recurrent vulvovaginal candidiasis caused by *Candida albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen.
	• Maintenance regimens: Oral fluconazole weekly for six months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.
	
	<u>Severe vulvovaginal candidiasis</u>
	• Severe vulvovaginitis is associated with lower clinical response rates in

Clinical Guideline	Recommendation(s)

	patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	<u>Non-albicans vulvovaginal candidiasis</u>
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. Options include longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for two weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.
	
	<u>Genital warts</u>
	• Treatment of genital warts should be guided by the preference of the patient, the available resources, and the experience of the health-care provider.
	• No definitive evidence suggests that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that influence selection of treatment include wart size, wart number, location of the wart, wart morphology, patient preference, convenience, adverse effects, and provider experience.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens (patient-applied):
	  o Podofilox 0.5% solution or gel.
	  o Imiquimod 5% cream.
	  o Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  o Cryotherapy with liquid nitrogen or cryoprobe.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  o Surgical removal
	• Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.
	
	<u>Cervical warts</u>
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	
	<u>Vaginal warts</u>
	• Recommended regimens:

Clinical Guideline	Recommendation(s)
	○ Cryotherapy with liquid nitrogen. ○ Trichloroacetic acid or bichloracetic acid 80 to 90%. <u>Urethral meatus warts</u> • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Podophyllin resin 10 to 15% in a compound tincture of benzoin. <u>Anal warts</u> • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Trichloroacetic acid or bichloracetic acid 80 to 90%. ○ Surgical removal.
American College of Obstetricians and Gynecologists: **Clinical Management Guidelines for Obstetrician-Gynecologists: Vaginitis[19] (2006)**	<u>Bacterial vaginosis</u> • Nonpregnant women with bacterial vaginosis can be treated with vaginal clindamycin, oral clindamycin, vaginal metronidazole, or oral metronidazole products. These agents seem to have comparable clinical efficacy and safety. • Oral metronidazole may be associated with significant gastrointestinal symptoms. Disulfiram-like reactions may occur with both oral and topical metronidazole. <u>Uncomplicated vulvovaginal candidiasis</u> • Women with uncomplicated vulvovaginal candidiasis can be treated successfully with any of the following options: ○ Butoconazole 2% sustained-release cream 5 g daily for one day. ○ Clotrimazole 1% cream 5 g daily for seven days. ○ Clotrimazole 2% cream 5 g daily for three days. ○ Clotrimazole 100 mg vaginal suppository daily for seven days. ○ Clotrimazole 200 mg vaginal suppository daily for three days. ○ Clotrimazole 500 mg vaginal suppository daily for one day. ○ Fluconazole 150 mg oral tablet daily for one day. ○ Miconazole 2% cream 5 g daily for seven days. ○ Miconazole 100 mg vaginal suppository daily for seven days. ○ Miconazole 200 mg vaginal suppository for three days. ○ Miconazole 1,200 mg vaginal suppository daily for one day. ○ Nystatin 100,000 units vaginal tablets daily for 14 days. ○ Terconazole 0.4% cream 5 g daily for seven days. ○ Terconazole 0.8% cream 5 g daily for three days. ○ Tioconazole 2% cream 5 g daily for three days. ○ Tioconazole 6.5% cream 5 g daily for one day. • Because all listed antifungal treatments seem to have comparable safety and efficacy, the choice of therapy should be individualized to the specific patient; factors such as ease of use, history of response or adverse reactions to prior treatments, and patient preference can all be taken into consideration. <u>Complicated vulvovaginal candidiasis</u> • Patients with complicated vulvovaginal candidiasis require more aggressive treatment to achieve relief of symptoms. • After initial intensive therapy for seven to 14 days to achieve mycologic remission, prolonged antifungal treatment with fluconazole, 150 mg weekly for six months, will successfully control more than 90% of symptomatic episodes and will lead to a prolonged protective effect in approximately 50% of women. • Although daily oral ketoconazole was previously described as an effective suppressive therapy in women with recurrent vulvovaginal candidiasis, weekly

Clinical Guideline	Recommendation(s)
	fluconazole has a lower risk of liver toxicity and should be used instead of ketoconazole. • For patients who are unable or unwilling to take fluconazole, prolonged maintenance therapy with intermittent topical agents, such as clotrimazole, 500 mg weekly or 200 mg twice a week, are acceptable options. Non-albicans vulvovaginal candidiasis • A standard course of topical imidazole therapy may be effective in up to 50% of such cases. • Therapy with vaginal boric acid, 600 mg capsules daily for a minimum of 14 days, seems to be effective for azole failures.

European (International Union Against Sexually Transmitted Infections/ World Health Organization): **Guideline on the Management of Vaginal Discharge[22] (2011)**	Bacterial vaginosis
	• Recommended regimens for bacterial vaginosis:
	  ○ Metronidazole 400 to 500 mg twice daily for five to seven days.
	  ○ Metronidazole 2 g in a single dose.
	  ○ Intravaginal metronidazole 0.75% gel once daily for five days.
	  ○ Tinidazole 2 g in a single dose.
	• Alternative regimens for bacterial vaginosis:
	  ○ Intravaginal metronidazole 0.75% gel once a day for five days.
	  ○ Intravaginal clindamycin 2% cream once daily for seven days.
	  ○ Clindamycin 300 mg twice daily for seven day.
	• Clindamycin and metronidazole have equal efficacy, comparing oral and vaginal formulations, both after one week and after one month of therapy. Approximately 58 to 88% will be cured after five days treatment with metronidazole or clindamycin. In most studies, clindamycin tended to have less adverse effects than metronidazole.
	• Vaginal application of metronidazole is as effective as oral administration.
	• Eradication at one month after vaginal clindamycin cream were 66 to 83% vs 68 to 87% for oral metronidazole.
	• Oral metronidazole, vaginal metronidazole 0.75% cream and vaginal clindamycin 2% cream have similar efficacy and side effect profile. Compared to oral clindamycin, vaginal clindamycin administration is associated with similar efficacy with fewer side effects.
	
	Vaginal candidiasis
	• Intravaginal and oral therapies are equally effective for vaginal candidiasis.
	• Treatment with azoles results in relief of symptoms and negative cultures among 80 to 90% of patients after either oral or topical treatment; only topical preparations should be used during pregnancy.
	• Recommended regimens for vaginal candidiasis:
	  ○ Fluconazole 150 mg orally as a single dose.
	  ○ Itraconazole 200 mg twice daily for one day.
	  ○ Clotrimazole vaginal tablet 500 mg once or 200 mg once daily for three days.
	  ○ Miconazole vaginal ovule 1,200 mg as a single dose or 400 mg once daily for three days.
	  ○ Econazole vaginal pessary 150 mg as a single dose.
	• Standard single dose treatments are as effective as longer courses.
	• In a severely symptomatic attack, symptomatic benefit is with fluconazole 150 mg treatment repeated after three days.

British Association for Sexual Health and Human Immunodeficiency Virus:	• Recommended regimens for bacterial vaginosis:
	  ○ Metronidazole 400 mg twice daily for five to seven days.
	  ○ Metronidazole 2 g in a single dose.
	  ○ Intravaginal metronidazole 0.75% gel once daily for five days.
	  ○ Intravaginal clindamycin 2% cream once daily for seven days.

Clinical Guideline	Recommendation(s)

National Guideline for the Management of Bacterial Vaginosis[23] (2012)	• Alternative regimens for bacterial vaginosis:
	  ○ Tinidazole 2 g in a single dose.
	  ○ Clindamycin 300 mg twice daily for seven days.
	• All these treatments have been shown to achieve cure rates of 70 to 80% after four weeks in controlled trials using placebo or comparison with oral metronidazole. Oral metronidazole treatment is established and usually well tolerated. Dosage and duration used in trials have varied from 400 mg twice daily for five days to 500 mg twice daily for seven days. The 2 g immediate dose may be slightly less effective at four week follow up.
	• Intravaginal metronidazole gel and clindamycin cream have similar efficacy. Metronidazole is less active against lactobacilli than clindamycin. Clindamycin is more active than metronidazole against most of the bacteria associated with bacterial vaginosis.
	• Oral clindamycin has only been evaluated in one study with short-term follow up, and in pregnant women.
	• Tinidazole has similar in vitro antibacterial activity and efficacy compared to metronidazole.

American Academy of Family Physicians: **Diagnosis and Treatment of Impetigo[20] (2007)**	• Topical antibiotics such as mupirocin and fusidic acid (not available in the United States) are the preferred first-line therapy(s) for impetigo involving limited body surface area. • Oral antibiotics (e.g., antistaphylococcal penicillins, amoxicillin/clavulanate, cephalosporins and macrolides) are effective for the treatment of impetigo; erythromycin is less effective. • Oral antibiotics should be considered for patients with impetigo who have more extensive disease and for disease associated with systemic symptoms. • Oral penicillin V, amoxicillin, topical bacitracin, and neomycin are not recommended for the treatment of impetigo. • Topical disinfectants such as hydrogen peroxide should not be used in the treatment of impetigo. • This guideline was published prior to the approval of retapamulin.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Treatment of Methicillin-resistant *Staphylococcus Aureus* Infections in Adults and Children[24] (2011)**	Impetigo and secondarily infected skin lesions (e.g., eczema, ulcers, or lacerations) in children • Topical mupirocin 2% ointment can be used. Methicillin-resistant *Staphylococcus Aureus* infections in neonates (neonatal pustulosis) • For mild cases with localized disease, topical treatment with mupirocin may be adequate in full-term neonates and young infants.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[25] (2005)**	Impetigo • Topical therapy with mupirocin is equivalent to oral systemic antimicrobials and may be used when lesions are limited in number. • The best topical agent is mupirocin, although resistance has been described; other agents, such as bacitracin and neomycin, are considerably less effective treatments. • Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *Staphylococcus Aureus* and *Streptococcus pyogenes*. Recurrent furuncles • The major method of controlling recurrent furunculosis is the use of antibacterial agents to eradicate staphylococcal carriage. • For persons with nasal colonization, one approach is the application of mupirocin ointment twice daily in the anterior nares for the first five days each

Clinical Guideline	Recommendation(s)
	month. This regimen reduces recurrences by approximately 50%. • Few systemic antibiotics attain adequate levels in the nasal secretions to achieve protracted elimination of staphylococci. • Clindamycin is an exception, and probably the best program for recurrent furunculosis caused by susceptible *Staphylococcus Aureus* is a single oral daily dose of 150 mg of this agent for three months, which decreases subsequent infections by approximately 80%. • This guideline was published prior to the approval of retapamulin.

International Society for Peritoneal Dialysis: **Reducing Risks of Peritoneal Dialysis-Related Infections[21] (2011)**	<u>General considerations</u>
	• Prevention of catheter infections (and thus peritonitis) is the primary goal of exit-site care.
	• Antibiotic protocols against *Staphylococcus Aureus* are effective in reducing the risk of *Staphylococcus Aureus* catheter infections.
	
	<u>Antibiotic protocol options for preventing exit-site infections</u>
	• Mupirocin:
	  o Daily after cleansing in all patients.
	  o Daily after cleansing in carriers only.
	  o In response to a positive exit-site culture for *Staphylococcus aureus* denoting carriage.
	  o Mupirocin ointment should be avoided in patients with polyurethane catheters and mupirocin cream should be substituted.
	• Gentamicin cream:
	  o Daily in all patients after cleansing.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antibacterials are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Antibacterials[1-15]

Indication	Single-Entity Agents					Combination Products	
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Retapamulin	Neomycin, Bacitracin, Polymyxin B and Hydrocortisone	Neomycin, Polymyxin B and Hydrocortisone
Skin Infections							
Treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*				✔ *	✔		
Treatment of primary and secondary skin infections		✔					
Treatment of corticosteroid-responsive dermatoses with secondary infection						✔	✔
Treatment of secondarily infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*				✔ †			
Vaginal Infections							
Treatment of bacterial vaginosis	✔		✔				

*Ointment formulation.
†Cream formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antibacterials are listed in Table 4. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individuals components listed in the table below.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antibacterials[1-15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Bacitracin	Not reported	Not reported	Not reported	Renal (10 to 40)	1.5
Clindamycin	0.6 to 11.0	60 to 95	Liver	Renal (<1)	1.5 to 5.0
Gentamicin*	5	0 to 30	Not reported	Renal	1.5 to 4.0
Hydrocortisone	Not reported	90	Liver	Renal	1 to 2
Metronidazole	2 to 56	<20	Liver (30 to 60)	Renal (60 to 80)	6 to 14
Mupirocin	No measureable absorption	95 to 97	Skin	Renal	0.32 to 0.58
Neomycin	No measurable absorption	0 to 88	Liver	Feces (97)	3
Polymyxin B	Not reported	Not reported	Not reported	Renal (<1)	6
Retapamulin	Not reported	94	Liver	Not reported	Not reported

*Greater absorption of drug with cream than ointment.

V. Drug Interactions

Significant drug interactions with the skin and mucous membrane antibacterials are listed in Table 5.

Table 5. Significant Drug Interactions with the Skin and Mucous Membrane Antibacterials[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Metronidazole	1	Anticoagulants	Metronidazole may potentiate the anticoagulant effect of warfarin, resulting in prolongation of the prothrombin time and an increased risk of bleeding.
Metronidazole	1	Disulfiram	Concurrent use may result in acute psychosis or a confusional state. Metronidazole vaginal gel should not be used within two weeks of disulfiram.
Clindamycin	2	Nondepolarizing muscle relaxants	Clindamycin may potentiate the action of nondepolarizing muscle relaxants, contributing to respiratory depression.
Metronidazole	2	Ethanol	Disulfiram-like reaction may occur with concurrent metronidazole and ethanol use.
Neomycin, bacitracin, polymyxin B, and hydrocortisone	2	Succinylcholine	Aminoglycosides (e.g., neomycin) may increase the neuromuscular blocking effects of succinylcholine.
Neomycin, polymyxin B, and hydrocortisone	2	Succinylcholine	Aminoglycosides (e.g., neomycin) may increase the neuromuscular blocking effects of succinylcholine.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antibacterials are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antibacterials[1-15]

Adverse Events	Single-Entity Agents					Combination Products	
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Retapamulin	Neomycin, Bacitracin, Polymyxin B and Hydrocortisone	Neomycin, Polymyxin B and Hydrocortisone
Central Nervous System							
Depression	-	-	<1	-	-	-	-
Dizziness	<1	-	2	✔	-	-	-
Fatigue	-	-	<1	-	-	-	-
Headache	-	-	5	✔	1 to 2	-	-
Pyrexia	<1	-	-	-	1	-	-
Vertigo	<1	-	-	-	-	-	-
Dermatological							
Acneiform eruptions	-	-	-	-	-	✔	✔
Application site erythema	-	-	-	-	<1	-	-
Application site irritation	-	-	-	-	2	-	-
Application site pruritus	-	-	-	-	2	-	-
Burning	-	-	-	✔	-	✔	✔
Cellulitis	-	-	-	✔	-	-	-
Contact dermatitis	-	-	-	-	<1	✔	✔
Dermatitis	-	-	-	✔	-	-	-
Dryness	-	-	-	✔	-	✔	✔
Eczema	-	-	-	-	1	-	-
Edema	-	-	-	✔	-	-	-
Erythema	<1	✔	-	✔	-	-	-
Folliculitis	-	-	-	-	-	✔	✔
Hypertrichosis	-	-	-	-	-	✔	✔
Hypopigmentation	-	-	-	-	-	✔	✔
Irritation	-	-	-	-	-	✔	✔
Maceration of skin	-	-	-	-	-	✔	✔
Miliaria	-	-	-	-	-	✔	✔
Perioral dermatitis	-	-	-	-	-	✔	✔
Pruritus	≤1	✔	<1	✔	2	✔	✔
Rash	<1	-	<1	✔	-	-	-

Adverse Events	Single-Entity Agents					Combination Products	
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Retapamulin	Neomycin, Bacitracin, Polymyxin B and Hydrocortisone	Neomycin, Polymyxin B and Hydrocortisone
Skin atrophy	-	-	-	-	-	✔	✔
Skin sensitization	-	-	-	-	-	-	✔
Stinging	-	-	-	✔	-	-	✔
Striae	-	-	-	-	-	✔	✔
Tenderness	-	-	-	✔	-	-	-
Urticaria	<1	-	-	✔	-	-	-
Gastrointestinal							
Abdominal bloating	-	-	<1	-	-	-	-
Abdominal gas	-	-	<1	-	-	-	-
Abdominal pain/cramps	<1	-	1	✔	-	-	-
Appetite decreased	-	-	1	-	-	-	-
Diarrhea	<1	-	1	✔	1 to 2	-	-
Gastrointestinal discomfort	-	-	7	-	-	-	-
Nausea	<1	-	4	✔	1	-	-
Taste perversion	-	-	2	✔	-	-	-
Thirst	-	-	<1	-	-	-	-
Ulcerative colitis	-	-	-	✔	-	-	-
Vomiting	<1	-	4	-	-	-	-
Xerostomia	-	-	<1	✔	-	-	-
Genitourinary							
Atrophic vaginitis	<1	-	-	-	-	-	-
Dark urine	-	-	<1	-	-	-	-
Dysuria	<1	-	-	-	-	-	-
Nephrotoxicity	-	-	-	-	-	✔	✔
Pelvic discomfort	-	-	3	-	-	-	-
Pyelonephritis	<1	-	-	-	-	-	-
Trichomonal vaginitis	1	-	-	-	-	-	-
Urinary tract infection	<1	-	-	-	-	-	-
Vaginal burning/irritation	<1	-	9	-	-	-	-
Vaginal candidiasis	≤13	-	10	-	-	-	-
Vaginal discharge	1	-	12	-	-	-	-
Vaginal pain	≤2	-	-	-	-	-	-
Vulvovaginal disorder	3 to 7	-	-	-	-	-	-
Vulvovaginal pruritus	>10	-	-	-	-	-	-

Adverse Events	Single-Entity Agents					Combination Products	
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Retapamulin	Neomycin, Bacitracin, Polymyxin B and Hydrocortisone	Neomycin, Polymyxin B and Hydrocortisone
Vulvovaginitis	4 to 6	-	-	-	-	-	-
Respiratory							
Cough	-	-	-	✔	-	-	-
Nasopharyngitis	-	-	-	-	1 to 2	-	-
Pharyngitis	-	-	-	✔	-	-	-
Respiratory tract congestion	-	-	-	✔	-	-	-
Rhinitis	-	-	-	✔	-	-	-
Other							
Allergic reaction	<1	-	-	-	-	-	✔
Bacterial infection	<1	-	-	-	-	-	-
Blepharitis	-	-	-	✔	-	-	-
Creatine phosphokinase increased	-	-	-	-	<1	-	-
Ear pain	-	-	-	✔	-	-	-
Endometriosis	<1	-	-	-	-	-	-
Epistaxis	<1	-	-	-	-	-	-
Fungal infection	1 to 2	-	-	-	-	-	-
Hypersensitivity	<1	-	-	-	-	✔	-
Hyperthyroidism	<1	-	-	-	-	-	-
Menstrual disorder	<1	-	-	-	-	-	-
Metrorrhagia	<1	-	-	-	-	-	-
Ocular hypertension	-	-	-	-	-	✔	-
Ototoxicity	-	-	-	-	-	✔	✔
Pain	<1	-	-	✔	-	-	-
Secondary infection	-	-	-	✔	-	✔	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antibacterials are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Antibacterials[1-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-entity Agents			
Clindamycin	Bacterial vaginosis: Vaginal cream: Cleocin®, insert one applicator full intravaginally once daily for three or seven days in non-pregnant patients and for seven days in pregnant patients; Clindesse®, insert one applicator full intravaginally once Vaginal suppository: insert once daily for three days	Safety and efficacy in children have not been established.	Vaginal cream: 2% Vaginal suppository: 100 mg
Gentamicin	Primary and secondary skin infections: Cream or ointment: apply to the lesions three to four times daily	Primary and secondary skin infections: Cream or ointment: apply to the lesions three to four times daily	Cream: 0.1% Ointment: 0.1%
Metronidazole	Bacterial vaginosis: Vaginal gel: MetroGel-Vaginal®, insert one applicator full one to two times daily for five days; Vandazole®, insert one applicator full once daily for five days	Safety and efficacy in children have not been established.	Vaginal gel: 0.75%
Mupirocin	Treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*: Ointment: apply to the affected area three times daily Treatment of secondarily infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*: Cream: apply to the affected area three times daily for 10 days	Treatment of impetigo due to *S. aureus* and *S. pyogenes* in children two months to 16 years of age: Ointment: apply to the affected area three times daily Treatment of secondarily infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes* in children three months to 16 years of age: Cream: apply to the affected area three times daily for 10 days	Cream: 2% Ointment: 2%
Retapamulin	Treatment of impetigo due to *S. aureus* and *S. pyogenes*: Ointment: apply to affected area (up to 100 cm^2 in total area) twice daily for five days	Treatment of impetigo due to *S. aureus* and *S. pyogenes* in children nine months of age and older: Ointment: apply to affected area (up to 2% total body surface area) twice daily for five days	Ointment: 1%
Combination Products			
Neomycin, bacitracin,	Treatment of corticosteroid-responsive dermatoses with secondary infection:	Safety and efficacy in children have not been	Ointment: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
polymyxin B, and hydrocortisone	Ointment: apply to the affected area two to four times daily for seven days	established.	
Neomycin, polymyxin B, and hydrocortisone	Treatment of corticosteroid-responsive dermatoses with secondary infection: Cream: apply to the affected area two to four times daily	Safety and efficacy in children have not been established.	Cream: 0.5%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antibacterials are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Skin and Mucous Membrane Antibacterials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bacterial Vaginosis				
Nyirjesy et al.[26] (2007) Clindamycin 2% vaginal cream as a single dose vs metronidazole 0.75% vaginal gel BID for 5 days	RETRO Nonpregnant women ≥18 years of age with a clinical diagnosis of bacterial vaginosis	N=55 21 to 30 days	Primary: Microbiologic, clinical, and therapeutic cure of bacterial vaginosis Secondary: Not reported	Primary: There were significant reductions in mean *Mobiluncus* scores from baseline to the test-of-cure visit in both treatment groups (P<0.0001 for both groups). The mean *Mobiluncus* score in the clindamycin group was less than in the metronidazole group at the test-of-cure visit (0.05 vs 0.33; P<0.0471), indicating a significantly greater decrease in the presence of *Mobiluncus* in the clindamycin group compared to the metronidazole group. Significantly more patients in the clindamycin group compared to the metronidazole group achieved microbiologic (57.5 vs 26.7%; P=0.04) and clinical cure (57.5 vs 26.7%; P=0.04) of bacterial vaginosis. There was no significant difference between the clindamycin and metronidazole groups with regards to therapeutic cure rates (P=0.09). Secondary: Not reported
Nyirjesy et al.[27] (2006) Clindamycin 2% vaginal cream as a single dose vs clindamycin 2% vaginal cream QD for 7 days	RETRO Nonpregnant women ≥18 years of age with a clinical diagnosis of bacterial vaginosis	N=408 21 to 30 days	Primary: Change in *Lactobacillus* scores from baseline to the test-of-cure visit Secondary: Not reported	Primary: *Lactobacillus* scores were similar between the three treatment groups at the test-of-cure visit (P=0.71). The percentages of patients with a score of four (reflecting no observed *Lactobacillus* morphotypes) were reduced to 34, 36, and 39% in the clindamycin single-dose, clindamycin multi-dose, and metronidazole groups, respectively (P<0.0001 for all treatment groups). At the test-of-cure visit, 43, 38, and 38% of patients in the clindamycin single-dose, clindamycin multi-dose, and metronidazole groups, respectively, had *Lactobacillus* scores of zero (reflecting fully restored *Lactobacillus*). The three treatment groups were comparable with respect

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metronidazole 0.75% vaginal gel BID for 5 days				to the distributions of *Lactobacillus* scores within the groups. The changes in *Lactobacillus* scores from baseline to the test-of-cure visit were similar across the three treatment groups (P=0.50). Secondary: Not reported
Faro et al.[28] (2005) Clindamycin 2% vaginal cream (Clindesse®) as a single dose vs clindamycin 2% vaginal cream (Cleocin®) QD	AC, MC, PG, RCT, SB Non-pregnant women ≥18 years of age, with bacterial vaginosis infections	N=540 30 days	Primary: Investigator cure, clinical cure, and therapeutic cure Secondary: Not reported	Primary: There were no statistically significant differences found in the cure rates between the Clindesse® and the Cleocin® treatment groups. The P values for investigator cure, clinical cure, and therapeutic cure were P=0.702, P=0.945, and P=0.572, respectively. Secondary: Not reported
McCormack et al.[29] (2001) Clindamycin 2% vaginal cream QD vs sulfonamide vaginal cream BID	DB, MC, RCT Nonpregnant women ≥16 years of age with symptomatic bacterial vaginosis	N=159 7 days, with follow-up visits at days 5 to 10 and 25 to 39	Primary: Clinical cure or improvement Secondary: Not reported	Primary: Clinical cure or improvement was seen in 69.6% of patients in the clindamycin group compared to 41.8% of patients in the triple sulfonamide group (P<0.0001). Among patients with a history of bacterial vaginosis, the cure rates at five to 10 days after treatment for clindamycin and sulfonamide were 25 and 51%, respectively (P<0.001); and, at 25 to 39 days post-treatment, the cure rates for clindamycin and sulfonamide were 63.9 and 29.4%, respectively (P<0.0001). Among patients with no history of bacterial vaginosis, the cure rates at five to 10 days after treatment for clindamycin and sulfonamide were 27.9 and 42.9%, respectively; and, the improvement rates were 46.5 and 35.7%, respectively (P=0.4). At 25 to 39 days post-treatment, the cure rates for clindamycin and sulfonamide were 44.2 and 46.4%, respectively (P=0.11).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The Gram stain evaluation showed fewer stains consistent with bacterial vaginosis for the clindamycin group as compared to the sulfonamide group, at both post-treatment evaluations (P<0.002). Secondary: Not reported
Paavonen et al.[30] (2000) Clindamycin 100 mg vaginal ovules QD for 3 days vs metronidazole 500 mg capsules BID for 7 days	AC, DB, MC, RCT Adult women diagnosed with bacterial vaginosis	N=399 52 days	Primary: Overall clinical outcome, reported as cure, failure, and non-assessable efficacy rate Secondary: Clinical status, symptoms of vaginitis or cervicitis at each follow-up visit, patient evaluation of efficacy at second follow-up visit, and adverse effects	Primary: No statistically significant difference between the two treatment groups was observed regarding the primary endpoint (95% CI, -10.6 to 13.4; P=0.810). Secondary: There was no statistically significant difference in clinical status, at either the first or second follow-up visit, between the two treatment groups (P>0.5). There was no significant difference in the proportion of patients who rated their vaginal infection as cured in the metronidazole treatment group (79.6%) compared to clindamycin treatment group (78.3%). There was no difference in the number of patients reporting symptoms of vaginitis and cervicitis at either the first or second follow-up visit. Treatment-related adverse effects were more frequent in the metronidazole group (16.3%), compared to the clindamycin treatment group (10.3%), but this difference was not statistically significant (P=0.104).
Austin et al.[31] (2005) Clindamycin vaginal ovules QD for 3 days vs metronidazole vaginal gel QD for	AC, DB, RCT Premenopausal, non-pregnant women ≥18 years of age diagnosed with bacterial vaginosis	N=119 90 days	Primary: Overall clinical outcome, microbiologic response Secondary: Not reported	Primary: The clinical response rate did not differ between the two treatment groups. At seven to 12 days, cure rates were 79 and 88% for metronidazole and clindamycin, respectively (P=0.3). At 35 to 45 days, cure rates were 62 and 55%, respectively (P=0.5). The rates were 58 and 55%, respectively, at days 70 to 90 after therapy (P=0.8). While both therapies resulted in decreased colonization by *Gardnerella vaginalis* and *Mycoplasma hominis* (P<0.001), only the metronidazole treatment led to a significant decrease in the frequency and concentration of *Prevotella bivia* and black-pigmented *Prevotella* species (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 days				Women treated with metronidazole had a significant decrease in colonization by *Ureaplasma urealyticum* (P<0.001) compared to clindamycin-treated women (P=0.3). Both *Porphyromonas* and nonpigmented *Prevotella* species decreased significantly following treatment with either regimen (P<0.001). Clindamycin-resistant subpopulations of *P. bivia* and black-pigmented *Prevotella* species emerged seven to 12 days after therapy even among patients initially colonized by clindamycin-susceptible strains. Secondary: Not reported
Ferris et al.[32] (1995) Clindamycin 2% vaginal cream QD for 7 days vs metronidazole vaginal gel BID for 5 days vs metronidazole 500 mg capsules BID for 7 days	AC, DB, RCT Premenopausal, non-pregnant women ≥18 years of age diagnosed with bacterial vaginosis	N=101 14 days	Primary: Cure rate, post-treatment vulvovaginal candidiasis Secondary: Not reported	Primary: There was no significant difference in cure rates for oral metronidazole (84.2%), metronidazole vaginal cream (75.0%), or clindamycin vaginal cream (86.2%; P=0.548). There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (12.5%), metronidazole vaginal cream (30.4%), or clindamycin vaginal cream (14.8%; P=0.272). Secondary: Not reported
Fischbach et al.[33] (1993) Clindamycin 2% vaginal cream QD for 7 days	AC, DB, MC, RCT Premenopausal, non-pregnant women ≥18 years of age diagnosed with	N=407 39 days	Primary: Cure rate, post-treatment vulvovaginal candidiasis	Primary: There was no significant difference in cure rate for oral metronidazole (78%) and clindamycin vaginal cream (83%). The incidence of drug-related adverse effects was similar in both groups, approximately 12%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metronidazole 500 mg capsules BID for 7 days	bacterial vaginosis		Secondary: Not reported	There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (4.7%) and clindamycin vaginal cream (8.5%). Secondary: Not reported
Arredondo et al.[34] (1992) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream BID for 7 days	DB, MC, RCT Women with symptomatic bacterial vaginosis	N=184 50 days	Primary: Total healing rate, relapse rate, failure rate, and adverse events Secondary: Not reported	Primary: Improvement in total healing was 87% for clindamycin and 79% for metronidazole (P>0.22). While 7% of patients randomized to the metronidazole group developed relapse of the disease following treatment, none of the patients receiving topical clindamycin experienced a relapse. The failure rates were 4.0 and 10.5% for clindamycin and 17.0 and 5.8% for metronidazole at first and second follow-up visits, respectively. Both drugs were well tolerated, with the most serious side effect, generalized rash, reported by a patient on metronidazole therapy. Secondary: Not reported
Andres et al.[35] (1992) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream BID for 7 days	DB, PC, PRO, RCT Non-pregnant women 18 to 60 years of age diagnosed with bacterial vaginosis	N=60 30 days	Primary: Cure rate, improvement rate, clinical failure assessed at the one-week and four-week follow-up visits, and adverse events Secondary: Not reported	Primary: There was no statistically significant difference in the proportion of patients who have either improved or were cured post-treatment between the metronidazole (82%) and clindamycin (97%) study groups at the one-week follow-up visit. There was no statistically significant difference in the proportion of patients who had either improved or were cured post-treatment between the metronidazole (94.1%) and clindamycin (89.5%) study groups at the four-week follow-up visit. There was no statistically significant difference in clinical failure rates among patients randomized to receive either of the two study drugs.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs. Secondary: Not reported
Schmitt et al.[36] (1992) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream 5 g QD for 7 days	DB, PC, RCT Nonpregnant women 18 to 60 years of age diagnosed with bacterial vaginosis	N=61 30 days	Primary: Overall healing rate (clinical and microbiological), symptomatic failure rate at the one-week and four-week follow-up visits, adverse events, and *Candida* infections Secondary: Not reported	Primary: There was no statistically significant difference in the overall cure rate between the metronidazole (87%) and clindamycin (72%) study groups at the one-week follow-up visit (P=0.32). One month later, 61% of patients in both groups remained cured. Symptomatic failure occurred in one patient receiving clindamycin and in no one on metronidazole therapy. There were fewer asymptomatic failures in the metronidazole group compared to the clindamycin treatment arm; however this difference was not statistically significant (P=0.16). Symptomatic *Candida* yeast infections developed in 12% of clindamycin-treated patients and 9% of patients on metronidazole therapy. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs. Secondary: Not reported
Higuera et al.[37] (1993) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream 5 g	DB, PC, RCT Nonpregnant women 16 to 60 years of age diagnosed with bacterial vaginosis	N=82 50 days	Primary: Cure rate, improvement, clinical failure rate, and relapse rate Secondary: microbiological cure rate, vaginal fluid description, patient's efficacy	Primary: There was no statistically significant difference in the proportion of patients who have either improved or were cured post-treatment between the metronidazole (82%) and clindamycin (86%) study groups at the one-week follow-up visit. There was no statistically significant difference in cure rate between the metronidazole (88%) and the clindamycin (90%) groups at the four-week follow-up visit. There was no statistically significant difference in failure rate between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD for 7 days			evaluation, and adverse effects	metronidazole (17.9%) and clindamycin (14.3%) treatment groups at the one-week and four-week follow-up visits. Secondary: There was no statistically significant difference in microbiological cure rate between the metronidazole (82%) and the clindamycin (86%) groups at the first follow-up visit. There was no statistically significant difference in patient self-reported cure rate between the metronidazole (82%) and clindamycin (86%) groups. There was a significantly higher percentage of patients in the clindamycin group (10%) with a gram stain compatible with bacterial vaginosis at the second follow-up visit compared to the metronidazole group (4%; P<0.04). At the second follow-up visit, there were a greater number of patients in the clindamycin group (14%) exhibiting vaginal fluid odor compared to the metronidazole group (4%). There was no significant difference in the incidence of side effects between the metronidazole group (22%) and clindamycin (15%) group.
Impetigo				
Goldfarb et al.[38] (1988) Mupirocin 2% topical ointment TID for 8 days vs erythromycin ethylsuccinate 40 mg/kg/day QID for 8 days	AC, RCT Children ≥3 months of age with impetigo	N=62 15 days	Primary: Clinical response, bacteriologic response, and adverse events Secondary: Not reported	Primary: There was no statistically significant difference in clinical or bacteriologic response between the two treatment groups. Children randomized to mupirocin treatment were free of side effects while the most common side effect reported in the erythromycin group was diarrhea. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dagan et al.[39] (1992) Mupirocin 2% topical ointment TID for 7 days vs erythromycin ethylsuccinate suspension 50 mg/kg/day (up to maximum daily dose of 750 mg daily) TID for 7 days	AC, DB, RCT Children ≤16 years of age with impetigo	N=102 8 days	Primary: Cure rate or improved lesion, worsening of lesion, and appearance of new lesions Secondary: Not reported	Primary: The mupirocin group exhibited a greater improvement compared to the erythromycin group in terms of cure rates, improved lesions, worsening of lesions, and bacterial colonization of the lesions (P<0.05). Secondary: Not reported
Koning et al.[40] (2012) Any program of topical or systemic treatment, including antibiotics, disinfectants or any other intervention for impetigo	SR Patients with primary and secondary impetigo	N=5,578 (68 trials) Variable duration	Primary: Cure as defined by clearance of crusts, blisters and redness as assessed by the investigator, and relief of symptoms as assessed by participants Secondary: Adverse effects	Primary: *Non-bullous impetigo* Topical antibiotics showed better cure rates or more improvement than placebo (pooled RR, 2.24; 95% CI, 1.61 to 3.13). This result was consistent for both mupirocin (RR, 2.21; 95% CI, 1.59 to 3.05) and retapamulin (RR, 1.64; 95% CI, 1.30 to 2.07). In one small study, bacitracin did not show a difference in cure rate compared to placebo (RR, 3.71; 95% CI, 0.16 to 84.29). No one topical antibiotic clearly showed greater efficacy over another. Pooling of 10 studies which compared topical mupirocin with oral erythromycin showed significantly better cure rates or more improvement with mupirocin (RR, 1.07; 95% CI, 1.01 to 1.13). No significant differences were observed between topical mupirocin and dicloxacillin, cephalexin or ampicillin. Bacitracin was significantly less effective than oral cephalexin in one small study, but no difference was seen between bacitracin and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				erythromycin or penicillin. *Bullous impetigo* Neomycin and bacitracin was significantly less effective than oral erythromycin (RR, 0.14; 95% CI, 0.02 to 0.99). Secondary: The reported number of side effects was low, with most being mild. Oral antibiotic treatment caused more side effects, especially gastrointestinal ones, than topical treatment.
Oranje et al.[41] (2007) Retapamulin 1% ointment BID for 5 days vs sodium fusidate 2% ointment TID for 7 days	MC, NI, RCT Patients ≥9 months of age with clinical diagnosis of primary bullous or nonbullous impetigo	N=519 14 days	Primary: Clinical response Secondary: Bacteriological responses at end of therapy and at follow-up	Primary: Patients in the clinical PP population had a statistically significant greater clinical success rate at the end of therapy with retapamulin treatment compared to sodium fusidate treatment (99.1 vs 94.0%; 95% CI, 1.1 to 9.0; P=0.003). Patients in the clinical ITT population had a clinical success rate of 94.8% at the end of therapy with retapamulin treatment compared to 90.1% observed with sodium fusidate treatment (95% CI, -0.4 to 9.7; P=0.062). Patients in the clinical PP population had a clinical success rate of 96.4% at follow-up with retapamulin treatment compared to 93.7% observed with sodium fusidate treatment (95% CI, -1.8 to 7.2; P=0.221). Patients in the clinical ITT population had a clinical success rate of 89.9% at follow-up with retapamulin treatment compared to 87.2% observed with sodium fusidate treatment (95% CI, -3.3 to 8.6; P=0.374). Secondary: Patients in the bacteriological PP population had a statistically significant greater bacteriological success rate at the end of therapy with retapamulin treatment compared to sodium fusidate treatment (99.2 vs 93.0%; 95% CI, 1.4 to 11.0; P=0.002). Patients in the bacteriological ITT population also had a statistically significant greater bacteriological success rate at the end of therapy with retapamulin compared to sodium fusidate treatment (95.1 vs 88.5%; 95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CI, 0.5 to 12.6; P=0.022). Patients in the bacteriological PP population had a bacteriological success rate of 96.6% at follow-up with retapamulin treatment compared to 92.5% observed with sodium fusidate treatment (95% CI, -1.4 to 9.6; P=0.106). Patients in the bacteriological ITT population had bacteriological success rate of 90.1% at follow-up with retapamulin compared to 84.7% observed with sodium fusidate treatment (95% CI, -1.8 to 12.5; P=0.134).
Koning et al.[42] (2008) Retapamulin 1% ointment BID for 5 days vs placebo ointment BID for 5 days	DB, MC, PC, RCT Patients ≥9 months of age with a clinical diagnosis of primary impetigo (bullous or nonbullous)	N=213 14 days	Primary: Clinical response rate at the end of therapy (seven days) Secondary: Not reported	Primary: A clinical response of 'success' was achieved by 86% of the ITT population at the end of therapy for the retapamulin group compared to 52% of the placebo group (P<0.0001). The clinical success rate (ITT) 14 days after start of treatment was 76 and 39% for retapamulin and placebo, respectively (P<0.0001). Secondary: Not reported
Infections: Catheter-Related				
Lok et al.[43] (2003) Bacitracin (500 U/g), gramicidin (0.25 mg/g), and polymyxin B (10,000 U/g) ointment applied to the central venous catheter at the end of each dialysis session for 2 weeks and then with each dressing change	DB, MC, RCT Patients ≥18 years of age with end-stage renal disease requiring hemodialysis, using a permanent cuffed catheter in the internal jugular vein as their primary source of vascular access	N=169 6 months	Primary: Incidence of infection, bacteremia, mortality, hospitalization, and catheter removal due to infections Secondary: Not reported	Primary: A smaller proportion of patients in the active group compared to placebo experienced an infection during the study duration (12 vs 34%; P=0.0013). It was calculated that treating five patients would prevent one infection (95% CI, 3 to 11). The proportion of patients experiencing a bacteremia was significantly higher in the placebo group compared to the active group (24 vs 10%; P=0.02). Treating seven patients would prevent one case of bacteremia (95% CI, 4 to 33). There were 13 deaths in the placebo group compared to three deaths in the treatment group during the study period (P=0.0041). It was calculated that treating eight patients would prevent one death (95% CI, 5 to 27). More patients in the placebo group compared to the active treatment group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				required hospitalization (24 vs 7%; P=0.0041). More patients in the placebo group compared to the active treatment group required catheter removal due to infections (27 vs 10%; P=0.0071). Secondary: Not reported
Chu et al.[44] (2008) Gentamicin cream vs mupirocin ointment	PRO Adult peritoneal dialysis patients attending an outpatient clinic in Hong Kong	N=95 475.6 patient-months (gentamicin) 538.7 patient-months (mupirocin)	Primary: Incidence of ESI Secondary: Not reported	Primary: Fifteen episodes of ESI occurred in 12 patients in the gentamicin group. The overall rate was 0.38 episodes/patient-year. Nine episodes of ESI were recorded in seven patients in the mupirocin group. The over-all rate was 0.20 episodes/patient-year. No significant results were found. Six patients in the gentamicin group developed 13 peritonitis episodes, whereas 12 peritonitis episodes were reported in 10 patients in the mupirocin group. No significant results were found. Secondary: Not reported
Xu et al.[45] (2010) Mupirocin vs placebo or no prophylaxis	MA Patients ≥18 years of age undergoing peritoneal dialysis	N=2,450 (14 trials) Variable duration	Primary: Incidence of ESI and peritonitis due to *S. aureus* Secondary: Not reported	Primary: Treatment with mupirocin decreased the risk of ESI by 72% (95% CI, 0.60 to 0.81; P<0.0001) and the risk of peritonitis by 70% (95% CI, 0.52 to 0.81; P<0.0001) due to *S. aureus*. Treatment with mupirocin reduced the risk of ESI and peritonitis due to all organisms by 57% (95% CI, 0.46 to 0.66; P<0.00001) and 41% (95% CI, 0.24 to 0.54; P<0.0001), respectively. Secondary: Not reported
Bernardini et al.[46] (2005) Mupirocin calcium 2% topical cream applied to the catheter exit site	DB, MC, RCT Patients ≥18 years of age on peritoneal dialysis	N=133 12 months	Primary: *P. aeruginosa* and *S. aureus* catheter infection rates Secondary: Gram-negative and	Primary: There was a statistically significant difference in *P. aeruginosa* catheter infection rate between the gentamicin and mupirocin treatment groups (0.0/year vs 0.11/year, respectively; P<0.003). *S. aureus* infections were infrequent in both the gentamicin and mupirocin treatment groups (0.06/year vs 0.08/year, respectively; P<0.44).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs gentamicin 0.1% topical cream, applied to the catheter exit site QD			gram-positive peritonitis, overall catheter infection, peritonitis rate, causative organism, catheter removal, and time to first catheter infection	Secondary: The rate of gram-positive and gram-negative catheter infections was lower in the gentamicin group compared to the mupirocin groups (0.23/year vs 0.54/year; P=0.005). Time to first catheter infection was longer with gentamicin compared to the mupirocin cream (P=0.03). Patients receiving gentamicin cream experienced a statistically significant decrease in peritonitis rates compared to mupirocin group (0.34/year vs 0.52/year; P=0.03), with a significant decrease in gram-negative peritonitis (0.02/year vs 0.15/year; P=0.003). Catheter removal as a result of infection was similar between mupirocin (0.09/year) and gentamicin (0.15/year) groups (P=0.45).
Mahaldar et al.[47] (2009) Mupirocin vs gentamicin	RETRO Patients ≥18 years of age on peritoneal dialysis who were using topical mupirocin or gentamicin and who had ≥6 months of follow-up data	N=100 11.8 months and 14.3 months for mupirocin and gentamicin, respectively	Primary: Incidence of ESI and peritonitis Secondary: Not reported	Primary: The ESI rate was 0.002 episodes/patient–month in the gentamicin group and 0.004 episodes/patient–month in the mupirocin group (P=0.45). The rate of gram-positive ESI was 0.002 episodes/patient–month in the gentamicin group and 0.001 episodes/patient–month in the mupirocin group (P=0.75). The rate of gram-negative ESI was zero in the gentamicin group and 0.002 episodes/patient–month in the mupirocin group (P=0.22). The peritonitis rate was 0.06 episodes/patient–month in the gentamicin group and 0.02 episodes/patient–month in the mupirocin group (P=0.07). The rate of gram-positive peritonitis was 0.05 episodes/patient–month in the gentamicin group and 0.01 episodes/patient–month in the mupirocin group (P=0.08). The rate of gram-negative peritonitis was 0.009 episodes/patient–month in the gentamicin group and 0.008 episodes/patient–month in the mupirocin group (P=0.83). Secondary: Not reported
Aykut et al.[48] (2010) Mupirocin applied	PRO Adults undergoing peritoneal dialysis	N=33 5 years	Primary: Incidence of ESI and peritonitis	Primary: A total of 28 episodes of ESI (0.62 episodes/patient per year) and 41 episodes of peritonitis (0.76 episodes/patient per year) were seen in 33 patients prior to mupirocin treatment. A total of 14 episodes of ESI (0.20

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to the exit-site once weekly vs mupirocin applied to the exit-site three times weekly	treatment		Secondary: Not reported	episodes/patient per year) and 34 episodes of peritonitis (0.54 episodes/patient per year) were observed in all groups of patients who used mupirocin one or three times a week for five years. The decrease was 28% in peritonitis (P=0.07) and 64% in ESI (P=0.03). In a subgroup analysis, patients were divided into those who used mupirocin once-a-week and those who used mupirocin three-times weekly. Among patients applying mupirocin once-weekly, there were 13 episodes of peritonitis and seven episodes of ESI. There were six episodes of peritonitis and one episode of ESI among patients applying mupirocin three times weekly. The rate of peritonitis was 56% lower (P=0.04) and the rate of ESI was 92% lower (P=0.03) in the group that applied mupirocin three times weekly compared to those who applied mupirocin once-weekly. Secondary: Not reported
Skin and Soft Tissue Infections				
Maddox et al.[49] (1985) Bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound TID vs placebo	DB, RCT Children with minor wounds	N=59 15 weeks	Primary: Prevention of streptococcal pyoderma Secondary: Not reported	Primary: Eighty-one percent of patients had positive normal skin cultures on one or more occasions. Nineteen children (32%) developed streptococcal pyoderma. Infection occurred in 47% of placebo-treated children compared to 15% of children treated with bacitracin, neomycin sulfate, and polymyxin B (NNT=32; P=0.01). Secondary: Not reported
Dire et al.[50] (1995) Bacitracin zinc, applied to the wound TID	DB, PC, PRO, RCT Patients with uncomplicated soft tissue wound admitted to the emergency	N=426	Primary: Wound infection rates Secondary: Not reported	Primary: Wound infection rates were 17.6% for petrolatum, 5.5% for bacitracin (NNT=8), 4.5% for bacitracin, neomycin sulfate, and polymyxin B (NNT=8), and 12.1% for silver sulfadiazine (NNT=18; P=0.0034). Sixty percent of the infections were stitch abscesses and were treated with local care only.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound TID vs silver sulfadiazine, applied to the wound TID vs petrolatum, applied to the wound TID	department within 12 hours of injury			There was no difference in rates of more serious infections between groups. One patient developed a hypersensitivity reaction to bacitracin, neomycin sulfate, and polymyxin B. Secondary: Not reported
Leyden et al.[51] (1987) Bacitracin, neomycin sulfate, and polymyxin B "triple-antibiotic" ointment (Neosporin®) applied to the wound BID vs bacitracin and polymyxin B ointment (Polysporin®)	AC, OL, RCT Healthy volunteers, with induced intradermal blister wounds contaminated with *S. aureus*	N=48 22 days	Primary: Healing rate, overall ranking of clinical appearance and the healing rate of wounds, infection rate, and *S. aureus* count after two applications of each test agent Secondary: Not reported	Primary: Contaminated blister wounds treated with the triple antibiotic and the Polysporin® ointments healed significantly faster (mean 9.2 and 8.8 days, respectively) compared to patients treated with benzalkonium chloride spray (14.2 days), merbromin (13.1 days), or those receiving no antibacterial treatment (13.3 days; $P<0.05$). There was no statistically significant difference between the two antibacterial ointments in terms of the overall ranking of clinical appearance and the healing rate of wounds. There was no statistically significant difference in infection rate between the antiseptic-treated and no-treatment wounds. Neosporin® ointment was statistically better in terms of overall ranking of clinical appearance and the healing rate of wounds compared to all other products except the Polysporin® ointment ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
applied to the wound BID vs benzalkonium chloride applied to the wound BID vs thimerosal applied to the wound BID vs hydrogen peroxide 3% applied to the wound BID vs tincture of iodine applied to the wound BID vs camphor and phenol applied to the wound BID vs merbromin applied to the wound BID				Following two applications of Neosporin® (triple-antibiotic) ointment, 83.3% of the wounds had a bacterial count of zero, significantly higher than seen with no treatment and all other products (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs wound protectant applied to the wound BID vs no treatment				
Berger et al.[52] (2000) Bacitracin, neomycin, and polymyxin B "triple-antibiotic" ointment (Neosporin®), applied to the wound BID vs bacitracin and polymyxin B "double-antibiotic" ointment (Polysporin®), applied to the wound BID vs non-occlusive gauze dressing	AC, PG, RCT Healthy volunteers >18 years of age, with dermabrasion wounds on the upper back, produced under anesthesia	N=70 14 days	Primary: Pigmentary composite score, textural composite score Secondary: Overall ranking of pigmentary changes, overall ranking of textural changes, and percentage area of the test site exhibiting scarring	Primary: The triple-antibiotic ointment treatment group had a statistically significant lower pigmentary composite score (2.6) at 90 days after study onset, compared to the group receiving gauze alone (4.2; P<0.001). Pigmentary composite score did not significantly differ between the double-antibiotic and the gauze-only group. The mean textural composite score at 45 days for the triple-antibiotic ointment group was statistically and clinically significantly different compared to the gauze treatment group (P<0.001). At 90 days, both the triple- and the double-antibiotic ointment groups had a statistically significantly lower textural composite score compared to the gauze-only group (P<0.001). Secondary: Both the pigmentary and the textural ranking significantly improved in the triple-antibiotic group compared to the gauze-treatment group at day 90 of the study (P<0.001). The double-antibiotic group exhibited significantly improved textural ranking compared to the gauze-treatment group at day 90 of the study (P<0.001). There was no statistical difference between any of the study groups in terms of percent area of scarring.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Contact dermatitis was the most frequent reason for study withdrawal, occurring in 2.9% of patients receiving either one of the antibiotic ointments.
Kraus et al.[53] (1998) Mupirocin calcium 2% topical cream TID vs cephalexin 250 mg QID	DB, RCT Patients with secondarily infected wounds (small lacerations, abrasions, or sutured wounds)	N=706 10 days	Primary: Clinical success rates at the end of therapy Secondary: Not reported	Primary: Clinical success at follow-up was equivalent in the two groups: 95.1 and 95.3% in the mupirocin cream and the cephalexin groups, respectively (95% CI, -4.0 to 3.6; P=0.89). The ITT success rate was 83.0% in both groups. Bacteriologic success at follow-up was also comparable: 96.9% in the mupirocin cream and 98.9% in the cephalexin groups (95% CI, -6.0 to 2.0; P=0.22). The occurrence of adverse experiences related to study treatment was similar for both groups, with fewer patients in the mupirocin cream group reporting diarrhea (1.1 vs 2.3% for cephalexin). Secondary: Not reported
Rist et al.[54] (2002) Mupirocin calcium 2% topical cream TID for 10 days vs cephalexin 250 mg QID for 10 days	DB, DD, MC, PG, RCT Patients ≥8 years of age, weighing >40 kg, with secondary eczema infection scored >8, on the total skin infection rating scale	N=159 10 days	Primary: Clinical response at the end of therapy Secondary: Bacteriological response, adverse events	Primary: There was no statistically significant difference in clinical response among the two treatment groups (P=0.29). Secondary: Bacteriological success, defined in terms of bacterial eradication, was statistically higher in the mupirocin group (50%) compared to the cephalexin group (28%; P=0.005). There was no significant difference in the incidence of adverse effects: diarrhea and nausea were the most common adverse events observed in the study (P=0.45).
Hood et al.[55] (2004) Mupirocin topical ointment applied to the wound TID	AC, RCT Emergency department patients with uncomplicated soft tissue wound 24	N=99 7 days	Primary: Presence of infection seven days after study onset	Primary: There was no statistically significant difference in wound infection incidence between the mupirocin and the neomycin, bacitracin, and polymyxin B treatment groups (4 vs 0%, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs neomycin, bacitracin, and polymyxin B ointment applied to the wound TID	hours or less before study enrollment		Secondary: Not reported	Not reported
Parish et al.[56] (2006) Retapamulin 1% ointment BID for 5 days vs cephalexin 500 mg capsules BID for 10 days	DB, DD, MC, NI, RCT Patients ≥9 months of age with underlying inflammatory skin disease (atopic dermatitis, psoriasis, or allergic contact dermatitis) experiencing one or more signs or symptoms of secondarily infected dermatitis	N=547 17 to 19 days	Primary: Clinical response at follow-up (total resolution of all signs and symptoms of infection such that no additional antibiotic necessary) Secondary: Clinical response at end of therapy, microbiologic response at follow-up and end of therapy	Primary: Patients in the PP clinical population had a clinical success rate of 85.9% at follow-up with retapamulin treatment compared to 89.7% observed with oral cephalexin treatment (95% CI, -9.9 to 2.3). Patients in the ITT clinical population had a clinical success rate of 82.9% at follow-up with retapamulin treatment compared to 86.3% observed with oral cephalexin treatment (95% CI, –9.7 to 2.9). Secondary: Patients in the PP clinical population had similar clinical success rates at end of therapy between retapamulin and oral cephalexin (92.0 vs 93.8%, respectively). Patients in the ITT clinical population also had similar clinical success rates at end of therapy between retapamulin and oral cephalexin (92.3 vs 91.8%, respectively). Patients in the PP bacteriologic group had similar microbiologic success rates at the end of therapy between retapamulin and oral cephalexin (93.0 vs 94.1%, respectively) and at follow-up (87.2 vs 91.8%, respectively). Patients in the ITT bacteriologic population had similar microbiologic success rates at the end of therapy between retapamulin and oral cephalexin (93.4 vs 91.3%, respectively) and at follow-up (83.5 vs 87.8%, respectively).
Free et al.[57] (2006)	DB, MC, RCT (two trials)	N=1,904 17 to 19 days	Primary: Clinical response at follow-up in the	Primary: Patients in the PP clinical population had comparable clinical success rates of 88.7 and 90.4% at follow-up with retapamulin treatment compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Retapamulin 1% ointment BID for 5 days vs cephalexin 500 mg capsules BID for 10 days	Patients ≥9 months of age with a secondarily infected traumatic lesion (abrasion, small laceration, sutured wound)		PP clinical population for both studies Secondary: Microbiologic response at follow-up in the PP clinical population for both studies	91.9 and 92.0% observed with oral cephalexin treatment (95% CI, -7.4 to 0.9) and (95% CI, -5.8 to 2.6) in each of the studies, respectively. Overall, clinical success rates for patients in the PP clinical population were 89.5% at follow-up with retapamulin treatment compared to 91.9% observed with oral cephalexin treatment combined for both studies (95% CI, -5.4 to 0.5). Secondary: Patients in the PP bacteriologic population had microbiologic success rates of 87.1 and 91.7% at follow-up with retapamulin treatment compared to 89.4 and 91.1% observed with oral cephalexin treatment in each of the studies, respectively. Overall, microbiologic success rates for patients in the PP bacteriologic population were 89.2% at follow-up with retapamulin treatment compared to 90.2% observed with oral cephalexin treatment combined for both studies.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ITT=intent-to-treat, MA=meta-analysis, MC=multicenter, NI=non inferiority, NNT=number needed to treat, OL=open-label, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blinded, SR=systematic review
Miscellaneous Abbreviations: ESI=exit-site infections, *P. aeruginosa=Pseudomonas aeruginosa; S. aureus=Staphylococcus aureus*

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Skin and Mucous Membrane Antibacterials

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Clindamycin	vaginal cream, vaginal suppository	Cleocin®*, Clindesse®	$$$	$$$$
Gentamicin	cream, ointment	N/A	N/A	$
Metronidazole	vaginal gel	MetroGel-Vaginal®*, Vandazole®*	$$$	$
Mupirocin	cream, ointment	Bactroban®*, Centany®*, Centany AT®	$$$-$$$$	$
Retapamulin	ointment	Altabax®	$$$	N/A
Combination Products				
Neomycin, bacitracin, polymyxin B, and hydrocortisone	ointment	Cortisporin®	$$$	N/A
Neomycin and polymyxin B†	irrigation solution	Neosporin G.U. Irrigant®*	$$$	N/A
Neomycin, polymyxin B, and hydrocortisone	cream	Cortisporin®	$$$	N/A

*Generic is available in at least one dosage form or strength.
†Product is primarily administered in an institution.
*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
N/A=Not available

X. Conclusions

The skin and mucous membrane antibacterials are approved for the treatment and/or prevention of various skin infections and bacterial vaginosis.[1-15] Most of the agents in this class are available in a generic formulation. Studies have demonstrated that prophylactic administration of topical antibiotics decreases infection rates in minor wounds.[49,50,55] Studies comparing topical mupirocin or retapamulin to oral antibiotics in patients with secondarily infected wounds also demonstrated similar clinical response rates.[38,53,56,57]

Due to the complications associated with bacterial vaginosis, all symptomatic women should be treated. Guidelines recommend oral or vaginal metronidazole, or vaginal clindamycin as initial therapy.[18-23] Cure rates do not differ between intravaginal clindamycin ovules and oral or intravaginal metronidazole formulations.[30,31] Clinical trials have demonstrated similar efficacy with metronidazole and clindamycin treatment regimens.[27,30-37]

Topical antibacterials have been shown to be effective for the treatment of impetigo in several clinical trials; however, there are relatively few studies that directly compare these agents.[38-42] According to the Infectious Diseases Society of America guidelines, mupirocin is the preferred treatment of impetigo, although resistance has been described. Other agents, such as bacitracin and neomycin, are less effective for the treatment of impetigo. The guidelines also state that topical therapy with mupirocin is equivalent to oral antimicrobials and may be used when lesions are limited in number. Retapamulin is a topical antibacterial which was not available when the guidelines were published in 2005.[25] Thus, the guidelines do not offer recommendations on the place in therapy for this agent. While there were no studies found in the medical literature directly comparing retapamulin and mupirocin, a 2012 Cochrane Systematic Review concluded that topical therapy consisting of mupirocin or retapamulin is probably equally effective in the treatment of impetigo. In contrast to mupirocin, no resistance has yet been reported with retapamulin.[40]

Topical antibacterials are also effective in preventing exit-site infections in patients receiving peritoneal dialysis; however, comparisons of different methods of exit-site care in randomized trials are limited.[44-48] The International Society for Peritoneal Dialysis guidelines recommend either mupirocin ointment or cream, or gentamicin cream daily after cleansing in all patients. The use of mupirocin ointment at the exit-site should be avoided in patients with polyurethane catheters, as structural damage to the catheter has been reported.[21]

There is insufficient evidence to support that one brand skin and mucous membrane antibacterial is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antibacterials within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antibacterial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Sept 22]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Oct 1]. Available from: http://www.thomsonhc.com/.
3. Lexi-Comp Online [database on the internet], Hudson (OH): Lexi-Comp, Inc.; 2013 [cited 2013 Oct 1]. Available from: http://www.lexi.com.
4. Cleocin® Vaginal Ovules [package insert on the internet]. New York (NY): Pharmacia & Upjohn Company; 2005 Nov [cited 2013 Sept 22]. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=553.
5. Clindesse® [package insert on the internet]. St. Louis (MO): Ther-Rx Corporation; 2005 Nov [cited 2013 Sept 22]. Available from: http://www.clindesse.com/pdf/PI.pdf.
6. Clindamycin Phosphate Vaginal Cream [package insert on the internet]. Peapack (NJ): Greenstone LLC; 2013 May [cited 2013 Sept 22]. Available from: http://labeling.greenstonellc.com/ShowLabeling.aspx?id=899.
7. MetroGel-Vaginal® [package insert on the internet]. Bristol (TN): Graceway Pharmaceuticals, LLC; 2009 July [cited 2013 Sept 22]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=8f974c5f-6b14-214e-f551-d096c332648d.
8. Vandazole® [package insert on the internet]. Minneapolis (MN): Upsher-Smith Laboratories; 2011 Jan [cited 2013 Sept 22]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021806s003lbl.pdf.
9. Bactroban® Cream [package insert on the internet]. Research Triangle Park (NC): GlaxoSmithKline; 2005 May [cited 2013 Sept 22]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=66763.
10. Bactroban® Ointment [package insert on the internet]. Research Triangle Park (NC): GlaxoSmithKline; 2005 May [cited 2013 Sept 22]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=78816.
11. Centany® [package insert on the internet]. Fairfield (NJ): Medimetriks Pharmaceuticals, Inc.; 2013 Jan [cited 2013 Sept 22]. Available from: http://www.medimetriks.com/sites/default/files/pi-files/Centany_PI_website.pdf.
12. Cortisporin® Cream [package insert on the internet]. Bristol (TN): Monarch Pharmaceuticals; 2003 Nov [cited 2013 Sept 22]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e86a5293-312d-4425-bf95-35e4d7149aed.
13. Cortisporin® Ointment [package insert on the internet]. Bristol (TN): Monarch Pharmaceuticals; 2003 Sept [cited 2013 Sept 22]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=097a7a8d-04d4-4736-c8b7-0796117457bf.
14. Neosporin® G.U.Irrigant Sterile [package insert on the internet]. Bristol (TN): Monarch Pharmaceuticals; 2003 May [cited 2013 Sept 22]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=1a9f81d8-277d-4f2c-39b0-412e01954f8a.
15. Altabax® [package insert on the internet]. Research Triangle Park (NC): GlaxoSmithKline; 2013 Jul [cited 2013 Sept 22]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7acc17e7-7041-46bf-f2b2-a615cbf99da6.
16. Fish DN, Pendland SL. Skin and soft tissue infections. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiological Approach. 9th ed. New York, NY: McGraw-Hill; 2014. http://www.accesspharmacy.com/content.aspx?aID=57487531. Accessed October 14, 2013.
17. Stulberg DL, Penrod MA, Blatny RA. Common bacterial infections. Am Fam Phys. 2002 Jul; 66(1):119-25.
18. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
19. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: Vaginitis. Obstet Gynecol. 2006 May;107(5):1195-206.
20. Cole C, Gazewood J. Diagnosis and treatment of impetigo. Am Fam Physician. 2007 Mar 15;75(6):859-64.
21. Piraino B, Bernardini J, Brown E, Figueiredo A, Johnson DW, Lye WC, et al. ISPD position statement on reducing the risks of peritoneal dialysis-related infections. Perit Dial Int. 2011 Nov-Dec;31(6):614-30.
22. European (International Union Against Sexually Transmitted Infections/World Health Organization). Guideline on the Management of Vaginal Discharge [guideline on the internet]. London (UK): European (International Union Against Sexually Transmitted Infections/World Health Organization); 2011 [cited 2013 Oct 1]. Available from: http://www.iusti.org/regions/europe/pdf/2011/Euro_Guidelines_Vaginal_Discharge_2011.Intl_Jrev.pdf.

23. British Association for Sexual Health and HIV: Clinical Effectiveness Group. UK National Guideline for the Management of Bacterial Vaginosis [guideline on the internet]. Cheshire (UK): British Association for Sexual Health and HIV; 2012 [cited 2013 Oct 1]. Available from: http://www.bashh.org/documents/4413.pdf.
24. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011 Feb 1;52(3):e18-55.
25. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
26. Nyirjesy P, McIntosh MJ, Steinmetz JI, Schumacher RJ, Joffrion JL. The effects of intravaginal clindamycin and metronidazole therapy on vaginal *Mobiluncus* morphotypes in patients with bacterial vaginosis. Sex Transm Dis. 2007 Apr;34(4):197-202.
27. Nyirjesy P, McIntosh MJ, Gattermeir DJ, Schumacher RJ, Steinmetz JI, Joffrion JL. The effects of intravaginal clindamycin and metronidazole therapy on vaginal lactobacilli in patients with bacterial vaginosis. Am J Obstet Gynecol. 2006 May;194(5):1277-82.
28. Faro S, Skokos CK. The efficacy and safety of a single dose of Clindesse vaginal cream vs a seven-dose regimen of Cleocin vaginal cream in patients with bacterial vaginosis. Infect Dis Obstet Gynecol. 2005 Sep;13(3):155-60.
29. McCormack WM, Covino JM, Thomason JL, Eschenbach DA, Mou S, Kapernick P, et al. Comparison of clindamycin phosphate vaginal cream with triple sulfonamide vaginal cream in the treatment of bacterial vaginosis. Sex Transm Dis. 2001 Oct;28(10):569-75.
30. Paavonen J, Mangioni C, Martin MA, Wajszczuk CP. Vaginal clindamycin and oral metronidazole for bacterial vaginosis: a randomized trial. Obstet Gynecol. 2000 Aug;96(2):256-60.
31. Austin MN, Beigi RH, Meyn LA, Hillier SL. Microbiologic response to treatment of bacterial vaginosis with topical clindamycin or metronidazole. J Clin Microbiol. 2005 Sep;43(9):4492-7.
32. Ferris DG, Litaker MS, Woodward L, Mathis D, Hendrich J. Treatment of bacterial vaginosis: a comparison of oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream. J Fam Pract. 1995 Nov;41(5):443-9.
33. Fischbach F, Petersen EE, Weissenbacher ER, Martius J, Hosmann J, Mayer H. Efficacy of clindamycin vaginal cream vs oral metronidazole in the treatment of bacterial vaginosis. Obstet Gynecol. 1993 Sep;82(3):405-10.
34. Arredondo JL, Higuera F, Hidalgo H, Narcio L, Casanova G, Beltran M, et al. Clindamycin vaginal cream vs oral metronidazole in the treatment of bacterial vaginosis. Arch AIDS Res. 1992;6(3):183-95.
35. Andres FJ, Parker R, Hosein I, Benrubi GI. Clindamycin vaginal cream vs oral metronidazole in the treatment of bacterial vaginosis: a prospective double-blind clinical trial. South Med J. 1992 Nov;85(11):1077-80.
36. Schmitt C, Sobel JD, Meriwether C. Bacterial vaginosis: treatment with clindamycin cream vs oral metronidazole. Obstet Gynecol. 1992 Jun;79(6):1020-3.
37. Higuera F, Hidalgo H, Sanches CJ, Valle A. Bacterial vaginosis: a comparative, double-blind study of clindamycin vaginal cream vs oral metronidazole. Curr Therap Res 1993 July;54(1):98-110.
38. Goldfarb J, Crenshaw D, O'Horo J, Lemon E, Blumer JL. Randomized clinical trial of topical mupirocin vs oral erythromycin for impetigo. Antimicrob Agents Chemother. 1988 Dec;32(12):1780-3.
39. Dagan R, Bar-David Y. Double-blind study comparing erythromycin and mupirocin for treatment of impetigo in children: implications of a high prevalence of erythromycin-resistant *Staphylococcus aureus* strains. Antimicrob Agents Chemother. 1992 Feb;36(2):287-90.
40. Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, et al. Interventions for impetigo. Cochrane Database Syst Rev. 2012 Jan 18;1:CD003261.
41. Oranje AP, Chosidow O, Sacchidanand S, Todd G, Singh K, Scangarella N, et al. Topical retapamulin ointment, 1%, vs sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blind, non inferiority study. Dermatology. 2007;215(4):331-40.
42. Koning S, van der Wouden JC, Chosidow O, Twynholm M, Singh KP, Scangarella N, et al. Efficacy and safety of retapamulin ointment as treatment of impetigo: randomized double-blind multicentre placebo-controlled trial. Br J Dermatol. 2008 May;158(5):1077-82.
43. Lok CE, Stanley KE, Hux JE, Richardson R, Tobe SW, Conly J. J Am Soc Nephrol. 2003 Jan;14(1):169-79.
44. Chu KH, Choy WY, Cheung CC, Fung KS, Tang HL, Lee W, et al. A prospective study of the efficacy of local application of gentamicin vs mupirocin in the prevention of peritoneal dialysis catheter-related infections. Perit Dial Int. 2008 Sep-Oct;28(5):505-8.
45. Xu G, Tu W, Xu C. Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. Nephrol Dial Transplant. 2010 Feb;25(2):587-92.

46. Bernardini J, Bender F, Florio T, Sloand J, Palmmontalbano L, Fried L, et al. Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis for patients. J Am Soc Nephrol. 2005 Feb;16(2):539-45.
47. Mahaldar A, Weisz M, Kathuria P. Comparison of gentamicin and mupirocin in the prevention of exit-site infection and peritonitis in peritoneal dialysis. Adv Perit Dial. 2009;25:56-9.
48. Aykut S, Caner C, Ozkan G, Ali C, Tugba A, Zeynep G, et al. Mupirocin application at the exit site in peritoneal dialysis patients: five years of experience. Ren Fail. 2010 Jan;32(3):356-61.
49. Maddox JS, Ware JC, Dillon HC. The natural history of streptococcal skin infection: prevention with topical antibiotics. J Am Acad Dermatol. 1985 Aug;13(2 Pt 1):207-12.
50. Dire DJ, Coppola M, Dwyer DA, Lorette JJ, Karr JL. Prospective evaluation of topical antibiotics for preventing infections in uncomplicated soft-tissue wounds repaired in the ED. Acad Emerg Med. 1995 Jan;2(1):4-10.
51. Leyden JL, Bartelt NM. Comparison of topical antibiotic ointments, a wound protectant, and antiseptics for the treatment of human blister wounds contaminated with *Staphylococcus aureus*. J Fam Pract. 1987 Jun;24(6):601-4.
52. Berger RS, Pappert AS, Van Zile PS, Cetnarowski WE. A newly formulated topical triple-antibiotic ointment minimizes scarring. Cutis. 2000 Jun;65(6):401-4.
53. Kraus SJ, Eron LJ, Bottenfield GW, Drehobl MA, Bushnell WD, Cupo MA. Mupirocin cream is as effective as oral cephalexin in the treatment of secondarily infected wounds. J Fam Pract. 1998 Dec;47(6):429-33.
54. Rist T, Parish LC, Capin LR, Sulica V, Bushnell WD, Cupo MA. A comparison of the efficacy and safety of mupirocin cream and cephalexin in the treatment of secondary infected eczema. Clin Exp Dermatol. 2002 Jan;27(1):14-20.
55. Hood R, Shermock KM, Emerman C. A prospective, randomized pilot evaluation of topical triple antibiotic vs mupirocin for the prevention of uncomplicated soft tissue wound infection. Am J Emerg Med. 2004 Jan;22(1):1-3.
56. Parish LC, Jorizzo JL, Breton JJ, Hirman JW, Scangarella NE, Shawar RM, et al. Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days vs oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized control trial. J Am Acad Dermatol. 2006 Dec;55(6):1003-13.
57. Free A, Roth E, Dalessandro M, Hiram J, Scangarella N, Shawar R, et al. Retapamulin ointment twice daily for 5 days vs oral cephalexin twice daily for 10 days for empiric treatment of secondarily infected traumatic lesions of the skin. Skinmed. 2006 Sep-Oct;5(5):224-32.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antivirals
AHFS Class 840406
February 12, 2014

I. Overview

The skin and mucous membrane antivirals are approved for the treatment of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).[1-7] Infection with HSV is associated with chronic, life-long viral infections.[8] The two most common manifestations are genital herpes and labial herpes. Genital herpes typically results from infection with HSV-2; however, either HSV type can lead to genital ulcers.[8,9] Initial primary genital HSV infections tend to be more severe with lesions persisting for several weeks. Clinical manifestations include painful genital ulcers, itching, dysuria, headache, fever, malaise and lymphadenopathy. Recurrent episodes are generally shorter and produce mainly localized vesicles, which progress through ulcerated and crusted stages for up to 10 days.[10] Labial herpes typically results from infection with HSV-1.[11] Initial primary episodes can be widespread and are associated with severe discomfort; recurrent episodes tend to be more localized.[9] Before skin lesions appear, there is often a prodrome phase consisting of pain, itching, tingling and burning.[9,11] Papules then present on the lip and infrequently on the palate, chin or the oral mucosa. This is followed by progression through ulcerated, crusted and healing stages within five days (for recurrent episodes).[11] Patients with recurrent labial herpes experience an average of one to six episodes per year.[9]

Treatment options for HSV infections include intravenous, oral and topical antiviral agents. No antiviral agent will eradicate HSV; therefore, treatment is aimed at managing, rather than curing, the disease. Oral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and in those with severe disseminated infection.[8] Topical antivirals reduce the duration of viral shedding and the length of time before all lesions become crusted; however, this route of administration is less effective than oral or intravenous routes.

The skin and mucous membrane antivirals that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Since the last review acyclovir ointment has become available generically. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Antivirals Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Acyclovir	cream, ointment	Zovirax®*	acyclovir, Zovirax®*
Penciclovir	cream	Denavir®	none
Combination Product			
Acyclovir and hydrocortisone	cream	Xerese®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antivirals are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antivirals

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines[12] (2010)**	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent

Clinical Guideline	Recommendation(s)
	episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir 200 mg orally five times daily for seven to 10 days, famciclovir 250 mg orally three times daily for seven to 10 days or valacyclovir 1,000 mg orally twice daily for seven to 10 days. Treatment can be extended if healing is incomplete after 10 days of therapy. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • The safety and efficacy of suppressive therapy have been documented among patients receiving daily therapy with acyclovir for as long as six years and with famciclovir or valacyclovir for one year. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy. • Recommended regimens for suppressive therapy of genital herpes include acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily, valacyclovir 500 mg orally once daily or valacyclovir 1,000 mg orally once daily. • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms being. • Recommended regimens for episodic treatment of genital herpes

Clinical Guideline	Recommendation(s)

	include acyclovir 400 mg orally three times daily for five days, acyclovir 800 mg orally twice daily for five days, acyclovir 800 mg orally three times daily for two days, famciclovir 125 mg orally twice daily for five days, famciclovir 1,000 mg orally twice daily for one day, famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days, valacyclovir 500 mg orally twice daily for three days or valacyclovir 1,000 mg orally once daily for five days.
	• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.
	• The sex partners of patients who have genital herpes can benefit from evaluation and counseling.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with human immunodeficiency virus (HIV) include acyclovir 400 to 800 mg orally twice daily, famciclovir 500 mg orally twice daily or valacyclovir 500 mg orally twice daily.
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV include acyclovir 400 mg orally three times daily for five to 10 days, famciclovir 500 mg orally twice daily for five to 10 days or valacyclovir 1,000 mg orally twice daily for five to 10 days.
	• The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established.
	• Infants exposed to HSV during birth should be followed carefully in consultation with a pediatric infectious disease specialist.
	
	<u>Pediculosis pubis (pubic lice infestation)</u>
	• Recommended regimens:
	  o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  o Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  o Ivermectin 250 µg/kg orally and repeated in two weeks.
	
	<u>Scabies</u>
	• Recommended regimens:
	  o Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  o Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Alternative regimens:
	  o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	
	<u>Bacterial vaginosis</u>
	• Recommended regimens for nonpregnant women include:
	  o Metronidazole 500 mg orally twice a day for seven days.
	  o Metronidazole 0.75% gel 5 g intravaginally for five days.
	  o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.
	• Alternative regimens for nonpregnant women include:
	  o Tinidazole 2 g orally once daily for two days.

Clinical Guideline	Recommendation(s)
	○ Tinidazole 1 g orally once daily for five days. ○ Clindamycin 300 mg orally twice daily for seven days. ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days. • Additional regimens include metronidazole (750 mg extended-release tablets once daily for seven days), or a single dose of clindamycin intravaginal cream, although data on these alternative regimens are limited. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • The topically applied azole drugs are more effective than nystatin. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: ○ Butoconazole 2% cream 5 g intravaginally for three days. ○ Butoconazole 2% cream 5 g single intravaginal application. ○ Clotrimazole 1% cream 5 g intravaginally for seven to 14 days. ○ Clotrimazole 2% cream 5 g intravaginally for three days. Miconazole 2% cream 5 g intravaginally for seven days. ○ Miconazole 4% cream 5 g intravaginally for three days. ○ Miconazole 100 mg vaginal suppository for seven days. ○ Miconazole 200 mg vaginal suppository for three days. ○ Miconazole 1,200 mg vaginal suppository, for one day. ○ Nystatin 100,000-unit vaginal tablet, one tablet for 14 days. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally for seven days. ○ Terconazole 0.8% cream 5 g intravaginally for three days. ○ Terconazole 80 mg vaginal suppository for three days. ○ Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent (four or more episodes in one year) or severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with uncontrolled diabetes, debilitation or immunosuppression. • Treatment: Each individual episode of recurrent vulvovaginal candidiasis caused by *Candida albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Maintenance regimens: Oral fluconazole weekly for six months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.

Clinical Guideline	Recommendation(s)

	Severe vulvovaginal candidiasis
	• Severe vulvovaginitis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	Non-albicans vulvovaginal candidiasis
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. Options include longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for two weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.
	
	Genital warts
	• Treatment of genital warts should be guided by the preference of the patient, the available resources, and the experience of the health-care provider.
	• No definitive evidence suggests that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that influence selection of treatment include wart size, wart number, location of the wart, wart morphology, patient preference, convenience, adverse effects, and provider experience.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens (patient-applied):
	  o Podofilox 0.5% solution or gel.
	  o Imiquimod 5% cream.
	  o Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  o Cryotherapy with liquid nitrogen or cryoprobe.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  o Surgical removal
	• Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.
	
	Cervical warts
	• For women who have exophytic cervical warts, a biopsy evaluation to

Clinical Guideline	Recommendation(s)

	exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	
	<u>Vaginal warts</u>
	• Recommended regimens:
	  o Cryotherapy with liquid nitrogen.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	
	<u>Urethral meatus warts</u>
	• Recommended regimens:
	  o Cryotherapy with liquid nitrogen.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	
	<u>Anal warts</u>
	• Recommended regimens:
	  o Cryotherapy with liquid nitrogen.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  o Surgical removal.

British Association for Sexual Health and Human Immunodeficiency Virus: **National Guideline for the Management of Genital Herpes**[13] **(2007)**	<u>Genital herpes</u> • Oral antiviral drugs are indicated within five days of the start of the episode and while new lesions are still forming. • Oral agents, acyclovir, valacyclovir and famciclovir all reduce the severity and duration of episodes. • Antiviral therapy does not alter the natural history of the disease. • Topical agents are less effective than oral agents. • Combined oral and topical treatment is of no benefit. • Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting. <u>Genital herpes with human immunodeficiency virus (HIV) infection</u> • Standard systemic antiviral drugs, as used to treat genital herpes in HIV-uninfected patients, have been shown to successfully treat genital herpes in patients with HIV. • Resistance to antiherpes drugs is more common in those with HIV co-infection and is associated with treatment failure of genital herpes. • Oral acyclovir, valacyclovir, and famciclovir are recommended for treatment of genital herpes. • In severe cases, initiating therapy with acyclovir 5 to 10 mg/kg body weight intravenously every eight hours might be necessary.
American College of Obstetricians and Gynecologists: **American College of Obstetricians and Gynecologists Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Gynecologic Herpes Simplex Virus Infections**[14] **(2004; reaffirmed 2009)**	• Acyclovir, valacyclovir and famciclovir are antiviral drugs approved for treatment of genital herpes. • Comparative trials of these medications suggest they have compatible clinical efficacy and result in comparable decrease in viral shedding. • Treatment should be offered for first episode, even if they appear to be mild initially. • Treatment of first episodes decreases lesions, viral shedding and symptoms, but does not affect the long-term natural history of infection. • Newly acquired HSV infections can have a prolonged course, with systemic and neurologic involvement that can be substantially ameliorated by using antiviral therapy. Oral therapy is recommended, except in severe cases in which a woman is unable to tolerate oral

Clinical Guideline	Recommendation(s)
	intake or has prominent neurologic involvement. Such patients should be hospitalized and treated with intravenous acyclovir. • Recurrent episodes of genital herpes can be managed effectively either with daily suppressive or episodic antiviral drugs. • Episodic therapy decreases the duration of the episode (lesion, pain and viral shedding) and is most effective when the patient initiates the therapy at prodrome or at the beginning of the episode. This form of therapy is most effective for a patient with infrequent symptomatic recurrences. • Topical antiviral medication is not effective therapy and does not add to the benefit of the oral medication; its use is discouraged.
World Health Organization: **Guidelines for the Management of Sexually Transmitted Infections**[15] **(2003)**	Genital herpes • There is no known cure for genital herpes, but the course of symptoms can be modified if systemic therapy, with acyclovir or its analogs, is started as soon as possible following the onset of symptoms. • Treatment can be expected to reduce the formation of new lesions, the duration of pain, the time required for healing and viral shedding. However, it does not appear to influence the natural history of recurrent disease. • Topical therapy with acyclovir produces only minimal shortening of the duration of symptomatic episodes and is not recommended. Genital herpes with HIV infection • Specific treatment for herpes genitalis is recommended as it offers clinical benefits to most symptomatic patients. • Drug options for genital herpes include acyclovir, valacyclovir and famciclovir.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antivirals are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Antivirals[1-7]

Indication	Single Entity Agents		Combination Product
	Acyclovir	Penciclovir	Acyclovir and Hydrocortisone
Herpes Simplex Virus Infections			
Management of initial genital herpes and in limited non–life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients	✔ †		
Treatment of recurrent herpes labialis	✔ §	✔	
Treatment of recurrent herpes labialis to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time			✔

§Cream formulation.
†Ointment formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antivirals are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antivirals[1-7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Acyclovir	Minimal	Not reported	Not reported	<0.02 to 9.40 (ointment) 0.04 (cream)	Not reported
Penciclovir	Minimal	Not reported	Not reported	Not reported	Not reported
Combination Product					
Acyclovir and hydrocortisone	Minimal	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane antivirals, no significant drug interactions have been reported.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antivirals are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antivirals[1-7]

Adverse Events	Single Entity Agents		Combination Product
	Acyclovir	Penciclovir	Acyclovir and Hydrocortisone
Dermatological			
Application site reaction	-	✔	-
Burning	30[†], <1[‡]	-	<1
Contact dermatitis	✔ [‡]	-	<1
Cracked lips	<1[‡]	-	-
Desquamation	<1[‡]	-	-
Dry lips	<1[‡]	-	<1
Dry skin	<1[‡]	-	<1
Eczema	✔ [‡]	-	-
Edema	✔ [†]	✔	-
Erythema	-	50	<1
Flakiness of the skin	<1[‡]	-	<1
Local anesthesia	-	<1	-
Pigmentation changes	-	-	<1
Pruritus	4[†], <1[‡]	✔	-
Rash	✔ [†]	✔	-
Skin discoloration	-	✔	-
Stinging	30[†], <1[‡]	-	<1
Tingling	-	-	<1
Urticaria	-	✔	-
Other			
Anaphylaxis	✔ [‡]	-	-
Angioedema	✔ [‡]	-	-
Headache	-	5	-

Adverse Events	Single Entity Agents		Combination Product
	Acyclovir	Penciclovir	Acyclovir and Hydrocortisone
Oropharyngeal edema	-	✔	-
Pain	30†	✔	-
Paresthesia	-	✔	-
Parosmia	-	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.
† Ointment formulation.
‡ Cream formulation.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antivirals are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Antivirals[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Acyclovir	Management of initial genital herpes and in limited non–life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients: Ointment: apply every three hours (six times/day) for seven days Recurrent herpes labialis: Cream: Apply five times/day for four days	Management of initial genital herpes and in limited non–life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients for individuals ≥12 years of age: Cream: apply five times/day for four days	Cream: 5% Ointment: 5%
Penciclovir	Recurrent herpes labialis: Cream: apply every two hours while awake for four days	Recurrent herpes labialis for individuals ≥12 years of age: Cream: apply every two hours while awake for four days	Cream: 1%
Combination Product			
Acyclovir and hydrocortisone	Recurrent herpes labialis to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time: Cream: apply five times/day for five days	Recurrent herpes labialis to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time for individuals ≥12 years of age: Cream: apply five times/day for five days	Cream: 5%-1%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antivirals are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Antivirals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Herpes Genitalis				
Luby et al.[16] (1984) Acyclovir 5% ointment applied 6 times/day at 3 hour intervals vs placebo	MC, PC, RCT Patients with recurrent genital herpes who experienced a prodrome more than 75% of the time before occurrence of actual lesions	N=309 5 days	Primary: Duration of viral excretion Secondary: Duration of ulceration/crusting of genital lesions, healing time of lesions, and duration of pain and itching	Primary: In female patients, the duration of viral excretion was less in the acyclovir group compared to placebo (1.1 vs 2.0 days; P=0.04). In male patients, there was no difference between the acyclovir and placebo groups (1.8 days). Secondary: There was no difference between placebo and acyclovir in ulceration and/or crusting time for male patients who had genital lesions present at the initial clinic visit (2.2 days). The mean duration of pain and itching in males treated with acyclovir compared to placebo was 3.7 and 3.8 days, respectively. The mean duration of pain and itching in females treated with acyclovir compared to placebo was 5.4 and 4.4 days, respectively.
Reichman et al.[17] (1983) Acyclovir 5% ointment applied 6 times/day at 3 hour intervals vs placebo	DB, PC, RCT Patients with culture-proven recurrent herpes simplex genitalis	N=88 5 days	Primary: Duration of virus shedding, time to crusting of lesions, time required for lesions to heal, time to cessation of pain Secondary: Not reported	Primary: The duration of virus shedding from lesions present at time of study entry was significantly reduced for men who received acyclovir compared to placebo (2.0 vs 3.2 days; P<0.05). In women, the duration of virus shedding was 1.6 days for those in the acyclovir group compared to 1.2 days for the placebo group. There was no significant difference between acyclovir and placebo in time to crusting, time required for lesion healing, time to cessation of pain, or frequency with which new lesions developed during the course of therapy. Secondary: Not reported
Corey et al.[18] (1982) Acyclovir 5%	DB, PC, RCT Patients with initial or	N=180 21 days	Primary: Mean duration of viral shedding from genital lesions, mean	Primary: Among acyclovir recipients with first episodes of genital herpes, the mean duration of viral shedding from genital lesions (2.0 vs 4.6 days), mean duration of local pain or itching (3.6 vs 6.7 days) and the mean time to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied 4 or 6 times/day vs placebo	recurrent episodes of genital herpes		duration of local pain or itching, mean time to healing of lesions Secondary: Not reported	healing of lesions (11.2 vs 15.8 days) were less than placebo (P<0.05). Among patients with recurrent genital herpes, the mean time to crusting and healing of lesions was 3.5 and 7.5 days, respectively, in acyclovir recipients compared to 5.0 days (P=0.03) and 9.7 days (P=0.07), respectively, in placebo recipients. Secondary: Not reported
Kinghorn et al.[19] (1983) Acyclovir 5% ointment applied 5 times/day vs placebo	DB, PC, RCT Patients diagnosed with a first or recurrent episode of genital herpes	N=113 14 days	Primary: Duration of pain, time to healing, duration of viral shedding, duration of new lesion formation Secondary: Not reported	Primary: For first episodes treated with acyclovir, the duration of pain (4 vs 8 days: P<0.05), time to healing (8 vs 14 days; P<0.001), duration of viral shedding (4 vs 11 days; P=0.001) and duration of new lesion formation (0 vs 2.5 days; P<0.001) were reduced compared to placebo. Patients with recurrent episodes in the acyclovir group showed reduced durations for all symptoms (3 vs 6 days; P<0.001), for time to healing (4 vs 6 days; P<0.01) and for the formation of new lesions (5 vs 29%; P<0.01) compared to placebo. Secondary: Not reported
Kinghorn et al.[20] (1986) Acyclovir 5% cream applied 5 times/day for 7 days and acyclovir 200 mg tablets 4 times/day vs placebo cream and acyclovir 200 mg tablets 4 times/day	DB, PC, RCT Patients ≥16 years of age who presented within 6 days of onset of symptoms of first episode genital herpes	N=49 7 days	Primary: Duration of viral shedding, duration of symptoms and time to healing of lesions Secondary: Not reported	Primary: Duration of viral shedding in the acyclovir cream group compared to placebo was not statistically significant (external lesions: 2.6 vs 2.0 days; urethra or cervix: 2.1 vs 1.7 days). The mean duration of viral shedding for women in the acyclovir cream group compared to placebo was not statistically significant (external lesions: 2.6 vs 2.8 days; cervix: 1.7 vs 1.8 days). The duration of symptoms of pain, dysuria and discharge showed no statistical significance between treatment groups. There was a decrease in the duration of itching with acyclovir cream compared to placebo (1.2 vs 2.2 days; P=0.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean duration of time to healing of lesions was not significantly different. Secondary: Not reported
Chen et al.[21] (2000) Penciclovir 1% cream applied 5 times/day vs acyclovir 3% cream applied 5 times/day	DB, MC, PG, RCT Patients 18 to 65 years of age with genital herpes and treatment was initiated within 24 hours of onset of the first sign of lesions	N=205 7 days	Primary: Time to healing, resolution of all symptoms, absence of blisters, cessation of new blisters, crusting and loss of crust Secondary: Not reported	Primary: A decrease in crusting time was noted in patients with primary first episodes of genital herpes with penciclovir compared to acyclovir (2.0 vs 3.0 days; P=0.03). The acyclovir group compared to the penciclovir group had a longer time to healing, absence of blisters, cessation of new blisters and loss of crust. None of these differences were found to be statistically significant. A comparison of clinical efficacy in terms of cure rate at day seven indicated that there was no difference between penciclovir and acyclovir treatment (P=0.53). Secondary: Not reported
Herpes Labialis				
Spruance et al[22] (1984) Acyclovir 5% ointment applied 4 times/day for 5 days vs placebo	DB, PC Patients with herpes simplex labialis	N=208 5 days	Primary: Decrease in median virus titers in lesions between the first and second clinic visit Secondary: Not reported	Primary: Acyclovir had a greater decrease in median virus titers in lesions compared to placebo (P=0.04). Antiviral effect occurred in the subgroup of patients who entered the study 0 to eight hours after the onset of lesions. No differences were found in patients who began treatment nine to 25 hours after lesion onset. The acyclovir group had a mean number of episodes per month of 0.38 compared to 0.45 in the placebo group (P=0.22). Secondary: Not reported
Shaw et al.[23] (1985)	DB, PC, RCT Patients ≥18	N=45 5 days	Primary: Healing time of original lesions, and	Primary: No significant differences were found in the criteria used to examine efficacy between acyclovir and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Acyclovir 5% cream applied 5 times/day vs placebo	years of age with at least three recurrences of herpes labialis a year		original lesion and fresh lesion combined; time to first crust on the original lesion and loss of crust from original lesion; duration of all symptoms Secondary: Not reported	The median healing times for acyclovir and placebo were nine and 10 days, respectively (P=0.82). The median duration of all symptoms was five days for the acyclovir group vs six days for the placebo group (P=0.33). Secondary: Not reported
Gibson et al.[24] (1986) Acyclovir 5% cream applied 4 times/day vs placebo	DB, PC, RCT Patients ≥16 years of age with six or more recurrences of herpes labialis per year	N=23 32 weeks (16 weeks of acyclovir application and 16 weeks of placebo)	Primary: Number of recurrent sores, number of days with sores present and number of days with signs/symptoms of disease present Secondary: Not reported	Primary: There was a significant difference in favor of the acyclovir group in mean number of doctor-confirmed recurrent sores (0.5 vs 1.1; P<0.05), mean number of sores present (9.5 vs 12.4; P<0.01) and mean number of days with no signs or symptoms of disease present (12.2 vs 17.4; P<0.001). There was no significant difference between the acyclovir and placebo groups in mean time to first patient recorded recurrence (40.7 vs 43.3), mean time to first doctor confirmed recurrence (64.2 vs 63.2) and mean number of patient recorded recurrent sores (1.6 vs 2.4). Secondary: Not reported
Raborn et al.[25] (1997) Acyclovir 5% cream applied 4 times/day at 4 hour intervals vs placebo	DB, MC, PC, RCT Patients ≥18 years of age who had experienced more than three episodes of sun-induced herpes labialis within the past year; first application	N=191 8 days	Primary: Number of lesions formed during treatment, number of lesions formed during follow-up Secondary: Not reported	Primary: The difference in the number of patients who had lesions form during treatment was not statistically significant in the acyclovir group compared to placebo (15/91 vs 23/90; P=0.20). During the four day follow-up period, a smaller percentage of patients with lesion formation were found in the acyclovir group compared to the placebo group (21 vs 40%; P<0.01). The proportion of patients with no lesion formation in either the treatment period or the four day follow-up was greater in the acyclovir group vs placebo (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	was to be applied 12 hours before intensive sun exposure			Secondary: Not reported
Spruance et al.[26] (2002) Acyclovir 5% cream applied 5 times daily vs placebo	DB, MC, PC, RCT (2 trials) Patients ≥18 years of age with a history of recurrent herpes labialis (at least three episodes in the past year)	N=1,385 4 days	Primary: Clinician-assessed duration of herpes labialis episode Secondary: Patient-assessed duration of pain, proportion of patients developing classical lesions (ulcers, vesicles, and crust)	Primary: The mean clinician-assessed duration of herpes labialis episode was significantly shorter for the patients treated with acyclovir cream vs patients treated with placebo cream in each of the two clinical trials (study 1; P=0.007, study 2; P=0.006). In study 1, the mean duration of herpes labialis episodes for patients with a known duration was 4.3 days in the acyclovir group compared to 4.8 days for the placebo group (P=0.010). In study 2, the durations of herpes labialis episodes for patients with a known duration was 4.6 days in the acyclovir group compared to 5.2 days for the placebo group (P=0.007). Secondary: The mean patient-assessed duration of pain was significantly shorter for patients in the acyclovir group compared to placebo in both studies (study 1; P=0.017, study 2; P=0.014). In study 1, the mean duration of pain was 2.9 days for patients in the acyclovir group compared to 3.2 days in the placebo group (P=0.024). In study 2, the mean duration of pain was 3.1 days for patients in the acyclovir group compared to 3.5 days for patients in the placebo group (P=0.027).
Evans et al.[27] (2002) Acyclovir/hydrocortisone 5%/1% cream applied 6 times/day for 5 days	DB, MC, RCT Patients ≥18 years of age who had a history of recurrent herpes labialis after exposure to	N=380 15 days	Primary: Development of lesions and time to healing, maximum lesion area, pain and tenderness Secondary:	Primary: Only 26% of patients developed delayed classical lesions (lesions that developed between 46 hours and seven days following UVR exposure) during treatment with acyclovir/hydrocortisone compared to 37% of patients treated with placebo (P=0.022). The patients in the acyclovir/hydrocortisone treatment group who developed delayed classical lesions had a median time to healing to normal skin of nine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	sunlight in the previous 12 months or who had ≥2 cold sores in the previous 12 months		Not reported	days compared to 10.1 days with placebo (P=0.037). The healing time measured as the time to the loss of the hard crust was reduced 19% by acyclovir/hydrocortisone from 6.8 to 5.4 days (P=0.084). Acyclovir/hydrocortisone reduced the median maximal lesion area of the delayed classical lesions by 28% (P=0.072). No significant treatment effects with respect to pain were observed in the study. A total of 76% of patients receiving acyclovir/hydrocortisone experienced pain compared to 81% of patients receiving placebo. A total of 42 patients receiving acyclovir/hydrocortisone who developed delayed classical lesions experienced tenderness, whereas 65 patients who were in the control group and who developed delayed classical lesions experienced tenderness (P=0.11). The patient opinion was more favorable for the patients treated with acyclovir/hydrocortisone than for those treated with placebo (P=0.006). Secondary: Not reported
Hull et al.[8] (2011) Acyclovir/hydrocortisone 5%/1% cream applied 5 times/day for 5 days vs acyclovir 5% cream applied 5 times/day for 5 days	DB, MC, RCT Patients ≥18 years of age with herpes simplex labialis who had experienced at least three episodes in the last year	N=2,437 3 weeks	Primary: Prevention of ulcerative herpes simplex labialis lesions Secondary: Episode duration of ulcerative lesions, time to lesion healing of ulcerative lesions, maximum lesion area for ulcerative lesions during the vesicular, ulcerative, and hard	Primary: The proportion of patients with nonulcerative lesions was higher in the acyclovir/hydrocortisone group (42%) than in the acyclovir group (35%; P=0.014) or in the placebo group (26%; P<0.0001). Treatments were more effective when started at an early lesion stage. This was significant for acyclovir/hydrocortisone (P=0.023) and for acyclovir (P=0.002) compared to placebo. Secondary: In patients who developed an ulcerative lesion (58% in the acyclovir-hydrocortisone group, 65% in the acyclovir group, and 74% in the placebo group), the mean duration of the ulcerative lesions to loss of hard crust was shorter in patients receiving acyclovir/hydrocortisone (5.7 days) than in those receiving placebo (6.5 days; P=0.008). The mean duration of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			crust stages, cumulative lesion area, duration of lesion tenderness	ulcerative lesions in patients receiving acyclovir was 5.9 days, which was not significantly different than acyclovir/hydrocortisone (P=0.365). The time for ulcerative lesions to heal was reduced by 1.4 days with acyclovir/hydrocortisone compared to placebo (P=0.002) and by 0.3 days compared to acyclovir (P=0.297). There was no significant difference in maximum lesion size of ulcerative lesions among the treatment groups. The cumulative lesion size of ulcerative lesions was not significantly different with acyclovir/hydrocortisone compared to acyclovir (P=0.096); however, favored acyclovir/hydrocortisone compared to placebo (P=0.005). The cumulative lesion size of "all lesions" favored acyclovir/hydrocortisone over acyclovir and placebo (P=0.014 and P<0.0001, respectively). The duration of tenderness of ulcerative lesions was five days with acyclovir/hydrocortisone and acyclovir compared to six days with placebo (P=0.019). There was no significant difference between acyclovir/hydrocortisone and acyclovir in the duration of tenderness of ulcerative lesions (P=0.838).
Strand et al.[28] (2012) Acyclovir/ hydrocortisone 5%/1% cream applied topically 5 times a day for 5 days	MC, OL Patients 12 to 17 years of age with a history of herpes simplex labialis and ≥2 recurrences during the past year	N=134 4 weeks	Primary: Adverse events, categorization of the recurrence as ulcerative or nonulcerative maximum lesion area Secondary: Not reported	Primary: Five adverse events occurred in five patients. Three were rated as mild in intensity and two of moderate intensity. Only one adverse event was considered to be related to the study medication (application site inflammation of moderate severity), leading to withdrawal from the study. Herpes simplex labials recurrence consisted of a single lesion in 126 (95.5%) and two lesions in six (4.5%) patients respectively. Overall, 78 patients (59.5%) had nonulcerative recurrences and 53 patients (40.5%) had ulcerative recurrences. The mean maximum lesion area in the 53 patients with ulcerative herpes lesions was 38.8±40.8 mm^2 (range six to 260 mm^2). Lesions healed completely in all evaluable patients, with normal skin and no signs or symptoms at the follow-up visit.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Spruance et al.[29] (1997) Penciclovir 1% cream applied every 2 hours while awake vs placebo	DB, MC, PC, PG, PRO, RCT Patients with a history of frequent episodes of herpes labialis; treatment was self-initiated by the patient within one hour of the first sign or symptoms of recurrence	N=1,573 4 days	Primary: Lesion healing, proportion of patients who lost their lesions by days six to eight Secondary: Time to loss of lesion pain	Primary: Healing of classical lesions based on the investigator-assessed data was found to be one day faster in the patients who received penciclovir compared to the patients who received placebo (5 vs 6 days; P<0.001). Patient-assessed healing time was found to be 0.7 days faster for penciclovir-treated patients compared to those who received placebo (4.8 vs 5.5 days; P<0.001). Investigator-assessed proportion of patients who lost classical lesions by days six, seven, and eight in the penciclovir group compared to the placebo group increased by 11, 9, and 7%, respectively (P<0.001, P<0.001, P=0.001). In the patient-assessed data, the proportion of patients who lost classical lesions by days six, seven, and eight in the penciclovir group compared to the placebo group increased by 11, 10, and 6%, respectively (P<0.001, P<0.001and P=0.001). Secondary: Time to loss of pain (3.5 vs 4.1 days; P<0.001) resolved more quickly for penciclovir treated patients compared to patients who applied the placebo control.
Boon et al.[30] (2000) Penciclovir 1% cream applied every 2 hours while awake vs placebo	DB, PC, PG, RCT Patients 18 to 81 years of age with a history of sun-induced herpes labialis with at least three recurrences a year	N=541 4 days	Primary: Clinician-recorded time to lesion healing and severity Secondary: Patient-recorded time of healing and severity of pain as well as other lesion symptoms	Primary: Penciclovir was significantly more effective than placebo in decreasing the time to lesion healing (P<0.001). Analysis of healing times for penciclovir patients who developed immediate lesions demonstrated a reduction of two days in median healing time compared to the placebo group (P<0.001). Secondary: The lesion-associated symptoms of itching, tingling, burning, tenderness, and numbness resolved significantly faster with penciclovir treatment than with placebo (P=0.026). The median loss of symptoms was seven days for penciclovir patients vs eight days for patients using placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fewer penciclovir treated patients rated their pain, itching, burning, and tenderness as moderate or severe compared to placebo (P<0.027).
Raborn et al.[31] (2002) Penciclovir 1% cream applied 6 times on day 1, then every 2 hours while awake vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a history of recurrent herpes simplex labialis who had ≥3 episodes/year that manifested as classical lesions	N=4,573 4 days	Primary: Healing of classical lesions Secondary: Resolution of lesion pain and duration of viral shedding	Primary: Lesion healing occurred significantly faster in the penciclovir group (4.9 days) than in the placebo group (5.5 days; P=0.0001). The percentage of cases healed by day six was significantly greater in the penciclovir group (70%) than in the placebo group (59%; P=0.001). The percentage of cases healed by day eight was significantly greater in the penciclovir group (85%) than in the placebo group (78%) as determined by the investigator (P=0.012). A similar finding was reported by the patient at day eight with the penciclovir group at 84% and the placebo group at 76% (P=0.002). Secondary: Resolution of lesion pain (days) was significantly different between the penciclovir group and the placebo group (3.5 vs 4.2 days; P=0.0001). There was a significant difference in healing in favor of penciclovir over placebo for early (P=0.001), late (P=0.0001) and vesicle (P=0.0115) stages. Loss of lesion pain also showed a significant difference in favor of the penciclovir group relative to the placebo group for early (P=0.0004), late (P=0.0001) and vesicle (P=0.0023) stages.
Femiano et al.[32] (2001) Penciclovir 1% cream applied every 2 hours vs acyclovir 5% cream applied every 2 hours	RCT Patients 12 to 47 years of age who had a history of frequent episodes of recurrent herpes labialis (at least five each year)	N=40 4 days	Primary: Clinicians' judgment of the appearance of vesiculation to crusting and patients' experience of pain Secondary: Not reported	Primary: In the prodromal acyclovir group, labial lesions reached a crusting stage by six days, with pain ceasing at day five. In the prodromal penciclovir group, both phases were reached earlier. The crusting phase was reached and pain ceased by day four, a difference that was significant (P=0.002041). In the disease therapy (appearance of vesicles) group, the acyclovir patients' clinical evolution and symptoms were similar to those seen in the absence of any therapy. The penciclovir patients, however, benefited from a reduction of 30% in the time to lesional crusting and a 20% reduction of the duration of pain compared to baseline and acyclovir (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Lin et al.[33] (2002) Penciclovir 1% cream applied up to 5 times/day vs acyclovir 3% cream applied up to 5 times/day	DB, MC, PG, RCT Patients 18 to 65 years of age with clinical diagnosis of herpes simplex facialis/labialis	N=248 7 days	Primary: Time to healing, resolution of all symptoms, absence of blisters, cessation of new blisters, crusting and loss of crust Secondary: Not reported	Primary: There was a trend towards shorter times in the penciclovir-treated primary cases, but the differences were not found to be statistically significant (P<0.08). In all groups treated with study medication, there was a significant reduction in scores relative to baseline (P<0.01). On days five and seven of treatment, the clinical scores in penciclovir-treated patients were significantly lower than those in the acyclovir-treated patients (P<0.01 and P<0.05, respectively). On day seven evaluations, treatment was recorded as a clinical cure in 75.4% of the penciclovir-treated patients and 64.9% of the acyclovir-treated patients. The difference was not statistically significant. Secondary: Not reported
Herpes Simplex Virus in Immunocompromised Patients				
Whitley et al.[34] (1984) Acyclovir 5% ointment applied 6 times/day vs placebo	DB, PC, RCT Immuno-compromised patients diagnosed with herpes simplex virus infections regardless of type	N=63 28 days	Primary: Viral clearance, resolution of pain, total lesion healing Secondary: Not reported	Primary: Individuals in the acyclovir group experienced acceleration in the clearance of virus (P=0.0006), resolution of pain (P=0.004) and total healing (P=0.038). Median differences between groups averaged 6 days for each of these parameters. Secondary: Not reported

Study abbreviations: DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial
Miscellaneous Abbreviations: UVR=ultraviolet radiation

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Antivirals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Acyclovir	cream, ointment	Zovirax®*	$$$$$	$$$$$
Penciclovir	cream	Denavir®	$$$	N/A
Combination Product				
Acyclovir and hydrocortisone	cream	Xerese®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The skin and mucous membrane antivirals are approved for the treatment of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).[1-7] Acyclovir cream is currently the only generic product available in the class.

Acyclovir ointment is approved for the treatment of genital herpes. Guidelines state that topical antiviral agents are less effective than oral agents, offer minimal clinical benefits, and do not recommend their use for this indication.[12-15] In clinical trials, topical acyclovir and penciclovir have been shown to be more effective than placebo.[16-20,22-26,29-31] One study directly compared topical formulations of acyclovir and penciclovir, which demonstrated similar efficacy among the agents.[21]

Acyclovir, penciclovir and acyclovir-hydrocortisone are approved for the treatment of recurrent herpes labialis.[5-7] They have been shown to decrease lesion healing time and duration of pain in clinical trials compared to placebo.[8,24-27,29-31] Although the results were statistically significant, the clinical significance is unknown. Healing times and duration of pain were reduced by ≤1 day compared to placebo.[8,23,26,27,29-31] Two studies directly compared acyclovir and penciclovir for the topical treatment of herpes labialis. In one study, penciclovir resulted in a quicker time to crusting and cessation of pain compared to acyclovir; however, there was no significant difference in time to healing.[32] In a second study, acyclovir and penciclovir demonstrated similar efficacy with regards to clinical cure rates and time to healing.[33] Hull et al compared combination therapy with acyclovir-hydrocortisone and acyclovir monotherapy in patients with recurrent herpes labialis.[8] The proportion of patients with nonulcerative lesions was significantly higher in the acyclovir-hydrocortisone group compared to the acyclovir monotherapy group. In patients who developed ulcerative lesions, there was no difference in the mean duration of lesions with acyclovir-hydrocortisone (5.7 days) compared to acyclovir (5.9 days; P=0.365). There was also no significant difference in the time for ulcerative lesions to heal, maximum lesion size, cumulative lesion size or duration of tenderness of ulcerative lesions.

There is insufficient evidence to support that one brand skin and mucous membrane antiviral is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antivirals within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antiviral is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Nov]. Available from: http://online.factsandcomparisons.com.
2. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2013 [cited 2013 Nov 2]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
3. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Nov 2]. Available from: http://www.thomsonhc.com/.
4. Zovirax® Cream [package insert]. Bridgewater (NJ): Valeant Pharmaceuticals North America LLC; 2011 Oct.
5. Zovirax® Ointment [package insert]. Bridgewater (NJ): Valeant Pharmaceuticals North America LLC; 2011 Aug.
6. Denavir® [package insert]. Roseland (NJ): New American Therapeutics, Inc.; 2011 Oct.
7. Xerese® [package insert]. Bridgewater (NJ): Valeant Pharmaceuticals North America LLC; 2012 Jan.
8. Hull CM, Harmenberg J, Arlander E, Aoki F, Bring J, Darpo B, et al. Early treatment of cold sores with topical ME-609 decreases the frequency of ulcerative lesions: A randomized, double-blind, placebo-controlled, patient-initiated clinical trial. J Am Acad Dermatol. 2011 Apr;64(4):696.e1-11.
9. Cernik C, Gallina K, Brodell R. The treatment of herpes simplex infections. Arch Intern Med. 2008 Jun 9;168(11):1137-44.
10. Albrecht MA. Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Nov 2]. Available from: http://www.utdol.com/utd/index.do.
11. Klein RS. Clinical manifestations and diagnosis of herpes simplex virus type 1 infection. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Nov 2]. Available from: http://www.utdol.com/utd/index.do.
12. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep. 2010;59(RR-12):1-110.
13. Clinical Effectiveness Group. 2007 national guideline for the management of genital herpes. London (UK): British Association for Sexual Health and HIV (BASHH); 2007. 26 p. Available at: http://www.bashh.org/documents/115/115.pdf. Accessed November 2013.
14. ACOG Committee on Practice Bulletins--Gynecology. ACOG practice bulletin: Clinical management guidelines for obstetrician-gynecologists, number 57, November 2004. Gynecologic herpes simplex virus infections. Obstet Gynecol. 2004 Nov;104(5 Pt 1):1111-8.
15. The World Health Organization (WHO): Guidelines for the management of sexually transmitted infections, revised version – 2003. Available at: http://hetv.org/resources/reproductive-health/mngt_stis/index.html. Accessed November 2013.
16. Luby JP, Gnann JW Jr, Alexander WJ, Hatcher VA, Friedman-Kien AE, Klein RJ, et al. A collaborative study of patient-initiated treatment of recurrent genital herpes with topical acyclovir or placebo. J Infect Dis. 1984 July;150(1):1-6.
17. Reichman RC, Badger GJ, Guinan ME, Nahmias AJ, Keeney RE, Davis LG, et al. Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. J Infect Dis. 1983 Feb;147(2):336-40.
18. Corey L, Benedetti JK, Critchlow CW, Remington MR, Winter CA, Fahnlander AL, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. Am J Med. 1982 Jul;73(1A):326-34.
19. Kinghorn GR, Turner EB, Barton IG, Potter CW, Burke CA, Fiddian AP. Efficacy of topical acyclovir cream in first and recurrent episodes of genital herpes. Antiviral Res. 1983 Dec;3(5-6):291-301.
20. Kinghorn GR, Abeywickreme I, Jeavons M, Barton I, Potter CW, Jones D, et al. Efficacy of combined treatment with oral and topical acyclovir in first episode genital herpes. Genitourin Med. 1986 Jun;62(3):186-8.
21. Chen XS, Han GZ, Guo ZP, Lu NZ, Chen J, Wang JB, et al. A comparison of topical application of penciclovir 1% cream with acyclovir 3% cream for treatment of genital herpes: a randomized, double-blind, multicenter trial. Int J STD AIDS. 2000 Sep;11(9):568-73.
22. Spruance SL, Crumpacker CS, Schnipper LE, Kern ER, Marlowe S, Arndt KA, et al. Early, patient-initiated treatment of herpes labialis with topical 10% acyclovir. Antimicrob Agents Chemother. 1984 May;25(5):553-5.

23. Shaw M, King M, Best JM, Banatvala JE, Gibson JR, Klaber MR. Failure of acyclovir cream in treatment of recurrent herpes labialis. Br Med J (Clin Res Ed). 1985 Jul 6;291(6487):7-9.
24. Gibson JR, Klaber MR, Harvey SG, Tosti A, Jones D, Yeo JM. Prophylaxis against herpes labialis with acyclovir cream—a placebo-controlled study. Dermatologica. 1986;172(2):104-7.
25. Raborn GW, Martel AY, Grace MG, McGaw WT. Herpes labialis in skiers: randomized clinical trial of acyclovir cream vs placebo. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997 Dec;84(6):641-5.
26. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. Antimicrob Agents Chemother. 2002 Jul;46(7):2238-43.
27. Evans TG, Bernstein DI, Raborn GW, Harmenberg J, Kowalski J, Spruance SL. Double-blind, randomized, placebo-controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced herpes labialis. Antimicrob Agents Chemother. 2002 Jun;46(6):1870-4.
28. Strand A, Böttiger D, Gever LN, Wheeler W. Safety and tolerability of combination acyclovir 5% and hydrocortisone 1% cream in adolescents with recurrent herpes simplex labialis. Pediatr Dermatol. 2012 Jan-Feb;29(1):105-10.
29. Spruance SL, Rea TL, Thoming C, Tucker R, Saltzman R, Boon R. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. JAMA. 1997 May 7;277(17):1374-9.
30. Boon R, Goodman JJ, Martinez J, Marks GL, Gamble M, Welch C. Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. Clin Ther. 2000 Jan;22(1):76-90.
31. Raborn GW, Martel AY, Lassonde M, Lewsi MA, Boon R, Spruance SL; Worldwide Topical Penciclovir Collaborative Study Group. Effective treatment of herpes simplex labialis with penciclovir combined results of two trials. J Am Dent Assoc. 2002 Mar;133(3):303-9.
32. Femiano F, Gombos F, Scully C. Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared to acyclovir (acyclovir). Oral Dis. 2001 Jan;7(1):31-3.
33. Lin L, Chen XS, Cui PG, Wang JB, Guo ZP, Lu NZ, et al. Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double blind, multicenter, acyclovir-controlled trial. J Dermatolog Treat. 2002 Jun;13(2):67-72.
34. Whitley RJ, Levin M, Barton N, Hershey BJ, Davis G, Keeney RE, et al. Infections caused by herpes simplex virus in the immunocompromised host: natural history and topical acyclovir therapy. J Infect Dis. 1984 Sep;150(3):323-9.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antifungals
AHFS Class 840408
February 12, 2014

I. Overview

The skin and mucous membrane antifungals are approved for the treatment of candidiasis, dermatitis, onychomycosis and dermatophyte infections.[1-21] Local cutaneous and mucous membrane infections with *Candida* species are generally benign and are the result of changes in the normal flora.[22] Seborrheic dermatitis is an inflammatory skin condition characterized by the formation of white or yellow flaky scales, which appear on oily areas, such as the scalp, face and upper trunk. Although the exact cause of seborrheic dermatitis is unknown, it is thought to be caused by a combination of overproduction of skin oil and colonization with *Malassezia*.[23] Onychomycosis is an infection of the nails which can be caused by any fungus, including dermatophytes, yeasts and non-dermatophyte molds. Dermatophyte infections are named by location (e.g., tinea corporis, tinea pedis, tinea unguium, tinea capitis, tinea cruris and tinea barbae). *Epidermophyton*, *Trichophyton* and *Microsporum* are the three dermatophytes that cause the majority of infections.[24]

The antifungal agents are classified based upon their chemical structure: allylamines (naftifine, terbinafine); imidazoles (butoconazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole, terconazole, tioconazole); benzylamines (butenafine); hydroxy pyridones (ciclopirox); polyenes (nystatin) and thiocarbamates (tolnaftate).[3] Most of these agents share a similar mechanism of action. They primarily block the enzyme responsible for breaking down sterol precursors, thereby inhibiting the formation of key cell membrane components (e.g., ergosterol) of the fungus. This action compromises the integrity of the cell membrane leading to growth inhibition and/or cell death.[3]

There are several combination products that are currently available, including benzoic acid-salicylic acid, clotrimazole-betamethasone, miconazole-zinc oxide-white petrolatum and nystatin-triamcinolone. The mechanism of action varies with each product. Benzoic acid has antifungal properties, while salicylic acid acts as a keratolytic agent to help soften/shed the outer layer of the skin. Products containing a corticosteroid (betamethasone and triamcinolone) help to control inflammation, which increases infection cure rates. Zinc oxide acts as a skin protectant and mild astringent with weak antiseptic properties.[1-3]

The skin and mucous membrane antifungals that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Many of the antifungals are available in a generic formulation. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Antifungals Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Butenafine	cream	Mentax®	none
Butoconazole	vaginal cream	Gynazole-1®	none
Ciclopirox	cream, gel, shampoo, solution, suspension	Ciclodan®*, Loprox®*, Penlac®*	ciclopirox
Clotrimazole	cream, solution, troche	N/A	clotrimazole
Econazole	cream	N/A	econazole
Ketoconazole	cream, foam, shampoo	Nizoral®*, Ketodan®*, Extina®*	ketoconazole
Miconazole	vaginal suppository	N/A	miconazole
Naftifine	cream, gel	Naftin®	none
Nystatin	cream, ointment, powder	N/A	nystatin
Oxiconazole	cream, lotion	Oxistat®	none
Sertaconazole	cream	Ertaczo®	none
Sulconazole	cream, solution	Exelderm®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Terconazole	vaginal cream, vaginal suppository	Terazol 3®*, Terazol 7®*, Zazole®*	terconazole
Combination Products			
Benzoic acid and salicylic acid	ointment	Bensal HP®	none
Clotrimazole and betamethasone	cream, lotion	Lotrisone®*	clotrimazole and betamethasone
Miconazole, zinc oxide, and white petrolatum	ointment	Vusion®	none
Nystatin and triamcinolone	cream, ointment	N/A	nystatin and triamcinolone

*Generic is available in at least one dosage form or strength.
N/A=Not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antifungals are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antifungals

Clinical Guideline	Recommendation(s)

Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Candidiasis[25] (2009)**	<u>Vulvovaginal candidiasis</u>
	• Several topical antifungal agents are effective for vulvovaginal candidiasis, and no agent or regimen is more effective than another.
	  ○ Butoconazole 2% cream 5 g intravaginally for three days.
	  ○ Butoconazole 2% cream 5 g (sustained release) for one day.
	  ○ Clotrimazole 1% cream 5 g intravaginally for seven to 14 days.
	  ○ Clotrimazole 100 mg vaginal tablet for seven days.
	  ○ Clotrimazole 100 mg vaginal tablet, two tablets for three days.
	  ○ Miconazole 2% cream 5 g intravaginally for seven days.
	  ○ Miconazole 100 mg vaginal suppository for seven days.
	  ○ Miconazole 200 mg vaginal suppository for three days.
	  ○ Miconazole 1,200 mg vaginal suppository for one day.
	  ○ Nystatin 100,000 unit vaginal tablet for 14 days.
	  ○ Tioconazole 6.5% ointment 5 g intravaginally for one day.
	  ○ Terconazole 0.4% cream 5 g intravaginally for seven days.
	  ○ Terconazole 0.4% cream 5 g intravaginally for three days.
	  ○ Terconazole 80 mg vaginal suppository for three days.
	• Uncomplicated vulvovaginal candidiasis can be effectively treated with either single-dose or short-course therapy, both of which achieve >90% response.
	• Complicated vulvovaginal candidiasis (approximately 10% of cases) is defined as severe or recurrent disease, non-albicans candidiasis, and/or vulvovaginal candidiasis in an abnormal host.
	• Complicated vulvovaginal candidiasis requires topical therapy administered intravaginally daily for approximately seven days or multiple doses of fluconazole (150 mg every 72 hours for three doses).
	• For recurrent vulvovaginal candidiasis, 10 to 14 days of induction therapy with a topical or oral azole, followed by a suppressive regimen for at least 6 months, is recommended. The most convenient and well-tolerated regimen is once weekly oral fluconazole at a dose of 150 mg. If fluconazole therapy is not feasible, topical clotrimazole (200 mg twice weekly) or clotrimazole (500 mg vaginal suppository once weekly) or other intermittent topical azole treatments are recommended.

Clinical Guideline	Recommendation(s)
	Oropharyngeal candidiasis • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for seven to 14 days is recommended. • For moderate to severe disease, oral fluconazole for seven to 14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days is recommended. Voriconazole or amphotericin B is recommended when treatment with other agents has failed. Intravenous echinocandin or amphotericin B can be used in treating patients with refractory disease. • For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines[26] (2010)**	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir 200 mg orally five times daily for seven to 10 days, famciclovir 250 mg orally three times daily for seven to 10 days or valacyclovir 1,000 mg orally twice daily for seven to 10 days. Treatment can be extended if healing is incomplete after 10 days of therapy. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • The safety and efficacy of suppressive therapy have been documented among patients receiving daily therapy with acyclovir for as long as six years and with famciclovir or valacyclovir for one year. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy. • Recommended regimens for suppressive therapy of genital herpes include acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily,

Clinical Guideline	Recommendation(s)

	valacyclovir 500 mg orally once daily or valacyclovir 1,000 mg orally once daily.
	• Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment.
	• Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms being.
	• Recommended regimens for episodic treatment of genital herpes include acyclovir 400 mg orally three times daily for five days, acyclovir 800 mg orally twice daily for five days, acyclovir 800 mg orally three times daily for two days, famciclovir 125 mg orally twice daily for five days, famciclovir 1,000 mg orally twice daily for one day, famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days, valacyclovir 500 mg orally twice daily for three days or valacyclovir 1,000 mg orally once daily for five days.
	• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.
	• The sex partners of patients who have genital herpes can benefit from evaluation and counseling.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with human immunodeficiency virus (HIV) include acyclovir 400 to 800 mg orally twice daily, famciclovir 500 mg orally twice daily or valacyclovir 500 mg orally twice daily.
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV include acyclovir 400 mg orally three times daily for five to 10 days, famciclovir 500 mg orally twice daily for five to 10 days or valacyclovir 1,000 mg orally twice daily for five to 10 days.
	• The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established.
	• Infants exposed to HSV during birth should be followed carefully in consultation with a pediatric infectious disease specialist.
	
	<u>Pediculosis pubis (pubic lice infestation)</u>
	• Recommended regimens:
	  ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  ○ Ivermectin 250 µg/kg orally and repeated in two weeks.
	
	<u>Scabies</u>
	• Recommended regimens:
	  ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  ○ Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Alternative regimens:
	  ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off

Clinical Guideline	Recommendation(s)

	after eight hours.
	
	Bacterial vaginosis
	• Recommended regimens for nonpregnant women include:
	  o Metronidazole 500 mg orally twice a day for seven days.
	  o Metronidazole 0.75% gel 5 g intravaginally for five days.
	  o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.
	• Alternative regimens for nonpregnant women include:
	  o Tinidazole 2 g orally once daily for two days.
	  o Tinidazole 1 g orally once daily for five days.
	  o Clindamycin 300 mg orally twice daily for seven days.
	  o Clindamycin 100 mg ovules intravaginally once at bedtime for three days.
	• Additional regimens include metronidazole (750 mg extended-release tablets once daily for seven days), or a single dose of clindamycin intravaginal cream, although data on these alternative regimens are limited.
	
	Uncomplicated vulvovaginal candidiasis
	• Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women.
	• Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis.
	• The topically applied azole drugs are more effective than nystatin.
	• Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy.
	• Recommended regimens include:
	  o Butoconazole 2% cream 5 g intravaginally for three days.
	  o Butoconazole 2% cream 5 g single intravaginal application.
	  o Clotrimazole 1% cream 5 g intravaginally for seven to 14 days.
	  o Clotrimazole 2% cream 5 g intravaginally for three days. Miconazole 2% cream 5 g intravaginally for seven days.
	  o Miconazole 4% cream 5 g intravaginally for three days.
	  o Miconazole 100 mg vaginal suppository for seven days.
	  o Miconazole 200 mg vaginal suppository for three days.
	  o Miconazole 1,200 mg vaginal suppository, for one day.
	  o Nystatin 100,000-unit vaginal tablet, one tablet for 14 days.
	  o Tioconazole 6.5% ointment 5 g single intravaginal application.
	  o Terconazole 0.4% cream 5 g intravaginally for seven days.
	  o Terconazole 0.8% cream 5 g intravaginally for three days.
	  o Terconazole 80 mg vaginal suppository for three days.
	  o Fluconazole 150 mg oral tablet in single dose.
	
	Complicated vulvovaginal candidiasis
	• Complicated vulvovaginal candidiasis is defined as recurrent (four or more episodes in one year) or severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with uncontrolled diabetes, debilitation or immunosuppression.
	• Treatment: Each individual episode of recurrent vulvovaginal candidiasis caused by *Candida albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen.

Clinical Guideline	Recommendation(s)

	• Maintenance regimens: Oral fluconazole weekly for six months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.
	
	<u>Severe vulvovaginal candidiasis</u>
	• Severe vulvovaginitis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	<u>Non-albicans vulvovaginal candidiasis</u>
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. Options include longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for two weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.
	
	<u>Genital warts</u>
	• Treatment of genital warts should be guided by the preference of the patient, the available resources, and the experience of the health-care provider.
	• No definitive evidence suggests that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that influence selection of treatment include wart size, wart number, location of the wart, wart morphology, patient preference, convenience, adverse effects, and provider experience.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens (patient-applied):
	  o Podofilox 0.5% solution or gel.
	  o Imiquimod 5% cream.
	  o Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  o Cryotherapy with liquid nitrogen or cryoprobe.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  o Surgical removal
	• Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.
	
	<u>Cervical warts</u>
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before

Clinical Guideline	Recommendation(s)

	treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	
	<u>Vaginal warts</u>
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90%.
	
	<u>Urethral meatus warts</u>
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	
	<u>Anal warts</u>
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  ○ Surgical removal.

British Association for Sexual Health and Human Immunodeficiency Virus: **National Guideline for the Management of Vulvovaginal Candidiasis[27] (2007)**	<u>Uncomplicated vulvovaginal candidiasis</u>
	• All topical and oral azole antifungals give an 80 to 95% clinical and mycological cure rate in acute vulvovaginal candidiasis in non-pregnant women. Nystatin preparations give a 70 to 90% cure rate.
	• Treatment regimens include:
	  ○ Clotrimazole pessary 500 mg stat.
	  ○ Clotrimazole pessary 200 mg for three nights.
	  ○ Clotrimazole pessary 100 mg for six nights.
	  ○ Clotrimazole 10% vaginal cream 5 g stat.
	  ○ Econazole pessary 150 mg stat.
	  ○ Econazole pessary 150 mg for three nights.
	  ○ Fenticonazole pessary 600 mg stat.
	  ○ Fenticonazole pessary 200 mg for three nights.
	  ○ Isoconazole vaginal tablet 300 mg two stat.
	  ○ Miconazole ovule 1.2 g stat.
	  ○ Miconazole pessary 100 mg for 14 nights.
	  ○ Nystatin vaginal cream (100,000 units) 4 g for 14 nights.
	  ○ Nystatin pessary (100,000 units) one to two for 14 nights.
	  ○ Fluconazole oral capsule 150 mg stat.
	  ○ Itraconazole oral capsule 200 mg twice daily for one day.
	
	<u>Recurrent vulvovaginal candidiasis (four or more episodes in one year)</u>
	• Principles of therapy include induction followed by a maintenance regimen for six months.
	• The recommended regimen is induction with fluconazole 150 mg capsule every 72 hours for three doses, followed by maintenance regimen of fluconazole 150 mg capsule once weekly for six months.
	• Alternative induction regimens include topical imidazole for 10 to 14 days.
	• Alternative maintenance regimens include:
	  ○ Clotrimazole pessary 500 mg once weekly for six months.
	  ○ Fluconazole 50 mg once daily for six months.
	  ○ Itraconazole 50 to 100 mg once daily for six months.
	  ○ Ketoconazole 100 mg once daily for six months.
	
	<u>Severe vulvovaginal candidiasis</u>
	• Fluconazole 150 mg should be repeated after three days as it improves

Clinical Guideline	Recommendation(s)

	symptomatic response, not recurrence.
	• If oral treatment is contraindicated, repeat a single dose pessary for seven days.
	• Low-dose corticosteroids may improve symptomatic relief in conjunction with antifungal therapy.
	
	Special populations
	• Single dose fluconazole 150 mg is recommended for *Candida albicans* in patients with diabetes mellitus.
	• Boric acid 600 mg intravaginal suppository once daily for 14 days is as effective as single dose fluconazole 150 mg in patients with diabetes mellitus.
	• Vulvovaginal candidiasis in human immunodeficiency virus infected women should be treated with conventional antifungal therapy.
	
	Non-albicans vulvovaginal candidiasis
	• *Candida glabrata* is susceptible to available azoles, while *Candida krusei* is resistant to fluconazole.
	• Two weeks of therapy is suggested although no data is available on optimum duration.
	• No comparative evidence is available for suggested treatments below:
	  ○ Nystatin pessaries (first-line therapy).
	  ○ Amphotericin B vaginal suppositories 50 mg once daily for 14 days.
	  ○ Boric acid vaginal suppositories 600 mg once daily for two to three weeks.
	  ○ Intravaginal flucytosine 5 or 1 g pessary alone or in combination with amphotericin for two weeks.

American College of Obstetricians and Gynecologists: **Clinical Management Guidelines for Obstetrician-Gynecologists: Vaginitis[28] (2006)**	Bacterial vaginosis
	• Nonpregnant women with bacterial vaginosis can be treated with vaginal clindamycin, oral clindamycin, vaginal metronidazole, or oral metronidazole products. These agents seem to have comparable clinical efficacy and safety.
	• Oral metronidazole may be associated with significant gastrointestinal symptoms. Disulfiram-like reactions may occur with both oral and topical metronidazole.
	
	Uncomplicated vulvovaginal candidiasis
	• Women with uncomplicated vulvovaginal candidiasis can be treated successfully with any of the following options:
	  ○ Butoconazole 2% sustained-release cream 5 g daily for one day.
	  ○ Clotrimazole 1% cream 5 g daily for seven days.
	  ○ Clotrimazole 2% cream 5 g daily for three days.
	  ○ Clotrimazole 100 mg vaginal suppository daily for seven days.
	  ○ Clotrimazole 200 mg vaginal suppository daily for three days.
	  ○ Clotrimazole 500 mg vaginal suppository daily for one day.
	  ○ Fluconazole 150 mg oral tablet daily for one day.
	  ○ Miconazole 2% cream 5 g daily for seven days.
	  ○ Miconazole 100 mg vaginal suppository daily for seven days.
	  ○ Miconazole 200 mg vaginal suppository for three days.
	  ○ Miconazole 1,200 mg vaginal suppository daily for one day.
	  ○ Nystatin 100,000 units vaginal tablets daily for 14 days.
	  ○ Terconazole 0.4% cream 5 g daily for seven days.
	  ○ Terconazole 0.8% cream 5 g daily for three days.
	  ○ Tioconazole 2% cream 5 g daily for three days.
	  ○ Tioconazole 6.5% cream 5 g daily for one day.
	• Because all listed antifungal treatments seem to have comparable safety and efficacy, the choice of therapy should be individualized to the specific

Clinical Guideline	Recommendation(s)
	patient; factors such as ease of use, history of response or adverse reactions to prior treatments, and patient preference can all be taken into consideration. Complicated vulvovaginal candidiasis • Patients with complicated vulvovaginal candidiasis require more aggressive treatment to achieve relief of symptoms. • After initial intensive therapy for seven to 14 days to achieve mycologic remission, prolonged antifungal treatment with fluconazole, 150 mg weekly for six months, will successfully control more than 90% of symptomatic episodes and will lead to a prolonged protective effect in approximately 50% of women. • Although daily oral ketoconazole was previously described as an effective suppressive therapy in women with recurrent vulvovaginal candidiasis, weekly fluconazole has a lower risk of liver toxicity and should be used instead of ketoconazole. • For patients who are unable or unwilling to take fluconazole, prolonged maintenance therapy with intermittent topical agents, such as clotrimazole, 500 mg weekly or 200 mg twice a week, are acceptable options. Non-albicans vulvovaginal candidiasis • A standard course of topical imidazole therapy may be effective in up to 50% of such cases. • Therapy with vaginal boric acid, 600 mg capsules daily for a minimum of 14 days, seems to be effective for azole failures.

European (International Union Against Sexually Transmitted Infections/ World Health Organization): **Guideline on the Management of Vaginal Discharge[29] (2011)**	Bacterial vaginosis
	• Recommended regimens for bacterial vaginosis:
	  ○ Metronidazole 400 to 500 mg twice daily for five to seven days.
	  ○ Metronidazole 2 g in a single dose.
	  ○ Intravaginal metronidazole 0.75% gel once daily for five days.
	  ○ Tinidazole 2 g in a single dose.
	• Alternative regimens for bacterial vaginosis:
	  ○ Intravaginal metronidazole 0.75% gel once a day for five days.
	  ○ Intravaginal clindamycin 2% cream once daily for seven days.
	  ○ Clindamycin 300 mg twice daily for seven day.
	• Clindamycin and metronidazole have equal efficacy, comparing oral and vaginal formulations, both after one week and after one month of therapy. Approximately 58 to 88% will be cured after five days treatment with metronidazole or clindamycin. In most studies, clindamycin tended to have less adverse effects than metronidazole.
	• Vaginal application of metronidazole is as effective as oral administration.
	• Eradication at one month after vaginal clindamycin cream were 66 to 83% vs 68 to 87% for oral metronidazole.
	• Oral metronidazole, vaginal metronidazole 0.75% cream and vaginal clindamycin 2% cream have similar efficacy and side effect profile. Compared to oral clindamycin, vaginal clindamycin administration is associated with similar efficacy with fewer side effects.
	
	Vaginal candidiasis
	• Intravaginal and oral therapies are equally effective for vaginal candidiasis.
	• Treatment with azoles results in relief of symptoms and negative cultures among 80 to 90% of patients after either oral or topical treatment; only topical preparations should be used during pregnancy.
	• Recommended regimens for vaginal candidiasis:
	  ○ Fluconazole 150 mg orally as a single dose.
	  ○ Itraconazole 200 mg twice daily for one day.

Clinical Guideline	Recommendation(s)
	○ Clotrimazole vaginal tablet 500 mg once or 200 mg once daily for three days. ○ Miconazole vaginal ovule 1,200 mg as a single dose or 400 mg once daily for three days. ○ Econazole vaginal pessary 150 mg as a single dose. • Standard single dose treatments are as effective as longer courses. • In a severely symptomatic attack, symptomatic benefit is with fluconazole 150 mg treatment repeated after three days.
Finnish Medical Society Duodecim: **Seborrheic Dermatitis[30] (2007)**	General considerations • Treatment does not cure the disease. Therefore, it must be repeated when the symptoms recur, or even prophylactically. Removing the thick scales and decreasing the amount of sebum • The scales can be softened with a cream containing salicylic acid and sulfur (but not Vaseline) or by wetting and washing. • Seborrheic skin should be washed more often than usual. Decreasing fungal growth • Washing the scalp with ketoconazole shampoo or selenium sulfide shampoo. • Topical treatment with creams containing imidazole derivatives. • Antimycotic on skin creases (rarely necessary). • Sometimes ultraviolet light therapy. Symptomatic topical treatment • Corticosteroid liniments for the scalp (from mild to potent). • Corticosteroid creams for other parts of the body (from mild to potent). • Moisturizing emollients after washing. • Ketoconazole shampoo and corticosteroid liniments must often be combined in therapy-resistant cases.
European Academy of Dermatology and Venereology: **Onychomycosis Treatment Guidelines[31] (2005)**	• Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions. • Oral monotherapy (terbinafine, itraconazole or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area involvement. • Combination therapy with systemic and topical treatments may be considered when a large portion of the nail plate is affected (>50%), when the nail matrix is involved, and in cases of treatment failure.
British Association of Dermatologists: **Guidelines for the Treatment of Onychomycosis[32] (2003)**	• Both topical and oral agents are available for the treatment of fungal nail infection. • Systemic therapy is almost always more successful than topical treatment. • While it is clearly possible to achieve clinical and mycological cure with topical nail preparations, these cure rates do not compare favorably with those obtained with systemic drugs. • Topical therapy can only be recommended for the treatment of superficial white onychomycosis and in very early cases of distal and lateral subungual onychomycosis where the infection is confined to the distal edge of the nail.

Clinical Guideline	Recommendation(s)
	• A combination of topical and systemic therapy may improve cure rates still further or possibly shorten the duration of therapy with the systemic agent.
European Society for Pediatric Dermatology: **Guidelines for the Management of Tinea Capitis in Children[33] (2010)**	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (six to 12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to those of griseofulvin in children with tinea capitis due to *Trichophyton* species, while requiring much shorter duration of treatment. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream or lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and hair for five minutes twice weekly for two to four weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with one week of topical fungicidal cream or lotion application is recommended.

British Association of Dermatologists: **Guidelines for the Management of Tinea Capitis[34] (2000)**	• The aim of treatment is to achieve a clinical and mycological cure as quickly as possible.
	• Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis.
	• Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole.
	• If there has been no clinical response and signs persist at the end of the treatment period, then the options include:
	  o Increase the dose or duration of the original drug.
	  o Change to an alternative antifungal.
	• Symptom-free carriers with light growth/low spore count on culture may be treated with twice weekly selenium or povidone shampoo.
	• The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antifungals are noted in Tables 3 through 5. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Agent Skin and Mucous Membrane Antifungals (Drugs A-M)[1-21]

Indication	Butenafine	Butoconazole	Ciclopirox	Clotrimazole	Econazole	Ketoconazole	Miconazole
Candidiasis							
Prophylactically to reduce the incidence of oropharyngeal candidiasis in immunocompromised patients				✔ *			
Treatment of cutaneous candidiasis			✔ †‡	✔ ‡§	✔	✔ ‡	
Treatment of oropharyngeal candidiasis				✔ *			
Treatment of vulvovaginal candidiasis		✔					✔
Dermatitis							
Topical treatment of seborrheic dermatitis						✔ ‡‖	
Treatment of seborrheic dermatitis of the scalp			✔ ¶#			‖	
Dermatophyte Infections							
Treatment of interdigital tinea pedis and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum*			✔ #				
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *E. floccosum, T. mentagrophytes,* and *T. rubrum*						✔ ‡	
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum, T. mentagrophytes, E. floccosum,* and *Microsporum canis*			✔ †‡				
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum, T. mentagrophytes, T. tonsurans, M. canis, Microsporum audouini, Microsporum gypseum,* and *E. floccosum*					✔		
Topical treatment of tinea versicolor caused by *Malassezia furfur*	✔		✔ †‡	✔ ‡§	✔	✔ ‡¶	
Onychomycosis							
Treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement caused by *T. rubrum*			✔ §				

*Troche formulation.
†Suspension formulation.
‡Cream formulation.
§Solution formulation.
‖Foam formulation.
¶Shampoo formulation.
#Gel formulation.

Table 4. FDA-Approved Indications for the Single Agent Skin and Mucous Membrane Antifungals (Drugs N-Z)[1-21]

Indication	Naftifine	Nystatin	Oxiconazole	Sertaconazole	Sulconazole	Terconazole
Candidiasis						
Treatment of cutaneous or mucocutaneous mycotic infections caused by *Candida. albicans* and other *Candida* species		✔				
Treatment of vulvovaginal candidiasis						✔
Dermatophyte Infections						
Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum*	✔ *					
Treatment of interdigital tinea pedis caused by *T. rubrum, T. mentagrophytes,* and *E. floccosum*	✔ †			✔		
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum, T. mentagrophytes,* and *E. floccosum*	✔ ‡		✔ § ‖			
Treatment of tinea cruris and tinea corporis caused by *T. rubrum, T. mentagrophytes, E. floccosum,* and *Microsporum canis*					✔ ¶	
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum, T. mentagrophytes, E. floccosum,* and *M. canis*					✔ §	
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum, T. mentagrophytes, Trichophyton tonsurans,* and *E. floccosum*	✔ #					
Treatment of tinea versicolor caused by *Malassezia furfur*			✔ §		✔ §¶	

*2% cream concentration.
†2% gel concentration.
‡1% cream concentration.
§Cream formulation.
‖Lotion formulation.
¶Solution formulation.
#1% gel concentration.

Table 5. FDA-Approved Indications for the Combination Skin and Mucous Membrane Antifungals[1-21]

Indication	Benzoic Acid and Salicylic Acid	Clotrimazole and Betamethasone	Miconazole, Zinc Oxide and White Petrolatum	Nystatin and Triamcinolone
Candidiasis				
Treatment of cutaneous candidiasis				✔
Dermatitis				
Treatment of diaper dermatitis when complicated by documented candidiasis			✔	
Treatment of inflammation and irritation associated with dermatitis, including certain eczematoid conditions	✔			
Dermatophyte Infections				
Treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum*		✔		
Miscellaneous				
Treatment of insect bites, burns and fungal infections	✔			

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antifungals are listed in Table 6. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individuals components listed in the table below.

Table 6. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antifungals[1-21]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Benzoic acid	Not reported	Not reported	Liver	Renal	Not reported
Betamethasone	12 to 14	64	Liver	Renal	5.6
Butenafine	Minimal	Not reported	Liver	Renal	35
Butoconazole	5.5	Not reported	Not reported	Renal (2.7) Feces (2.8)	21 to 24
Ciclopirox	Solution: 1.3	94 to 98	Liver	Renal (<10)	Cream: 1.7 Gel: 5.5
Clotrimazole	Skin: <1	Not reported	Not reported	Renal (<1) Feces	3.5 to 5.0
Econazole	Minimal	98	Not reported	Renal (<1) Feces (<1)	Not reported
Ketoconazole	Negligible	Not reported	Not reported	Renal (13) Bile	Not reported
Miconazole	<2	90 to 93	Liver	Renal (<1) Feces (50)	Not reported
Naftifine	2.5 to 6.0	Not reported	Liver (14 to 29)	Renal (64) Feces (36)	2 to 3 days
Nystatin	Minimal	Not reported	Not reported	Feces	Not reported
Oxiconazole	Minimal	Not reported	Not reported	Renal (<1)	Not reported
Salicylic acid	9.3 to 25.1	50 to 80	Not reported	Renal (95)	2 to 3
Sertaconazole	Minimal	Not reported	Not reported	Not reported	Not reported
Sulconazole	8.7	Not reported	Not reported	Renal (6.7) Feces (2)	Not reported
Terconazole	5 to 16	95	Liver	Renal (32 to 56) Feces (47 to 52)	6.9
Triamcinolone	Not reported	Not reported	Liver	Renal Bile	2 to 3

V. Drug Interactions

Significant drug interactions with the skin and mucous membrane antifungals are listed in Table 7.

Table 7. Significant Drug Interactions with the Skin and Mucous Membrane Antifungals[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Econazole and miconazole	1	Anticoagulants	Pharmacologic effects of anticoagulants may be increased by these agents, especially following application to the groin area in the elderly. Bleeding may occur.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antifungals are listed in Tables 8 to 10.

Table 8. Adverse Drug Events (%) Reported with the Single Agent Skin and Mucous Membrane Antifungals (Drugs A-M)[1-21]

Adverse Events	Butenafine	Butoconazole	Ciclopirox	Clotrimazole	Econazole	Ketoconazole	Miconazole
Central Nervous System							
Dizziness	-	-	-	-	-	✔ *	-
Headache	-	-	✔	-	-	✔ *	1
Dermatological							
Abnormal hair texture	-	-	-	-	-	✔ †	-
Acne	-	-	✔	-	-	✔ *	-
Allergic reaction	-	-	-	-	-	✔ *	-
Alopecia	-	-	✔	-	-	<1†	-
Blistering	-	-	-	✔ *‡	-	-	-
Burning	1	-	34§, <1*†‡ ‖	✔ *‡	3	4*, ✔ †¶	-
Contact dermatitis	<2	-	✔	-	-	✔	-
Dry skin	-	-	✔	-	-	✔	-
Edema	-	-	-	✔ *‡	-	-	-
Erythema	<2	-	✔	✔ *‡	3	✔ *¶	-
Facial edema	-	-	✔	-	-	✔ *	-
Hair discoloration	-	-	✔	-	-	✔ †	-
Hypersensitivity reaction	-	-	-	-	-	✔ †	-
Impetigo	-	-	-	-	-	✔ *	-
Irritation	<2	-	✔	✔ *‡	-	✔ *, <1†	-
Nail discoloration	-	-	-	-	-	✔ *	-
Nail disorder	-	-	✔	-	-	-	-
Oily hair/skin	-	-	-	-	-	✔ †	-
Pain	-	-	✔	-	-	✔ *	-
Peeling	-	-	-	✔ *‡	-	-	-
Pruritus	<2	-	✔	✔	3	✔	-
Pustules	-	-	-	-	-	✔ *	-
Pyogenic granuloma	-	-	-	-	-	✔ *	-
Rash	-	-	✔	-	✔	✔ †¶	✔
Scalp pustules	-	-	-	-	-	✔ †	-
Stinging	1	-	-	✔ *‡	3	5*	-
Urticaria	-	-	-	✔ *‡	-	✔ †	-

Adverse Events	Butenafine	Butoconazole	Ciclopirox	Clotrimazole	Econazole	Ketoconazole	Miconazole
Gastrointestinal							
Abdominal cramping	-	✔	-	-	-	-	2
Abdominal pain	-	✔	-	-	-	-	-
Nausea	-	-	-	✔ #	-	-	-
Pelvic pain	-	✔	-	-	-	-	-
Unpleasant mouth sensation	-	-	-	✔ #	-	-	-
Vomiting	-	-	-	✔ #	-	-	-
Genitourinary							
Itching	-	✔	-	-	-	-	2
Soreness	-	✔	-	-	-	-	-
Swelling	-	✔	-	-	-	-	-
Vaginal irritation	-	-	-	-	-	-	2
Vulvar/vaginal burning	-	✔	-	-	-	-	2
Other							
Abnormal liver function tests	-	-	-	✔ #	-	-	-
Keratoconjunctivitis sicca	-	-	-	-	-	✔ *	-
Ocular irritation/swelling	-	-	-	-	-	✔ *	-

✔ Percent not specified.
- Event not reported or incidence <1%.
*Cream formulation.
†Shampoo formulation.
‡Solution formulation.
§Gel formulation.
‖Suspension formulation.
¶ Foam formulation.
# Troche formulation.

Table 9. Adverse Drug Events (%) Reported with the Single Agent Skin and Mucous Membrane Antifungals (Drugs N-Z)[1-21]

Adverse Events	Naftifine	Nystatin	Oxiconazole	Sertaconazole	Sulconazole	Terconazole
Central Nervous System						
Headache	-	-	-	-	-	21 to 30
Dermatological						
Burning	5 to 6	-	≤1	✔	3	-
Contact dermatitis	-	✔	<1	✔	-	-
Desquamation	-	-	-	✔	-	-
Dry skin	3	-	-	✔	-	-
Eczema	-	-	<1	-	-	-
Erythema	≤2	-	<1	✔	1	-

Adverse Events	Naftifine	Nystatin	Oxiconazole	Sertaconazole	Sulconazole	Terconazole
Fissure	-	-	<1	-	-	-
Folliculitis	-	-	<1	-	-	-
Hyperpigmentation	-	-	-	✔	-	-
Hypersensitivity reaction	-	✔	-	-	-	-
Irritation	2	-	<1	-	-	-
Maceration	-	-	<1	-	-	-
Nodules	-	-	<1	-	-	-
Pain	-	-	<1	-	-	-
Papules	-	-	<1	-	-	-
Pruritus	1 to 2	-	<2	✔	3	-
Rash	<1	-	<1	-	-	-
Scaling	-	-	<1	-	-	-
Skin tenderness	<1	-	-	-	-	-
Stinging	5 to 6	-	<1	-	3	-
Stevens-Johnson syndrome	-	✔	-	-	-	-
Tenderness	-	-	-	✔	-	-
Gastrointestinal						
Abdominal pain	-	-	-	-	-	3
Genitourinary						
Dysmenorrhea	-	-	-	-	-	6
Vaginal burning	-	-	-	-	-	5 to 15
Vaginal irritation	-	-	-	-	-	3
Vaginal itching	-	-	-	-	-	5
Vaginal pain	-	-	-	-	-	4
Other						
Chills	-	-	-	-	-	<2
Cough	-	-	-	-	-	1 to 3

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 10. Adverse Drug Events (%) Reported with the Combination Skin and Mucous Membrane Antifungals[1-21]

Adverse Events	Benzoic Acid and Salicylic Acid	Clotrimazole and Betamethasone	Miconazole, Zinc Oxide and White Petrolatum	Nystatin and Triamcinolone
Dermatological				
Acne	-	-	-	✔
Acneiform eruptions	-	✔	-	-
Blistering	-	✔	✔	-

Adverse Events	Benzoic Acid and Salicylic Acid	Clotrimazole and Betamethasone	Miconazole, Zinc Oxide and White Petrolatum	Nystatin and Triamcinolone
Burning	✔	2*	✔	✔
Contact dermatitis	-	✔	✔	✔
Dry skin	-	2*	✔	✔
Ecchymoses	-	✔	-	-
Edema	-	<1†	-	-
Erythema	-	✔	✔	-
Folliculitis	-	✔	-	✔
Hypertrichosis	-	✔	-	✔
Hypopigmentation	-	✔	-	✔
Inflammation		-	✔	-
Irritation	-	✔	-	✔
Maceration of skin	-	✔	-	✔
Miliaria	-	✔	-	-
Pain	-	-	✔	-
Peeling	-	✔	-	-
Perioral dermatitis	-	✔	-	-
Pruritus	-	✔	✔	✔
Rash	-	<1†	✔	
Skin atrophy	-	✔	-	✔
Skin exfoliation	-	-	✔	-
Stinging	-	<1*	-	-
Striae	-	✔	-	-
Urticaria	-	✔	-	-
Gastrointestinal				
Vomiting	-	-	✔	-
Other				
Benign intracranial hypertension	-	✔	-	-
Cushing's syndrome	-	✔	-	-
Growth retardation	-	✔	-	-
Paresthesia	-	2†	-	-
Secondary infection	-	<1†	-	✔
Sensitization	-	✔	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
*Lotion formulation.
†Cream formulation.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antifungals are listed in Table 11.

Table 11. Usual Dosing Regimens for the Skin and Mucous Membrane Antifungals[1-21]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Butenafine	Topical treatment of tinea versicolor caused by *Malassezia furfur*: Cream: apply to the affected area once daily for two weeks	Topical treatment of tinea versicolor caused by *Malassezia furfur* in patients ≥12 years of age: Cream: apply to the affected area once daily for two weeks	Cream: 1%
Butoconazole	Vulvovaginal candidiasis: Vaginal cream: insert one applicator full intravaginally once	Safety and efficacy in children have not been established.	Vaginal cream: 2%
Ciclopirox	Cutaneous candidiasis; Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*; topical treatment of tinea versicolor caused by *Malassezia furfur*: Cream, suspension: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Treatment of interdigital tinea pedis and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Gel: apply to the affected area twice daily for four weeks Treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement caused by *T. rubrum*: Solution: apply to the affected nails once daily Seborrheic dermatitis of the scalp: Gel: apply to the affected scalp area twice daily for four weeks Shampoo: wet hair and apply one to two teaspoons to scalp;	Cutaneous candidiasis; Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*; topical treatment of tinea versicolor caused by *Malassezia furfur* in patients ≥10 years of age: Cream, suspension: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Treatment of interdigital tinea pedis and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum* in patients ≥16 years of age: Gel: apply to the affected area twice daily for four weeks Treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement caused by *T. rubrum* in patients ≥12 years of age: Solution: apply to the affected nails once daily Seborrheic dermatitis of the scalp in patients ≥16 years of age: Gel: apply to the affected scalp	Cream: 0.77% Gel: 0.77% Shampoo: 1% Solution: 8% Suspension: 0.77%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	lather and leave on hair and scalp for three minutes, then rinse off; repeat treatment twice per week for four weeks	area twice daily for four weeks Shampoo: wet hair and apply one to two teaspoons to scalp; lather and leave on hair and scalp for three minutes, then rinse off; repeat treatment twice per week for four weeks	
Clotrimazole	Treatment of cutaneous candidiasis; topical treatment of tinea versicolor caused by *M. furfur*: Cream, solution: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Prophylactically to reduce the incidence of oropharyngeal candidiasis in immunocompromised patients; treatment of oropharyngeal candidiasis: Troche: dissolve one troche in mouth five times daily for two weeks; for prophylaxis, dissolve one troche in mouth three times daily	Treatment of cutaneous candidiasis; topical treatment of tinea versicolor caused by *M. furfur*: Cream, solution: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Prophylactically to reduce the incidence of oropharyngeal candidiasis in immunocompromised patients; treatment of oropharyngeal candidiasis in patients three years of age and older: Troche: dissolve one troche in mouth five times daily for two weeks; for prophylaxis, dissolve one troche in mouth three times daily	Cream: 1% Solution: 1% Troche: 10 mg
Econazole	Cutaneous candidiasis: Cream: apply to the affected area twice daily for two weeks Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *Microsporum audouini*, *Microsporum gypseum*, and *E. floccosum*; topical treatment of tinea versicolor caused by *M. furfur*: Cream: apply to the affected area once daily for two weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *M. audouini*, *M. gypseum*, and *E. floccosum*: Cream: apply to the affected area once daily for one month	Cutaneous candidiasis: Cream: apply to the affected area twice daily for two weeks Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *M. audouini*, *M. gypseum*, and *E. floccosum*; topical treatment of tinea versicolor caused by *M. furfur*: Cream: apply to the affected area once daily for two weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *M. audouini*, *M. gypseum*, and *E. floccosum*: Cream: apply to the affected area once daily for one month	Cream: 1%
Ketoconazole	Cutaneous candidiasis: Cream: apply to the affected area once daily for two weeks	Seborrheic dermatitis in patients ≥12 years of age: Foam: apply to the affected	Cream: 2%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Seborrheic dermatitis: Cream: apply to the affected area twice daily for four weeks or until clinical clearing Foam: apply to the affected area twice daily for four weeks Treatment of tinea cruris and tinea corporis caused by *E. floccosum*, *T. mentagrophytes*, and *T. rubrum:* Cream: apply to the affected area once daily for two weeks Treatment of tinea pedis caused by *E. floccosum*, *T. mentagrophytes*, and *T. rubrum*: Cream: apply to the affected area once daily for six weeks Topical treatment of tinea versicolor caused by *M. furfur*: Cream: apply to the affected area once daily for two weeks Shampoo: apply to the affected area and a wide margin surrounding this area; lather, leave in place for five minutes, and then rinse off with water; one application of the shampoo should be sufficient	area twice daily for four weeks	Foam: 2% Shampoo: 2%
Miconazole	Vulvovaginal candidiasis: Vaginal suppository: insert one suppository intravaginally at bedtime for three days	Vulvovaginal candidiasis: Vaginal suppository: insert one suppository intravaginally at bedtime for three days	Vaginal suppository: 200 mg
Naftifine	Treatment of tinea corporis, tinea cruris, tinea pedis caused by subseptale species: Cream, gel: Apply to the affected area and surrounding skin once daily for up to two weeks (2%) or up to four weeks (1%)	Safety and efficacy in children have not been established.	Cream: 1% 2% Gel: 1% 2%
Nystatin	Treatment of cutaneous or mucocutaneous mycotic infections caused by *Candida. albicans* and other *Candida* species: Cream, ointment, powder: apply to the affected area two to three times daily until healing is complete	Treatment of cutaneous or mucocutaneous mycotic infections caused by *Candida. albicans* and other *Candida* species in neonates and older: Cream, ointment, powder: apply to the affected area two to three times daily until healing is complete	Cream: 100,000 units/g Ointment: 100,000 units/g Powder: 100,000 units/g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Oxiconazole	Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream, lotion: apply to the affected area one to two times daily for two weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream, lotion: apply to the affected area one to two times daily for one month Treatment of tinea versicolor caused by *Malassezia furfur*: Cream: apply to the affected area once daily for two weeks	Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream: apply to the affected area one to two times daily for two weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream: apply to the affected area one to two times daily for one month Treatment of tinea versicolor caused by *Malassezia furfur*: Cream: apply to the affected area once daily for two weeks	Cream: 1% Lotion: 1%
Sertaconazole	Treatment of interdigital tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream: apply to the affected area twice daily for four weeks	Treatment of interdigital tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum* in patients ≥12 years of age: Cream: apply to the affected area twice daily for four weeks	Cream: 2%
Sulconazole	Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis*; treatment of tinea versicolor caused by *Malassezia furfur*: Cream, solution: apply to the affected area one to two times daily for at least three weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis:* Cream: apply to the affected area twice daily for four weeks	Safety and efficacy in children have not been established.	Cream: 1% Solution: 1%
Terconazole	Vulvovaginal candidiasis: Vaginal cream (0.4%): insert one applicator full once daily at bedtime for seven days Vaginal cream (0.8%): insert one applicator full once daily at bedtime for three days Vaginal suppository: insert one suppository intravaginally once daily at bedtime for three days	Safety and efficacy in children have not been established.	Vaginal cream: 0.4% 0.8% Vaginal suppository: 80 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Combination Products			
Benzoic acid and salicylic acid	Treatment of inflammation and irritation associated with dermatitis, including certain eczematoid conditions; treatment of insect bites, burns and fungal infections: Ointment: apply to the affected area twice daily	Safety and efficacy in children have not been established.	Ointment: 6%/3%
Clotrimazole and betamethasone	Treatment of tinea cruris and tinea corporis caused by *T. rubrum, T. mentagrophytes, and E. floccosum:* Cream, lotion: apply to the affected area twice daily for up to two weeks; maximum, 45 g per week Treatment of tinea pedis caused by *T. rubrum, T. mentagrophytes, and E. floccosum*: Cream, lotion: apply to the affected area twice daily for up to four weeks; maximum, 45 g per week	Treatment of tinea cruris and tinea corporis caused by *T. rubrum, T. mentagrophytes, and E. floccosum* in patients ≥17 years of age: Cream, lotion: apply to the affected area twice daily for up to two weeks; maximum, 45 g per week Treatment of tinea pedis caused by *T. rubrum, T. mentagrophytes, and E. floccosum* in patients ≥17 years of age: Cream, lotion: apply to the affected area twice daily for up to four weeks; maximum, 45 g per week	Cream: 1%/0.05% Lotion: 1%/0.05%
Miconazole, zinc oxide, and white petrolatum	Not applicable	Treatment of diaper dermatitis when complicated by documented candidiasis in patients four weeks of age and older: Ointment: apply to the affected area at each diaper change for seven days	Ointment: 0.25%/15%
Nystatin and triamcinolone	Treatment of cutaneous candidiasis: Cream, ointment: apply to the affected area twice daily for up to 25 days	Treatment of cutaneous candidiasis: Cream, ointment: apply to the affected area twice daily for up to 25 days	Cream: 100,000 u/g/0.1% Ointment: 100,000 u/g/1%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antifungals are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Skin and Mucous Membrane Antifungals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Candidiasis (Cutaneous)				
Bagatell et al.[35] (1985) Ciclopirox 1% cream applied BID vs clotrimazole 1% cream applied BID vs placebo In study A, patients received either ciclopirox or vehicle. In study B, patients received either ciclopirox or clotrimazole.	2 DB, MC, PG, RCT Patients 12 to 75 years of age with stable or exacerbating skin lesions that were clinically and mycologically diagnosed as cutaneous candidiasis	N=240 28 days	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: In the first week of therapy for study A, significant differences favoring the active drug were observed in patients treated with ciclopirox compared to placebo in terms of clinical and mycological cures (90 vs 50%, respectively; P<0.001). At the two-week follow-up period, 83 and 82 to 89% of patients treated with ciclopirox achieved clinical and mycological cure, respectively (P<0.001) compared to 14 and 34 to 46% of patients treated with vehicle achieved clinical and mycological cure, respectively (P<0.001). At the final post treatment visit, 27 and 12% of patients treated with ciclopirox and vehicle, respectively, achieved both clinical and mycological cure (P<0.001). After two weeks of therapy in study B, 17 and 0% of patients treated with ciclopirox and clotrimazole, respectively, achieved clinical cure (P<0.05). After three weeks, 38 and 21% of patients treated with ciclopirox and clotrimazole, respectively, achieved clinical cure (P<0.05). After four weeks of treatment, both treatment groups showed similar results. After two weeks of therapy, a greater proportion of patients treated with ciclopirox achieved both clinical and mycological cure compared to patients treated with clotrimazole (15 vs 0%; P=0.006). However, there was no significant difference between treatment groups relative to mycological cure. Secondary: No adverse events were reported.
Rajan et al.[36] (1983) Clotrimazole 1% cream applied BID	DB, PG, RCT Patients with clinically proven cutaneous candidiasis	N=41 3 weeks	Primary: Efficacy parameters (fungal culture, microscopic preparation,	Primary: At week two, 62.5 and 85.7% of patients treated with sulconazole and clotrimazole, respectively, had negative fungal cultures. At week three, 62.5 and 33.3% of patients treated with sulconazole and clotrimazole, respectively, had negative fungal cultures. At this time,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sulconazole 1% cream applied QAM and placebo QHS			physician's assessment of overall improvement) Secondary: Adverse events	seven and three patients treated with sulconazole and clotrimazole, respectively, failed treatment. Although both treatment groups experienced improvement in certain symptoms of infection, there was no significant difference between the two treatment groups (erythema; P=0.45, scaling; P=0.69, itching; P=0.88). At week three, the physician's assessment of overall infection improvement for sulconazole- and clotrimazole-treated patients was 70.6 and 88.9%, respectively. Secondary: Five patients treated with sulconazole reported adverse effects, which included itching of various degrees of severity. No adverse effects were reported by patients treated with clotrimazole.
Tanenbaum et al.[37] (1983) Miconazole 2% cream applied BID vs sulconazole 1% cream applied QD vs sulconazole 1% cream applied BID vs placebo In study A, patients received either sulconazole	2 DB, PG, RCT Patients with cutaneous candidiasis	N=96 3 weeks	Primary: Mycological cure rate, signs of inflammation, itching, and clinician rated overall clinical status Secondary: Adverse effects	Primary: At the end of three weeks in study A, 100% of patients treated with sulconazole and 10% of patients who received the vehicle had negative results on the potassium hydroxide test; 100% of patients treated with sulconazole and 0% of patients who received the vehicle had negative cultures. At the end of three weeks in study B, 100% of patients receiving sulconazole and miconazole were negative on the potassium hydroxide test; 80 and 92% of sulconazole and miconazole patients, respectively, had negative cultures. At the end of three weeks in study A, 100% of patients treated with sulconazole and 26% of patients who received the vehicle were free of signs of inflammation; 89 and 21% of sulconazole and vehicle patients, respectively, were free of itching. At the end of three weeks in study B, 100 and 92% of sulconazole and miconazole patients, respectively, were free of signs of inflammation; 89 and 83% of sulconazole and miconazole patients, respectively, were free of itching. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or vehicle given BID. In study B, patients received either sulconazole given QD or miconazole given BID.				One patient receiving the vehicle experienced itching. Erythema and/or pruritus was reported by six patients treated with sulconazole and three patients treated with miconazole.
Beveridge et al.[38] (1977) Nystatin cream vs nystatin-triamcinolone cream	DB, MC, PG, RCT Patients 6 months to 71 years of age with confirmed bilateral lesions of the flexures (secondary to *Candida*)	N=31 14 days	Primary: Eradication of *Candida*, clinical progress of lesions, patient preference for agent, and physician preference for agent Secondary: Adverse events	Primary: There was little difference in clinical cure (38.7 vs 45%) and mycological cure rates (87.1 vs 83.8%) between nystatin and nystatin-triamcinolone treatments, respectively. There was no significant difference in the preference for either treatment in terms of the patient's or physician's perspective (P>0.05). Secondary: Two patients treated with the creams reported burning and stinging. One patient treated with nystatin monotherapy complained of burning and one patient reported pustules.
Candidiasis (Oropharyngeal)				
Kirkpatrick et al.[39] (1978) Clotrimazole 10 mg troche five times daily vs placebo	DB, RCT Patients with chronic oral candidiasis for at least 6 months with poor response to nystatin or gentian violet	N=20 2 weeks	Primary: Clinical response, mycological response Secondary: Adverse events	Primary: Clinical and laboratory results were negative in more patients treated with clotrimazole compared to patients receiving placebo (six vs one, respectively; P<0.001). Secondary: No adverse events were reported with either study group.
Owens et al.[40] (1984) Clotrimazole 10 mg troche TID	DB, PRO, RCT Patients with leukemia or solid malignant	N=84 27 to 81 days	Primary: Signs and symptoms of oral candidiasis, culture	Primary: Oral thrush was observed after nine days in patients with leukemia, after three weeks in renal transplant patients, and after three weeks patients with solid malignant neoplasms (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	neoplasms who were treated with chemotherapy; renal transplant patients treated with an immunosuppressant to prevent graft rejection		Secondary: Adverse events	Oral candidiasis occurred in 13 and 57% of patients treated with clotrimazole and placebo, respectively (P<0.0005). Of the renal transplant patients, eight and 57% of patients treated with clotrimazole and placebo, respectively, had oral candidiasis (P<0.01). Of the leukemic patients, 37.5 and 62.5% of patients treated with clotrimazole and placebo, respectively, had oral candidiasis (P>0.05). Of the patients with solid malignant neoplasms, 0 and 67% of patients treated with clotrimazole and placebo, respectively, had oral candidiasis (P<0.05). Of the patients treated with clotrimazole, a significant improvement was observed in patients with malignant neoplasms (P<0.05) and renal transplant patients (P<0.05), but not patients with leukemia (P>0.05). Secondary: One case of abnormal jaw sensations and nausea was reported.
Vazquez et al.[41] (2010) Miconazole 50 mg buccal tablet QD (MBT) vs clotrimazole 10 mg troche 5 times daily (CT) Patients who were receiving antiretroviral therapy prior to the study were maintained on their regimen during the 14-day antifungal	DB, MC, RCT Patients ≥18 years of age with HIV infection and OPC	N=578 14 days	Primary: Clinical cure (defined as complete resolution of lesions and symptoms of OPC) at TOC visit (days 17 to 22) in the ITT and PP populations Secondary: Clinical cure at day seven, clinical success at day seven and at the TOC visit, mycological cure rate at the TOC visit, evidence of relapse by day 35,	Primary: The clinical cure rate in the MBT group was non-inferior to the CT group in both the ITT and PP populations at the TOC visit. In the ITT population, 61% of patients treated with MBT experienced clinical cure compared to 65% treated with CT (95% CI, -0.124 to 0.034). In the PP population, 68% of MBT-treated patients experienced clinical cure compared to 74% of CT-treated patients (95% CI, -0.140 to 0.022). Secondary: There were no significant differences between treatment groups in clinical cure rate at day seven, or in clinical success rate at day seven or at the TOC visit, in either the ITT or PP populations. At the TOC visit, mycological cure was not significantly different among the treatment groups (ITT and PP populations). In the ITT population, 27% of MBT patients and 25% of CT patients experienced mycological cure (P=0.58). In the PP population, 30% of MBT patients and 27% of CT patients experienced mycological cure (P=0.44). In the ITT population, 27.9% of patients receiving MBT experienced a relapse by day 35. In the CT group, relapse occurred in 28.1% of patients who were clinically cured at the TOC visit and evaluable for relapse (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment.			and time to relapse	CI, -9.5 to 9.1; P=0.96). In the PP population, the percentages were 26.9 and 27.6% for the MBT and CT treatment groups, respectively (95% CI, -10.3 to 8.8; P=0.88). In the ITT population, the mean time to relapse was 16.0 and 15.5 days in the MBT and CT groups, respectively (P=0.7). In the PP population, the mean time to relapse was 16.2 days for MBT and 15.9 days for the CT group (P=0.7). Compliance was comparable between the treatment groups. The mean duration of adhesion was comparable between the MBT group and the CT group that received placebo buccal tablets. Total number of tablets that detached within the first six hours after placement was 6.3% of the MBTs and 5.7% of the placebo buccal tablets. An equal number of active and placebo buccal tablets were replaced in each treatment group. Adverse events were comparable between treatment groups. The most frequently reported treatment-emergent AEs were diarrhea, headache, nausea, and vomiting. The majority of patients in each treatment arm had no gingival inflammation at the application site at end of treatment. Patient-rated assessments for oral comfort were similar in both groups. There were decreases in severity for gum pain, dysgeusia, and dry mouth over the treatment period.
Candidiasis (Vulvovaginal)				
Droegemueller et al.[42] (1984) Butoconazole 2% cream insert 1 applicator full intravaginally QD vs clotrimazole 100 mg vaginal tablet insert 2 tablets intravaginally QD	DB, MC, PG, RCT Patients with confirmed vulvovaginal candidiasis	N=253 3 days	Primary: Clinical cure, microbiologic cure Secondary: Adverse effects	Primary: At eight days post treatment, 95 and 91% of patients treated with butoconazole and clotrimazole, respectively, achieved microbiologic cure. At 30 days post treatment, 80 and 74% of patients treated with butoconazole and clotrimazole, respectively, were infection-free. The difference in microbiologic cure between the two treatments was not significant (P value not reported). At eight days post treatment, 77 and 75% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. At 30 days post treatment, 82 and 74% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. The difference in clinical cure between the two treatments was not significant (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Eighty-two percent and 72% of patients treated with butoconazole and clotrimazole, respectively, had a complete absence of candidal signs and symptoms. Secondary: Patients treated with either butoconazole or clotrimazole reported increased local vulvar or vaginal irritation and burning.
Hajman et al.[43] (1988) Butoconazole 2% cream insert 1 applicator full intravaginally QHS (for 3 days) vs clotrimazole 1% cream insert 1 applicator full intravaginally QHS (for 6 days)	PG, RCT, SB Patients 19 to 63 years of age with confirmed vulvovaginal candidiasis	N=63 3 to 6 days	Primary: Clinical cure, microbiological cure, therapeutic cure Secondary: Adverse events	Primary: The difference between the clinical response of patients treated with butoconazole at the initial vs final visit was significant and indicated improvement in signs and symptoms of vulvovaginal candidosis, such as vaginal discharge, itching, burning, erythema, and swelling (P<0.001). Clinical response in patients treated with butoconazole was greater, though not clinically significant, compared to patients treated with clotrimazole (53.3 vs 38.7%, respectively). At seven days after treatment, 85.7 and 89.7% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. At this time, 93.3 and 77.4% of patients treated with butoconazole and clotrimazole, respectively, achieved microbiological cure (e.g., negative cultures). Likewise, 82.1 and 72.4% of patients treated with butoconazole and clotrimazole, respectively, achieved therapeutic cure. At one month after treatment, 86.7 and 96.4% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. At this time, 76.7 and 67.7% of patients treated with butoconazole and clotrimazole, respectively, achieved microbiological cure (e.g., negative cultures). Likewise, 66.7 and 64.5% of patients treated with butoconazole and clotrimazole, respectively, achieved therapeutic cure. There was no significant difference between treatment groups in terms of clinical, microbiological, and therapeutic cure rates. Secondary: No adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Brown et al.[44] (1999) Butoconazole 2% cream insert 1 applicator full intravaginally QHS (for 1 day) vs miconazole 2% cream insert 1 applicator full intravaginally QHS (for 7 days)	MC, PG, RCT Patients with confirmed vulvovaginal candidiasis	N=205 1 to 7 days	Primary Clinical cure, microbiological cure Secondary: Adverse events	Primary: For butoconazole-treated patients, symptoms declined after treatment from 20 to 1% from day one to day seven since treatment initiation. At eight to 10 days post treatment, 92 and 87% of patient improved clinically and had negative cultures, respectively. At 30 days post treatment, 88 and 74% of patients improved clinically and had negative cultures, respectively. For the miconazole-treated patients, symptoms declined after treatment from 23 to 19% after the first dose. At eight to 10 days post treatment, 92 and 87% of patient improved clinically and had negative cultures, respectively. At 30 days post treatment, 86 and 77% of patients improved clinically and had negative cultures, respectively. All parameters between butoconazole and miconazole therapies were not different with the exception of the difference in the rapidity of severe symptom relief after the first dose of butoconazole compared to miconazole (P=0.01). Secondary: No systemic events were reported. Vulvovaginal irritation (e.g., burning, itching) was reported.
Kaufman et al.[45] (1989) Butoconazole 2% cream insert 1 applicator full intravaginally QHS (for 3 days) vs miconazole 2% cream insert 1 applicator full intravaginally QHS (for 7 days)	MC, PG, RCT Patients 18 to 61 years of age with confirmed vulvovaginal candidiasis	N=225 3 to 7 days	Primary: Microbiological cure, clinical cure Secondary: Adverse events	Primary: At days eight to 10 post treatment, 88 and 91% of patients treated with butoconazole and miconazole, respectively, were Candida free (P=0.888); 80 and 82% of patients treated with butoconazole and miconazole, respectively, were clinically cured (P=0.541). At 30 days post treatment, 73 and 69% of patients treated with butoconazole and miconazole, respectively, were Candida free (P=2.14); 78 and 80%, of patients treated with butoconazole and miconazole, respectively, were clinically cured (P=0.996); 59 and 52% of patients treated with butoconazole and miconazole experienced therapeutic cure. All parameters between butoconazole and miconazole therapies were not different. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Minimal side effects were reported from both butoconazole- and miconazole-treated patients including vaginal irritation.
Jacobson et al.[46] (1985) Butoconazole 1% cream insert 1 applicator full (5 g) intravaginally QD vs butoconazole 2% cream insert 1 applicator full (5 g) intravaginally QD vs miconazole 2% cream insert 1 applicator full (5 g) intravaginally QD	DB, MC, PG, RCT Patients 13 to 39 years of age with confirmed vulvovaginal candidiasis	N=130 6 days	Primary: Microbiological cure, clinical cure, and relapse rate Secondary: Adverse effects	Primary: On day eight, 98, 91, and 83% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, achieved negative fungal cultures. Likewise, 78, 75, and 68% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, achieved clinical cure at this visit. After 30 days from the end of treatment, 82, 80 and 68% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, maintained negative fungal cultures; therefore, relapse rate was low. Likewise, 73, 67, and 66% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, maintained clinical cure at this visit. The differences between cure rates of the three treatment groups were not significant (P values not reported). Secondary: Two patients in each treatment group reported side effects (i.e., headache, vaginal burning, leakage of cream, and bleeding).
Brown et al.[47] (1986) Butoconazole 1% cream insert 1 applicator full intravaginally QD (for 3 days) vs	DB, MC, PG, RCT Patients 17 to 67 years of age with confirmed vulvovaginal candidiasis	N=580 3 to 6 days	Primary: Microbiological cure, clinical cure, and therapeutic cure Secondary: Adverse events	Primary: Clinical and microbiological cure rates were greater in all butoconazole- and miconazole-treated patients compared to placebo (P<0.003 for each comparison). There was no significant difference in microbiologic and clinical cure rate between different butoconazole regimens and butoconazole compared to miconazole. There was no significance difference in therapeutic cure rates in patients treated with butoconazole 1% for six days and placebo. All other treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
butoconazole 1% cream insert 1 applicator full intravaginally QD (for 6 days) vs butoconazole 2% cream insert 1 applicator full intravaginally QD (for 3 days) vs butoconazole 2% cream insert 1 applicator full intravaginally QD (for 6 days) vs miconazole 2% cream insert 1 applicator full intravaginally QD (for 6 days) vs placebo				groups demonstrated statistical significance in this parameter (P<0.001). Secondary: Systemic adverse events were not observed. The most common adverse events associated with all study groups were local side effects.
Hirsch et al.[48] (1989) Clotrimazole 200	MA Patients with confirmed	N=1,800 (16 trials) 1 to 7 days	Primary: Clinical cure rate Secondary:	Primary: According to the MA, the most effective regimens of terconazole were the 80 mg suppository for three days, 240 mg suppositories for one day, and the 0.4% cream for seven days. The 240 mg suppository for one day was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg vaginal tablets insert 1 tablet intravaginally QD (for 3 days) vs clotrimazole 1% cream insert 1 applicator full (5 g) intravaginally QHS (for 7 days) vs econazole 150 mg suppositories* (for 3 days) vs miconazole 2% cream insert 1 applicator full (5 g) intravaginally QHS (for 7 days) vs terconazole 40 to 240 mg vaginal suppositories or terconazole 0.2% to 0.8% vaginal cream	vulvovaginal candidiasis		Adverse effects	more effective than the 80 mg suppository for three days. The clinical efficacies of the 0.4% and 0.8% cream formulations for seven days were comparable. At four weeks from the start of treatment, 92% patients receiving terconazole 80 mg suppositories achieved clinical cure; 88% for terconazole 240 mg suppository for one day, 94% for terconazole 0.8% cream for five days, 90% for terconazole 0.4% cream for seven days. After four weeks, mycological cure rates with terconazole 0.2% cream were similar to miconazole 2% cream but less compared to terconazole 0.4% cream. After four weeks, mycological cure rates were 100 and 80% for terconazole 0.4% cream and clotrimazole 1% cream, respectively, for nonpregnant patients. After four weeks, mycological cure rates were 92 and 89% for terconazole 0.4% cream and clotrimazole 1% cream, respectively, for pregnant patients. After four weeks, mycological cure rates were similar between terconazole 80 mg suppositories and econazole 150 mg suppositories for pregnant and nonpregnant patients. After four weeks, mycological cure rates were similar between terconazole 80 mg and 240 mg suppositories and clotrimazole 240 mg tablets. Secondary: Vaginal burning was reported by 2, 2, and 1% of patients taking terconazole 80 mg vaginal suppositories, terconazole 0.4% vaginal cream, and terconazole 0.8% vaginal cream, respectively. Regimens comprised of terconazole 240 mg vaginal suppository were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Young et al.[49] (2001) Clotrimazole vs econazole* vs hydrargaphen* vs miconazole vs nystatin vs terconazole vs placebo	MA Patients with vulvovaginal candidiasis	10 trials Variable duration	Primary: Clinical cure rate Secondary: Not reported	Primary: According to data from five trials, patients treated with topical azoles achieved greater cure compared to patients treated with nystatin (OR, 0.21; 95% CI, 0.06 to 0.29). According to data from one trial, there was no significant difference between patients treated with nystatin compared to hydrargaphen* (OR, 0.14; 95% CI, 0.05 to 1.84). According to data from trials with clotrimazole, the following results were reported: treatment with clotrimazole was more effective than placebo (OR, 0.14; 95% CI, 0.06 to 0.31); treatment with clotrimazole was similar regardless of single or multiple (i.e., three to four days) dosing; treatment with clotrimazole for seven days was more efficacious compared to treatment for four days (OR, 11.7; 95% CI, 4.21 to 29.15); treatment with clotrimazole was similar regardless of seven-day or 14-day treatment duration (OR, 0.41; 95% CI, 0.16 to 1.05); treatment with clotrimazole and terconazole had similar efficacy (OR, 1.41; 95% CI, 0.28 to 7.10). Secondary: Not reported
Thomason et al.[50] (1990) Miconazole 100 mg vaginal suppositories insert 1 suppository intravaginally	DB, RCT Patients with confirmed vulvovaginal candidiasis	N=29 7 days	Primary: Microbiologic cure, clinical cure, and therapeutic cure Secondary: Adverse events	Primary: At eight to 10 days, 100% of patients treated with terconazole achieved clinical, microbiologic, and therapeutic cure. At that time, 100, 89, and 89% of patients treated with miconazole achieved clinical, microbiologic, and therapeutic cure, respectively. At that time, 44, 33, 33% of patients receiving placebo achieved clinical, microbiologic, and therapeutic cure, respectively. Terconazole and miconazole treatment groups showed significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QHS vs terconazole 80 mg vaginal suppositories insert 1 suppository intravaginally QHS (for 3 days) vs placebo				improvements in clinical, microbiologic, and therapeutic cure compared to placebo (P<0.05). There was no significant difference in cure rates between miconazole and terconazole treatment groups. Secondary: No adverse events were reported.
Corson et al.[51] (1991) Miconazole 2% cream insert 1 applicator full (5 g) intravaginally QD vs terconazole 0.4% cream insert 1 applicator full (5 g) intravaginally QD vs terconazole 0.8% cream insert 1 applicator full (5 g) intravaginally	DB, MC, RCT Patients 17 to 61 years of age with signs and symptoms of vulvovaginal candidiasis, microbiologically-confirmed vulvovaginal candidiasis, and either history of being postmenopausal for 2 years or using an effective means of contraception	N=574 7 days	Primary: Clinical response, microbiological response, therapeutic cure, and relapse Secondary: Adverse events	Primary: Relative to demographics, the use of contraceptives appears to have a negative effect on cure rate across all treatment groups; patients not on contraceptives achieved a higher cure rate (P=0.01). Between eight to 10 days post treatment (visit one), the microbiologic cure rates for terconazole 0.4%, terconazole 0.8%, and miconazole 2% were 91.1, 86.9, and 83.6%, respectively; clinical cure rates were 95.5, 93.4, and 91.6%, respectively; the therapeutic cure rates were 87.9, 83.8, and 81.3%, respectively. The microbiologic cure rates of patients treated with terconazole 0.4% were higher than that of patients treated with miconazole 2% (91.1 vs 83.6%; P=0.02). There was no significant difference for other comparisons. After seven days of treatment, patients treated with terconazole 0.4%, terconazole 0.8%, and miconazole 2% had complete symptom relief rates of 83.3, 77.0, and 79.5%, respectively. There was no significant difference between treatment groups. After seven days of treatment, patients treated with terconazole 0.4%, terconazole 0.8%, and miconazole 2% had combined clinical and microbiological cure rates of 87.9, 83.8, and 81.3%, respectively. There was no significant difference between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD				Between 30 to 35 days post treatment (visit two), there were no significant differences in microbiologic, clinical, or therapeutic cure rates in the treatment groups. Secondary: There was no significant difference in the number of patients who reported adverse effects in the terconazole 0.4%, terconazole 0.8%, and miconazole 2% treatment groups (61.1, 62.2, 57.2%), respectively. Adverse reactions most commonly reported involved the central nervous system or genital-reproductive system. Although no P values were provided, investigators claim that patients treated with terconazole 0.4% had significantly less side effects associated with the genital- reproductive system compared to the other groups, that patients treated with the lower strength of terconazole had significantly lower rates of pruritus and metrorrhagia, that patients treated with miconazole experienced more vulvovaginal symptoms and rhinorrhea compared to both terconazole groups, that patients treated with terconazole 0.4% experienced more pyrexia compared to the other groups.
Thomason et al.[52] (1989) Miconazole 2% vaginal cream (for 7 days) vs miconazole 100 mg vaginal suppositories (for 7 days) vs terconazole 0.4% vaginal cream (for	MA Patients ≥18 years of age with vulvovaginal candidiasis	N=1,259 3 to 7 days	Primary: Clinical cure rate, mycological cure rate, and relapse rate Secondary: Adverse events	Primary: Terconazole cream and suppository formulations were more efficacious compared to placebo (P<0.001 for both comparisons). Studies of terconazole cream showed 87.3 to 95.5%, 76.9 to 91.1%, and 10.4 to 22.2% in terms of clinical, microbiologic cure, and relapse (at day 35) rates, respectively. After 10 days, mycological cure rates were similar between terconazole 0.4% cream and 2% miconazole cream; however, in trials with a large number of patients, microbiologic cure rates were higher in terconazole- vs, miconazole-treated patients. Studies of terconazole 80 mg suppositories showed ranges of 90 to 92.2% for rates of clinical cure, 80.4 to 85% for rates of microbiologic cure, and 20.0 to 28.1% for relapse rates (at day 35). After 10 days, mycological cure rates were similar between terconazole 80 mg suppositories and miconazole 100 mg suppositories used for seven days. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
7 days) vs terconazole 80 mg vaginal suppositories (for 3 days) vs terconazole 80 mg vaginal suppositories (for 3 days) vs placebo				The adverse effects associated with terconazole therapies were minimal. Frequency of common adverse effects was similar between terconazole and miconazole suppositories. Relative to cream formulations, skin rash was associated with terconazole and rhinorrhea, pain and burning was associated with miconazole.
Martins et al.[53] (2012) Nystatin vaginal cream 25,000 U/g QD for 7 days vs fluconazole 150 mg orally once weekly for 2 weeks	OL, PG Patients 15 to 83 years of age with vaginal *Candida* species	N=60 1 to 2 weeks	Primary: Mycological cure Secondary: Not reported	Primary: Treatment with nystatin resulted in similar overall mean cure rate compared to treatment with fluconazole (74 vs 87%; P>0.05). Treatment with nystatin resulted in 93% cure rate for *C. albicans* and 44.4% cure rate for non-*albicans* species. Treatment with fluconazole resulted in 82.4% cure rate for *C. albicans* and 100% cure rate for non-*albicans* species. Secondary: Not reported
Onychomycosis				
Gupta et al.[54] (2000) Ciclopirox 8% nail	2 DB, MC, PC, PG Patients 18 to 70 years of age with	N=560 48 weeks	Primary: Mycological cure rate, treatment success, treatment	Primary: In study A, there was significant improvement in mycological cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (29 vs 11%, respectively;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lacquer applied QD vs placebo	mild to moderate toenail onychomycosis caused by dermatophytes		cure, and negative culture Secondary: Adverse effects	P<0.001). In study B, there was significant improvement in mycological cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (36 vs 9%, respectively; P<0.001). In study A, there was significant improvement in culture results in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (84 vs 37%, respectively; P<0.001). In study B, there was significant improvement in culture results in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (84 vs 44%, respectively; P<0.001). In study A, there was a significant difference between ciclopirox and the vehicle in terms of treatment success (6.5 vs 0.9%, respectively; P=0.031). In study B, there was significant improvement in treatment success in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (12 vs 0.9%, respectively; P=0.001). In study A, there was no significant difference between ciclopirox and the vehicle in terms treatment cure (5.5 vs 0.9%, respectively; P=0.059). In study B, there was significant improvement in treatment cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (8.5 vs 0%, respectively; P=0.001). Secondary: In study A, adverse effects associated with ciclopirox compared to vehicle were mainly localized site reactions including erythema (4 vs 1%, respectively); tingling sensation, pain or intermittent burning (3 vs 2%, respectively) and changes in nail shape or color (2 vs 1%, respectively). In study B, adverse effects associated with ciclopirox compared to vehicle were mainly localized site reactions including erythema (10 vs 2%, respectively); tingling sensation, pain or intermittent burning (0 vs 1%, respectively) and changes in nail shape or color (3 vs 3%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Brenner et al.[55] (2007) Ciclopirox 8% nail lacquer applied QD	MC, OL Diabetic patients with distal subungual onychomycosis	N=49 48 weeks	Primary: Clinical improvement as determined by involved area, severity, subungual hyperkeratosis, and signs or symptoms Secondary: Not reported	Primary: After 48 weeks of treatment, 63.4% of patients experienced clinical improvement, success, or cure with ciclopirox. At the end of the study, 85.7% of patients had at least a mycologic improvement; 54.3% achieved mycologic cure. Treatment improvement, success, or cure was achieved in 84.4% of patients at the end of the study. Patients experienced improvement in the diseased area of the nail (63.4%), nail surface (56.1%), nail color (48.8%), and nail thickness (65.9%). Physicians rated most patients (78.9%) as experiencing at least a slight improvement in the target nail; 52.6% of patients were rated as experiencing a fair-to-good improvement, and 7.9% were rated as experiencing an excellent improvement. Patient-rated effectiveness was good or excellent in 73.7% of patients. Secondary: Not reported
Shemer et al.[56] (2010) Ciclopirox 8% nail lacquer applied QD	OL Patients with DLSO and LSO	N=40 9 months	Primary: Clinical nail status, KOH examination and mycological culture Secondary: Not reported	Primary: After nine months, eight patients (22%) had complete cure (clinical and mycological) of the toenails. Five patients had both marked clinical improvement of their toenails and mycological cure. Nine patients had mild improvement and three patients had moderate improvement of their toenail status. Eight patients (66%) still showed fungal hyphae at KOH examination and/or positive culture. Eleven patients (31%) had no clinical improvement in their toenails and all had positive mycological cultures at the end of the study. No adverse effects were noted throughout the treatment period. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gupta et al.[54] (2000) Ciclopirox 8% nail lacquer applied QD vs placebo	MA Randomized trials, mostly OL and MC, conducted in Europe, Asia, North America, and South America with patients with extensive finger and/or toe nail involvement of onychomycosis caused by dermatophytes or non-dermatophytes (e.g., *Candida* species)	N=2,075 (13 trials) 6 months	Primary: Mycological cure, clinical cure, and clinical response for ciclopirox therapies Secondary: Adverse effects	Primary: Mycological cure rates ranged from 46.7 to 85.7%, clinical cure ranged from zero to 56.9%, and clinical response ranged from 36.7 to 86% when ciclopirox was used according to dosing regimens ranging from QD to twice weekly. The lowest-reported clinical cure and response rates were associated with the twice-weekly regimens. The highest reported clinical cure and response rates were associated with the QD regimens. Average relapse rate was 20.7% at up to six months of treatment. Secondary: Minimal local side effects were associated with ciclopirox therapy. Reported side effects included nail changes, burning, stinging, erythema, pain, and skin reactions.
Seborrheic Dermatitis				
Aly at el.[57] (2003) Ciclopirox 0.77% gel applied BID vs placebo	DB, MC, PC, RCT Patients 19 to 85 years of age with moderate, stable or exacerbating, inflammatory seborrheic dermatitis of the scalp	N=178 28 days	Primary: Clinical evaluation, efficacy evaluation Secondary: Adverse events	Primary: At days 22, 29, and at the study endpoint (final visit, up to day 33), patients treated with ciclopirox achieved greater than 75% improvement in global evaluation scores compared to those treated with placebo (P=0.01). At days 15 (P=0.01), 22 (P=0.001), 29 (P=0.001), and at the study endpoint (P=0.001), total patient signs and symptom scores were higher in patients treated with ciclopirox compared to placebo. Twenty-nine percent of patients treated with ciclopirox rated the medication as cosmetically acceptable. Secondary: A burning sensation was reported in 13 and 9% in ciclopirox and placebo-treated patients, respectively.
Vardy et al.[58] (2000)	DB, PC, PRO, RCT Patients ≥15 years	N=82 4 weeks	Primary: Symptom scores, clinical cure, and	Primary: At the end of four weeks of treatment, 93 and 41% of patients treated with ciclopirox and placebo, respectively, had improvement or clearing of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciclopirox 1% shampoo applied twice weekly vs placebo	of age with mild to moderate seborrheic dermatitis of the scalp		clinical assessments Secondary: Not reported	infections (P<0.00001). No recurrence was observed at two weeks post treatment. At the two-week checkup, four-week checkup, and at two weeks post treatment, there was greater improvement in overall symptoms scores in patients treated with ciclopirox compared to patients treated with placebo (P=0.022, P<0.001, and P=0.014, respectively). After four weeks of treatment, both patient and physician assessment scores showed a significant difference in clinical response favoring ciclopirox at weeks four (P=0.00001 for both comparisons) and six (P=0.00059 and P<0.00023, respectively). Secondary: Not reported
Lebwohl et al.[59] (2004) Ciclopirox 1% shampoo applied twice weekly vs placebo	DB, PC, RCT Patients with a mild to pronounced expression of stable or exacerbating seborrheic dermatitis of the scalp	N=499 4 weeks	Primary: Effective treatment for status, scaling, and erythema Secondary: Clearance and improvement, sum scores of scaling, itching, and erythema	Primary: Effective treatment was noted in 65 subjects (26.0%) in the ciclopirox group compared to 32 patients (12.9%) in the vehicle group (OR, 2.383; 95% CI, 1.494 to 3.799; P=0.0001). Secondary: Clearance was obtained for 10.0% of patients in the ciclopirox group and 3.2% of patients in the vehicle group. Improvement of disease status from baseline by ≥3 points occurred in 42.4% of patients in the ciclopirox group and 24.1% of patients in the vehicle group (P<0.001). At the end of treatment period, there was no significant difference in the changes in the status of seborrheic dermatitis between the two groups. Sum scores of scaling, itching and erythema during the study period in the ciclopirox group were reduced from a mean of 8.5 to a mean of 4.6 (3.9-point reduction) at week four. Reductions of means in the vehicle group were from 8.7 to 6.1 at week four (2.6-point reduction). This difference between groups was significant in favor of ciclopirox at both week two (P=0.0003) and week four (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Shuster et al.[60] (2005) Study Segment A Ciclopirox 1% shampoo applied once or twice weekly for 4 weeks vs placebo Study Segment B Ciclopirox 1% shampoo applied prophylactically once weekly or every 2 weeks for 12 weeks vs placebo	DB, MC, PC, RCT Patients 18 to 88 years of age with stable or exacerbating seborrheic dermatitis of the scalp	Study Segment A N=949 4-weeks Study Segment B N=428 12-weeks	Study Segment A Primary: Effectively treated for status, scaling, and inflammation Secondary: Cleared for status, scaling, inflammation, and itching Study Segment B Primary: Relapse rate Secondary: Not reported	Study Segment A Primary: Ciclopirox was more effective than vehicle. Twice- and once-weekly shampooing produced response rates of 58.5 and 45.5%, respectively, compared to 31.6% in the vehicle treatment group (P<0.001 and P<0.001, respectively). Secondary: Higher response rates were demonstrated with ciclopirox than with placebo (ciclopirox twice weekly, 23.1% [P<0.001)]; ciclopirox once weekly, 17% [P=0.4]; placebo, 10%). Study Segment B Primary: Relapses occurred in 14.7% of patients using prophylactic ciclopirox once weekly, 22.1% of those using prophylactic ciclopirox once every two weeks, and 35.5% in the placebo group (P<0.001 and P<0.001, respectively). Secondary: Not reported
Green et al.[61] (1987) Ketoconazole 2% cream applied to the affected skin area and ketoconazole 2% shampoo applied to the hair two to three times weekly	DB, PC, RCT Patients 16 to 78 years of age with seborrheic dermatitis of the face and possible seborrheic dermatitis of the scalp and/or chest/back	N=20 4 weeks	Primary: Degree of seborrheic dermatitis, patient assessment of facial rash, scalp itching, and scalp scaling Secondary: Not reported	Primary: After four weeks, patients treated with ketoconazole experienced a significant improvement in seborrheic dermatitis of the face (P<0.01) according to clinical assessment grading. As opposed to patients receiving the placebo agents, patients treated with ketoconazole showed improved visual analog scores for facial rash at three weeks (P<0.05) and four weeks (P<0.01). Six out of ten patients receiving ketoconazole experienced significant reduction in scalp scaling (P<0.05). Patients receiving the placebo experienced no change or improvement in clinical or visual analog scores.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: Not reported
Piérard-Franchimont et al.[62] (2001) Ketoconazole 1% shampoo applied to the hair twice weekly vs ketoconazole 2% shampoo applied to the hair twice weekly	OL, PG, RCT Patients 20 to 69 years of age with severe dandruff and seborrheic dermatitis	N=66 4 weeks	Primary: Squamometry *Malassezia* spp. counts, clinical assessment Secondary: Adverse events, relapse rate	Primary: After two and four weeks of treatment, ketoconazole 2% was more effective than ketoconazole 1% relative to decreasing flakiness and *Malassezia* spp. counts (P<0.001). At week two, at treatment endpoint, and at the follow-up, ketoconazole 2% was associated with a greater improvement on *Malassezia* spp. counts compared to patients on ketoconazole 1% (P=0.001, P<0.001, and P=0.001, respectively). At week 2, at treatment endpoint, and at the follow-up, ketoconazole 2% was associated with a greater improvement of global clinical evaluation scores compared to patients on ketoconazole 1% (P<0.001, P<0.001, P<0.001, respectively). Secondary: One patient treated with ketoconazole 1% reported seborrhea. During follow-up, there were less relapses for patients previously treated with ketoconazole 2% compared to ketoconazole 1%.
Carr et al.[63] (1987) Ketoconazole 2% shampoo applied to the hair QD for 4 weeks, then Johnson's® baby shampoo applied to the hair for 4 weeks, then placebo for 4 weeks	DB, PC, RCT, XO Patients 25 to 65 years of age with seborrheic dermatitis on the scalp	N=20 12 weeks	Primary: Degree of scalp scaling, patient assessment of scalp itching and scaling Secondary: Not reported	Primary: Seventy-four percent of patients treated with ketoconazole 2% shampoo experienced a significant improvement in clinical scores characterizing the degree of scalp scaling compared to patients receiving placebo (P<0.01). Patients treated with ketoconazole 2% shampoo experienced a significant improvement in scalp itching (P<0.01) and scalp scaling (P<0.05); there was no difference found in patients receiving the placebo shampoo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 4 weeks, then Johnson's® baby shampoo applied to the hair for 4 weeks, then ketoconazole 2% shampoo applied to the hair QD for 4 weeks				
Ratnavel et al.[64] (2007) Ketoconazole 2% shampoo applied 3 times per week for 4 weeks vs ciclopirox 1.5% shampoo applied 3 times per week for 4 weeks vs placebo	DB, PG, RCT Patients with seborrheic dermatitis of the scalp	N=350 8 weeks	Primary: Scalp area affected, severity of scaling, erythema, itching and scaling, and overall signs and symptoms Secondary: Not reported	Primary: The reductions in affected scalp area from day one to days 15, 29, and 43 were all significantly greater with ciclopirox shampoo than with placebo (P=0.001), but did not differ significantly from the reductions observed with ketoconazole. Ciclopirox was non-inferior to ketoconazole. The percentage reduction in the patients' assessments of itching and scaling of the scalp was significantly greater with ciclopirox than placebo at day 29 (P=0.011 and P=0.003, respectively), but there were no significant differences between the two active shampoos. At day 29, the improvement in the patients' assessments of overall signs and symptoms was significantly greater with ciclopirox shampoo than with placebo (P<0.001) or ketoconazole (P=0.030). The improvement was also greater with ciclopirox than placebo at day 15 (P<0.05). The technician's assessment of scaling showed a greater reduction from day one to day 29 with ciclopirox than placebo (P=0.022) as was the reduction from day one to day 43 (P=0.012). The reduction in erythema was also greater with ciclopirox than placebo at day 29 (P=0.019). There were no significant differences between active and placebo treatment with respect to erythema. The technician's assessment of global change showed ciclopirox shampoo to be better than placebo at day 29 and day 43 (P<0.001 for both days); no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				differences between the two active shampoos were detected. Secondary: Not reported
Squire et al.[65] (2002) Ketoconazole 2 % shampoo applied 3 times per week for 4 weeks vs ciclopirox 1.5% and salicylic acid 3% shampoo applied 3 times per week for 4 weeks	RCT, SB, SC Patients 12 to 70 years of age mild, moderate or severe dandruff and/or seborrheic dermatitis of the scalp	N=161 8 weeks	Primary: Clinical assessments of dandruff and safety Secondary: Not reported	Primary: For both treatment groups, there was a significant decrease in the clinical assessment of dandruff scores at day 29 compared to day one (P<0.001). However, there was no significant difference among the treatment groups. Scores remained significantly lower after the cessation of therapy for two weeks (day 43) than on day one (P<0.05). Both treatments significantly improved clinical assessments of seborrheic dermatitis, patients' self-assessments of dandruff, overall scalp itching, and itching of area of seborrheic dermatitis (P<0.05). Scores remained significantly lower after the cessation of treatment for two weeks (day 43) than at the start of treatment (day one; P<0.05). For both treatment groups, the mean scores for the global evaluation of clinical change indicated an improvement in condition over time, with scores lower than five (no change), at each assessment day after the start of treatment. Only the between-treatment change at day 43 was statistically significant (P<0.05), with lower mean scores in the ketoconazole group. There were similar mean scores for both treatment groups for the patients' overall rating of treatment at the end of treatment (day 29), with 72% of patients in the ciclopirox/salicylic acid group and 56% of patients in the ketoconazole group rating their treatment as 'good', 'very good' or 'excellent'. The between-treatment comparison was not statistically significant (P>0.05). The most common adverse events were pruritus, rhinitis, seborrhea and skin irritation. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Koc et al.[66] (2009) Ketoconazole 2% cream applied BID vs pimecrolimus 1% cream applied BID	OL, RCT Patients with mild to moderate seborrheic dermatitis	N=48 6 weeks	Primary: Treatment efficacy (symptoms of erythema, scaling and infiltration) Secondary: Not reported	Primary: In both treatment groups, there was a significant decrease in erythema, scaling and infiltration criteria (P<0.05). Clinical improvements were as follows: 81.4 and 78.3% for erythema, 86.1 and 87.2% for scaling, and 93.3 and 94.6% for infiltration in the pimecrolimus and ketoconazole groups, respectively. The mean percentage decrease in the total clinical severity scores was 86.2 and 86.1% in the pimecrolimus and ketoconazole groups, respectively (P>0.05). Adverse events were observed in 12 patients in the pimecrolimus group and four patients in the ketoconazole group. Burning sensation, pruritus, irritation, and erythema were more common in the pimecrolimus group than in the ketoconazole group (P<0.05). Secondary: Not reported
Pierard-Franchimont et al.[67] (2002) Ketoconazole 2% shampoo twice applied to the hair weekly for 4 weeks vs zinc pyrithione 1% shampoo applied to the hair at least twice weekly for 4 weeks	MC, OL, PG, RCT Adults with seborrheic dermatitis of the scalp or severe noninflammatory dandruff	N=343 4 week treatment phase 4 week follow-up phase	Primary: Overall cure Secondary: Relapses, TDSS	Primary: The proportions of clinical responders who experienced marked improvement or clearing of their scalp condition at the treatment endpoint were similar for the ketoconazole (86%) and zinc pyrithione (82%) groups. The shift in the global scores was significantly greater for ketoconazole both at the end of treatment and at completion of the follow-up phase (P<0.05). The overall clearing was greater in the ketoconazole group (57%) than in the zinc pyrithione group (44%; P<0.01). Secondary: Relapse rates were 39% in the ketoconazole group compared to 51% in the zinc pyrithione group (P<0.03). The ketoconazole group showed a significantly greater improvement from baseline in TDSS than the zinc pyrithione at treatment endpoint (P<0.02)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and at the end of the follow-up period (P<0.04).
Tinea Infections				
Reyes et al.[68] (1998) Butenafine 1% cream applied QD vs placebo	DB, MC, PC, RCT Patients with interdigital tinea pedis rated with a minimum erythema score of 2 and a minimum score of 2 for either pruritus or scaling	N=105 4 weeks	Primary: Mycological cure, investigator global assessment of clinical response, patient's assessment of change, and effective treatment Secondary: Adverse effects	Primary: Patients who received butenafine were more likely to experience mycological cure at four weeks compared to placebo (91 vs 63%, respectively; P<0.01). Mycological cure persisted in patients receiving butenafine four weeks after the end of the four-week treatment period compared to the placebo (83 vs 38%, respectively; P<0.001). According to the investigator global response, patients receiving butenafine had significantly better clinical response to compared to placebo at four (P=0.03) and eight weeks (P<0.001). According to the patient's assessment of clinical response, a greater number of patients receiving butenafine described improvement in signs and symptoms compared to those receiving placebo (P<0.001). Effective treatment as determined by mycological cure rate and sign/symptom improvement was greater with patients receiving butenafine compared to patients who received placebo at four (58 vs 31%, respectively; P<0.01) and eight weeks (68 vs 25%, respectively; P<0.001). Secondary: One patient receiving butenafine experienced moccasin-type tinea pedis of the plantar surface; one patient experienced hyperbilirubinemia.
Tschen et al.[69] (1997) Butenafine 1% cream applied QD vs placebo	DB, PC, RCT Patients with interdigital tinea pedis with a minimum erythema score of 2 and a minimum score of 2 for either pruritus and scaling	N=80 4 weeks	Primary: Mycological cure, investigator global assessment of clinical response, patient's assessment of change, and effective treatment Secondary: Safety, tolerability	Primary: Patients who received butenafine were more likely to experience mycological cure at four weeks compared to placebo (88 vs 33%). According to the investigator global response, patients receiving butenafine had significantly better clinical response as compared to those treated with placebo at four weeks (P<0.01) and at eight weeks (P=0.001). Effective clinical response persisted in patients receiving butenafine compared to placebo at eight weeks (clinical response at four weeks was 68 vs 40%, respectively; [P<0.01]; at eight weeks was 78 vs 35%, respectively; [P<0.001]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				According to the patient's assessment of clinical response, a greater number of patients receiving butenafine described somewhat or great improvement in signs and symptoms compared to those receiving placebo at four weeks (P=0.003) and eight weeks (P<0.001). Effective treatment as determined by mycological cure rate and sign/symptom improvement was greater with patients receiving butenafine compared to patients who received placebo at two weeks (55 vs 23%, respectively; P=0.001) and eight weeks (70 vs 23%, respectively; P=0.012). Secondary: One patient receiving butenafine experienced mild burning sensations at the site of application, whereas four patients receiving placebo experienced burning, itching, stinging, a red streak, and/or a high serum lactate dehydrogenase concentration.
Singal et al.[70] (2005) Butenafine 1% cream applied QD for 2 weeks vs clotrimazole 1% cream applied BID for 4 weeks	DB, RCT Patients ≥14 years of age with localized tinea cruris and localized tinea corporis	N=80 8 weeks	Primary: Clinical and mycological cure Secondary: Not reported	Primary: The clinical assessment score, clinical cure rates, and mycological cure rates were similar for the butenafine and clotrimazole treatment groups at four and eight weeks of treatment. In the butenafine group, relapse was not observed in any patient, while two patients in the clotrimazole group became KOH-positive again at eight weeks and one of them also had evidence of clinical relapse. Secondary: Not reported
Aly et al.[71] (2003) Ciclopirox 0.77% gel applied BID vs placebo	2 DB, MC, RCT Patients 16 to 80 years of age with clinically diagnosed, stable or exacerbating interdigital tinea pedis with or	N=317 28 days	Primary: Treatment success (mycological and clinical cure) Secondary: Global clinical response, signs and symptoms severity	Primary: At the end of the study, 60 and 6% of patients treated with ciclopirox and placebo, respectively, achieved treatment success, greater than 75% clinical improvement (P=0.05). This significant difference in treatment success between ciclopirox and placebo was observed at days 26, 43 and at the study endpoint (final visit, up to day 50; P=0.05). Secondary: At the end of the study, 40 and 4% of the patients treated with ciclopirox

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	without plantar involvement with positive culture and potassium hydroxide test		scores, mycological evaluation, mycological cure, and treatment cure	and placebo, respectively, had complete clinical cure. This significant difference in clinical cure between ciclopirox and placebo was observed at days 26, 43 and at the study endpoint (P=0.05). At the end of the study, 66 and 16% of patients treated with ciclopirox and placebo, respectively, had either cleared or excellent improvement relative to the infection (P=0.05). At two weeks post treatment, 85 and 16% of patients treated with ciclopirox and placebo, respectively, were mycologically cured (P=0.05). At the end of the treatment, 46 and 24% of patients treated with ciclopirox and placebo, respectively, described treatment as cosmetically acceptable.
Gupta et al.[72] (2005) Ciclopirox 0.77% gel applied QD vs ciclopirox 0.77% gel applied BID vs placebo	DB, PC, PRO, RCT Patients 18 to 70 years of age with moderate interdigital tinea pedis and secondary bacterial infection	N=100 8 weeks	Primary: Global clinical evaluation score, subject clinical evaluation score, clinical cure, mycological cure, and complete cure; clinical evaluation scores ranged from one excellent to seven worse Secondary: Adverse effects	Primary: There was no significant difference in improved evaluation scores between QD or BID applications of ciclopirox. However, both QD and BID ciclopirox treatment groups showed significant improvement in evaluation scores compared to placebo at week eight (2.06 vs 6.17; P=0.0003 and 2.41 vs 6.17; P=0.0036, respectively). There was no significant difference in improved mycological cure rates between QD or BID applications of ciclopirox. However both QD and BID ciclopirox treatment groups showed significant improvement in mycological cure rate compared to placebo at week eight (82.8 vs 43.8%; P=0.013 and 80.8 vs 43.8%; P=0.007, respectively). There was a significant difference in complete cure rate between twice-daily ciclopirox and placebo (50.0 vs 12.5%, respectively; P=0.014). Other comparisons were not significant. Secondary: The most common reported adverse effects were local site reactions of burning or itching. There was no significant difference in the incidence of adverse effects between treatment groups.
Aly et al.[73] (1989)	DB, MC, PG, RCT Patients with	N=134 28 days	Primary: Clinical cure, mycological cure	Primary: On day 29, patients treated with ciclopirox lotion experienced greater mycological response compared to patients receiving the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciclopirox 1% cream applied BID vs ciclopirox 1% lotion applied BID vs placebo	clinically and mycologically confirmed plantar, interdigital, or vesicular tinea pedis		Secondary: Adverse events	(P<0.001). On day 43, patients treated with ciclopirox lotion compared to placebo achieved greater clinical cure (45 vs 27%, respectively; P=0) and mycological cure (76 vs 43%, respectively; P=0). Secondary: Pruritus and burning were reported with ciclopirox use.
Wu et al.[74] (1991) Ciclopirox 1% cream applied BID to TID	OL, OS Patients living in temperate climates with culture or microscopically confirmed onychomycosis and/or tinea pedis	N=49 3 to 24 months	Primary: Clinical cure, mycological cure Secondary: Adverse effects	Primary: For onychomycosis, 14 and 36% of patients treated with ciclopirox were cured and showed improvement, respectively. Cure was influenced by the degree of nail plate affected; moderate involvement correlated to a better cure rate. For tinea pedis, 42 and 45% of patients treated with ciclopirox were cured and showed improvement, respectively. Secondary: Paronychia was reported as a side effect, possibly due to excessive application of the agent.
Bogaert et al.[75] (1986) Ciclopirox 1% cream applied BID vs clotrimazole 1% cream applied BID vs placebo	2 DB, MC, PG, RCT Patients with tinea corporis or tinea cruris	N=229 28 weeks	Primary: Clinical evaluation, assessment of treatment response Secondary: Safety, tolerance	Primary: In study A, patients treated with ciclopirox demonstrated significant improvement in clinical and mycological cure rate compared to the patients receiving placebo at six weeks (61 vs 15%; P<0.001). In study B, there was no significant difference in clinical and mycological cure rate between treatment groups receiving ciclopirox or clotrimazole creams (64 vs 69%; P value not reported). Secondary: In study A, no side effects associated with ciclopirox were reported; one patient receiving placebo reported transient burning. In study B, one patient receiving ciclopirox reported pruritus and one patient receiving clotrimazole reported burning, pruritus, and worsening of lesions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
In study A, patients received either ciclopirox 1% cream BID or placebo. In study B, patients received either ciclopirox 1 % cream BID or clotrimazole 1 % cream BID.				
Chen et al.[76] (2010) Ciclopirox 1% shampoo applied twice weekly vs selenium sulfide 1% shampoo applied twice weekly Treatments were an adjunct to an 8-week course of ultra micronized griseofulvin, which was dosed 10 to 12 mg/kg/day.	DB, RCT Children 1 to 12 years of age with a clinical diagnosis of tinea capitis	N=44 Treatment: 8 to 12 weeks Follow-up: 4 weeks post-treatment	Primary: Mycological cure (defined as having zero dermatophyte colonies on Mycosel agar) Secondary: Not reported	Primary: Overall, 30.3% of children had negative cultures at two weeks, 42.4% of children at four weeks, 18.2% of children at eight weeks, and 3.0% of children at 12 weeks, for a total of 93.9% of children mycologically cured by 12 weeks. Among children treated with griseofulvin and selenium sulfide shampoo, 25.0% demonstrated negative cultures at two weeks, 50.0% of children at four weeks, 16.7% of children at eight weeks, and no additional children at 12 weeks, for a total of 91.7% of children mycologically cured by eight weeks. Among children treated with griseofulvin and ciclopirox shampoo, 33.3% demonstrated negative cultures at two weeks, 38.1% of children at four weeks, 19.0% of children at eight weeks, and 4.7% of children at 12 weeks, for a total of 95.2% of children mycologically cured by 12 weeks. There was no significant difference among the treatment groups at two weeks (P=0.71), four weeks (P=1.0), eight weeks (P=1.0), or 12 weeks (P=1.0). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wortzel et al.[77] (1982) Clotrimazole applied BID vs betamethasone dipropionate applied BID vs betamethasone dipropionate and clotrimazole combination cream applied BID	DB, MC, RCT Patients with confirmed tinea cruris	N=45 2 weeks	Primary: Clinical cure, microbiological cure Secondary: Adverse events	Primary: At the end of two weeks, 80, 20 and 13% of patients treated with the combination product, clotrimazole only, and betamethasone only, respectively, achieved either complete cure or excellent response to therapy. At the end of two weeks, 87, 100 and 46% of patients treated with the combination product, clotrimazole only, and betamethasone only, respectively, had negative culture. Two weeks after treatment, 93, 100 and 40% of patients treated with the combination product, clotrimazole only, and betamethasone only, respectively, achieved either complete cure or excellent response to therapy. Relative to overall clinical rating of the treatment, the combination product was better than clotrimazole (P=0.013) and betamethasone (P=0.001); clotrimazole was better than betamethasone (P=0.001). Secondary: One patient treated with betamethasone reported severe burning and tingling.
Katz et al.[78] (1984) Clotrimazole 1 cream applied BID vs betamethasone dipropionate 0.05% cream applied BID vs	DB, MC, PG, RCT Patients with a confirmed diagnosis of moderate to severe tinea cruris or tinea corporis	N=331 2 weeks	Primary: Total signs and symptoms severity score/clinical response ratings, and mycologic findings Secondary: Adverse events	Primary: Patients treated with clotrimazole had higher total signs and symptoms scores at baseline (P<0.05). At days seven, 14, and 28, patients diagnosed with tinea cruris and treated with the combination product had better total signs and symptoms scores compared to patients treated with clotrimazole (P<0.05). At days 14 and 28, patients diagnosed with tinea cruris and treated with the combination product had better total signs and symptoms scores compared to patients treated with betamethasone dipropionate (P<0.05). At days seven and 28, patients diagnosed with tinea corporis and treated with the combination product had better total signs and symptoms scores compared to patients treated with clotrimazole (P<0.05). At days 14 and 28, patients diagnosed with tinea corporis and treated with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betamethasone dipropionate 0.05% and clotrimazole 1% combination cream applied BID				combination product had better total signs and symptoms scores compared to patients treated with betamethasone dipropionate (P<0.05). According to mycologic responses, the combination product and clotrimazole were more effective than betamethasone dipropionate (63 and 51 vs 32%, respectively; P<0.05). Secondary: Two patients treated with the combination product reported mild macular papular eruption and/or mild paresthesia. Eight patients treated with betamethasone dipropionate reported paresthesia and/or severe pain followed by a papular eruption. Three patients treated with clotrimazole reported paresthesia.
Kamalam et al.[79] (1980) Clotrimazole vs econazole	DB, OS Patients 45 days to 36 years of age with confirmed tinea infections	N=45 3 to 60 days	Primary: Clinical cure, microscopically negative results Secondary: Adverse events	Primary: At six weeks post treatment, 98 and 2% of all patients achieved complete or partial cure, respectively, regardless of treatment with either clotrimazole or econazole. For econazole-treated patients, clinical cure was observed in approximately 14 days (range, five to 29 days) and microscopically negative results were seen in one to two weeks. At six weeks post treatment, all cases were cured. For clotrimazole-treated patients, clinical cure was observed in approximately 16.5 days (range, three to 44 days) and microscopically negative results were seen in one to six weeks. At six weeks post treatment, there was one case not cured. Secondary: No adverse effects were reported. There was one report of a recurrence after two weeks of stopping therapy.
Dehghan et al.[80] (2010) Clotrimazole 1% cream applied BID for 2 weeks	DB, RCT Patients with hyperpigmented tinea versicolor	N=120 Treatment: 2 weeks Follow-up:	Primary: Clinical response Secondary: Not reported	Primary: At week two in the fluconazole group, 30 and 66% of patients showed complete and incomplete clinical response, respectively. Clinical response was not seen in 4% of patients. In the clotrimazole group, 49.1 and 47.3% of patients showed complete and incomplete clinical response, respectively. Clinical response was not seen in 3.6% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluconazole 400 mg orally as a single dose		12 weeks		At week four in the fluconazole group, 81.2 and 18.8% of patients showed complete and incomplete clinical response, respectively. In the clotrimazole group, 94.9 and 5.1% of patients showed complete and incomplete clinical response, respectively (P=0.044). At week 12 in the fluconazole group, 92 and 2% of patients showed complete and incomplete clinical response, respectively. Recurrence or no clinical response was seen in 6% of patients. In the clotrimazole group, 81.8 and 0% of patients showed complete and incomplete clinical response, respectively. Recurrence or no clinical response was seen in 18.2% of patients (P=0.77). No complications were seen in either group. Secondary: Not reported
Sivayathorn et al.[81] (1979) Clotrimazole 1% cream applied TID vs miconazole 2% cream applied TID vs tolnaftate 2% cream applied TID vs Whitfield's Ointment® (3%	DB, RCT Patients 2 to 72 years of age with superficial dermatophytoses	N=101 2 weeks	Primary: Clinical response, mycological cure Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 50, 73.68, 77.78, and 81.48% of patients treated with Whitfield's Ointment®, tolnaftate, clotrimazole, and miconazole, respectively. Mycological cure was reported in 21.42, 63.16, 59.26, and 77.78% of patients treated with Whitfield's Ointment®, tolnaftate, clotrimazole, and miconazole, respectively. Although miconazole demonstrated the highest clinical and mycological cure rate, there was no significant difference between clotrimazole, miconazole, and tolnaftate treatment groups (P>0.05). Clotrimazole, miconazole, and tolnaftate therapies were more efficacious compared to Whitfield's Ointment® (P<0.05). Secondary: There were no reported adverse reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salicylic acid, 6% benzoic acid) applied TID				
Clayton et al.[82] (1973) Clotrimazole 1% cream applied BID vs nystatin 100,000 U/g ointment applied BID vs Whitfield's Ointment® (3% salicylic acid, 6% benzoic acid) applied BID	AC, DB, RCT Patients 13 to 63 years of age with either confirmed tinea corporis, tinea pityriasis, erythrasma, or *Candida* infections	N=103 4 weeks	Primary: Clinical cure, mycological cure Secondary: Not reported	Primary: Relative to patients with confirmed tinea corporis, there was no significant difference in efficacy in patients treated with clotrimazole or Whitfield's Ointment®. Relative to patients with confirmed tinea pityriasis, there was no significant difference in efficacy in patients treated with clotrimazole or Whitfield's Ointment®. Relative to patients with confirmed erythrasma, there was no significant difference in efficacy in patients treated with clotrimazole or Whitfield's Ointment®. Relative to patients with Candida infections, there was no significant difference in efficacy in patients treated with clotrimazole or nystatin. Secondary: Not reported
Lassus et al.[83] (1983) Clotrimazole 1% cream applied BID vs sulconazole 1% cream applied BID	DB, PG Patients with microbiologically confirmed dermatomycosis	N=40 4 weeks	Primary: Clinical signs and symptoms, overall clinical improvement, and cosmetic acceptability Secondary: Adverse events	Primary: Patients with signs and symptoms of scaling and erythema responded better to sulconazole than clotrimazole at weeks two ($P<0.05$), three ($P<0.01$), and four ($P<0.05$) of treatment. There was no significant difference in the other signs and symptoms regardless of therapy. Overall clinical improvement at weeks two, three, and four was greater with sulconazole (94.8, 100, and 100%, respectively) compared to clotrimazole (73.7, 78.9, and 83.4%, respectively). Secondary: One patient from each treatment group experienced an allergic reaction during the first week of therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tanenbaum et al.[84] (1989) Clotrimazole 1% cream applied BID vs sulconazole 1% cream applied QAM and placebo QPM vs sulconazole 1% cream applied BID vs placebo In study A, patients received either sulconazole applied QAM and placebo QPM or clotrimazole applied BID. In study B, patients received either sulconazole applied BID or placebo BID.	2 DB, PG, RCT Male patient with tinea cruris or tinea corporis	N=117 3 weeks	Primary: Microbiological cure, culture conversion, and overall clinical evaluation Secondary: Adverse events	Primary: In study A, there was no significant difference between treatment groups throughout the study relative to microbiological cure or culture conversion. In study B, there was a significant improvement in culture conversion and microbiological cure for patients treated with sulconazole compared to placebo at week two (P=0.0001) and week three (P=0.0001). By week three, 100% of patients treated with either clotrimazole or sulconazole achieved complete or partial clearing compared to 30% of patients receiving placebo; there was no statistical difference between active treatment groups. In study B, patients treated with sulconazole had a significant improvement in overall clinical evaluation compared to placebo (P=0.0001). Secondary: In study A, four patients receiving clotrimazole cream reported moderate to severe side effects, including erosive primary irritation, fissuring, and erythema. In study B, six patients receiving placebo experienced primary irritant reactions (erosions, burning).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tham et al.[85] (1987) Clotrimazole 1% solution applied BID vs sulconazole 1% solution applied QAM and placebo QHS	RCT Patients 14 to 62 years of age with microscopically confirmed tinea versicolor	N=84 3 weeks	Primary: Clinical assessment, investigator assessment, patient assessment, and negative microscopy Secondary: Adverse effects	Primary: Reduced rates of itching, scaling, and erythema did not differ between treatment groups at weeks two and three (P>0.05). Potassium hydroxide results did not differ (P>0.05) between patients treated with sulconazole or clotrimazole at weeks two (67 vs 72%, respectively) and three (76 vs 93%, respectively). Investigator assessed clinical efficacy was 63 and 65% in patients treated with sulconazole and clotrimazole, respectively (P=0.8911). Overall evaluation by the patients was similar (P=0.2197). After six weeks post treatment, negative microscopy was maintained by 79 and 92% of patients taking sulconazole and clotrimazole, respectively. This difference was not significant. Secondary: Five patients who were treated with sulconazole reported adverse effects which included mild itching and burning. Eight patients who were treated with clotrimazole reported adverse effects such as severe itching, biting sensation, stickiness of product, and skin peeling.
Patel et al.[86] (1999) Clotrimazole 1% cream applied BID for 4 weeks vs terbinafine 1% cream applied BID for 1 week, then placebo for 3 weeks	DB, MC, PG, RCT Patients with confirmed interdigital tinea pedis	N=104 4 weeks	Primary: Mycological cure Secondary: Effective treatment, complete cure, perceived efficacy, relapse rate, and adverse events	Primary: After one week of treatment, 84.6 and 55.8% of patients treated with terbinafine and clotrimazole, respectively, were culture negative (P=0.001). There was no significant difference between study groups with regards to mycological cure at weeks four, eight, and 12 weeks. Secondary: There was no significant difference in effective treatment and complete cure between the treatment groups. Throughout the study, both patients and investigators evaluated the treatments as very good to good in 75 to 80% of cases. Relapse rate was 15 and 19% in patients treated with terbinafine and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				clotrimazole, respectively. Most commonly reported adverse effects included burning, hypersensitivity, stinging, and exacerbation of pruritus.
Lassus et al.[87] (1984) Econazole 1% cream applied BID vs sulconazole 1% cream applied BID	DB, PG, RCT Patients with confirmed dermatophytoses	N=38 4 weeks	Primary: Microbiological cure, clinical cure, overall clinical improvement, relapse, and cosmetic acceptability Secondary: Adverse effects	Primary: By week two, every patient achieved microbiological cure with the exception of one patient treated with sulconazole. By week four, all patients achieved microbiological cure. Both treatment groups responded well to treatment leading to significant reductions in itching, scaling, and erythema. However, by week four, two and three patients treated with sulconazole and econazole, respectively, were still mildly symptomatic. There was no significant difference between treatment groups in terms of overall clinical improvement. The diagnosis of tinea pedis in 80% of the study patients did not influence the study results. At week 10, all patients treated with sulconazole remained symptom- and microbiologically-free of infection, whereas three patients treated with econazole experienced clinical relapses. Relative to cosmetic acceptability, 90 and 79% of patients treated with sulconazole and econazole, respectively, rated the acceptability as excellent. There was no significant difference in cosmetic acceptability. Secondary: One patient treated with econazole reported an allergic reaction. One patient treated with sulconazole reported a case of eczema.
Bonifaz et al.[88] (2000) Ketoconazole 2% cream applied QD for 14 days vs	OL, PG, PRO, RCT Patients 12 to 79 years of age with confirmed tinea corporis and tinea cruris	N=65 7 to 14 days	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: Clinical cure was not significant between the two treatment groups (P=0.088). Mycological cure was achieved in 94 and 69% of patients treated with terbinafine and ketoconazole, respectively (P=0.027) Combined clinical and mycological overall cure was achieved in 72 and 31% of patients treated with terbinafine and ketoconazole, respectively

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
terbinafine 1% gel applied QD for 7 days				(P=0.002). Of note, the demographic data revealed an unequal distribution of patients in terms of gender (P=0.015); the ketoconazole study group had more male patients compared to the terbinafine study group. Secondary: One patient treated with terbinafine and three patients treated with ketoconazole reported dermatitis-like side effects. Terbinafine was better tolerated than ketoconazole (P=0.003)
Tanenbaum et al.[89] (1982) Miconazole 2% cream applied BID vs sulconazole 1% cream applied BID	DB, PG, RCT Patients 18 to 65 years of age with cutaneous dermatomycosis	N=96 3 to 4 weeks	Primary: Mycological cure, clinical cure, and relapse rate Secondary: Adverse events	Primary: At the end of four weeks in patients treated for tinea pedis, 100% of patients treated with sulconazole and 67% of patients treated with miconazole were mycologically cured. After the end of three weeks in patients treated for tinea cruris/corporis, 91% of patients treated with sulconazole and 100% of patients treated with miconazole were mycologically cured. At the end of three weeks, 91 and 100% of patients treated with sulconazole and miconazole, respectively, reported significant or complete clearing of symptoms. Relapse rates were reported as 16 and 35% in patients treated with sulconazole and miconazole, respectively. Secondary: Two patients treated with miconazole reported severe irritant dermatitis. One patient treated with sulconazole experiences moderate-to-severe itching.
Tanenbaum et al.[90] (1984) Miconazole 2% cream applied BID vs	DB, MC, PG, RCT Patients with confirmed tinea versicolor	N=181 3 weeks	Primary: Clinical cure, mycological cure Secondary: Adverse events	Primary: At the end of the study, 93 and 87% of patients treated with sulconazole and miconazole were mycologically cured (P=0.6198). At this time, clinical cure was achieved in 89 and 82% of patients treated with sulconazole and miconazole (P=0.2431). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulconazole 1% cream applied BID				Patients treated with miconazole reported stinging, itching, dermatitis, or irritation. Patients treated with sulconazole reported itching, stinging/burning, dryness/scaling, and fissure/cracking.
Jordon at el.[91] (1990) Naftifine 1% cream applied QD vs placebo	DB, RCT Patients 14 to 67 years of age with confirmed tinea cruris or tinea corporis	N=70 4 weeks	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: After two weeks, 79 and 31% of patients treated with naftifine and placebo, respectively, achieved mycological cure (P<0.001). At this time, patients treated with naftifine had better resolution of erythema (P<0.001), scaling (P=0.007), and pruritus (P<0.001) compared to patients using placebo. This significant trend favoring naftifine persisted throughout the treatment period (86 vs 30%, respectively; P<0.001) and two weeks post treatment (66 vs 26%, respectively; P=0.002). Secondary: Two patients treated with placebo reported adverse events, while none were reported by patients treated with naftifine.
Parish et al.[92] (2011) Naftifine 2% cream QD for 2 weeks vs placebo	DB, MC, PC, RCT Patients 12 years of age and older with a clinical diagnosis of *T. cruris*	N=334 4 weeks	Primary: Complete cure Secondary: Mycological cure, treatment effectiveness, clinical cure, and clinical success	Primary: At week two, complete cure was achieved by 5% of patients treated with naftifine compared to 0% of patients treated with placebo (P<0.025). At week four, complete cure was achieved by 25% of patients treated with naftifine compared to 3% of patients treated with placebo (P<0.001). Secondary: At week two, mycological cure was achieved by 67% of patients treated with naftifine compared to 11% of patients treated with placebo (P<0.001). At week four, mycological cure was achieved by 72% of patients treated with naftifine compared to 16% of patients treated with placebo (P<0.001). At week two, treatment effectiveness was achieved by 52% of patients treated with naftifine compared to 9% of patients treated with placebo (P<0.001). At week four, treatment effectiveness was achieved by 60% of patients treated with naftifine compared to 10% of patients treated with placebo (P<0.001). At week two, clinical cure was achieved by 10% of patients treated with naftifine compared to 5% of patients treated with placebo (P<0.257). At week four, clinical cure was achieved by 33% of patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				naftifine compared to 10% of patients treated with placebo (P<0.001). At week two, clinical success was achieved by 74% of patients treated with naftifine compared to 5% of patients treated with placebo (P<0.001). At week four, clinical success was achieved by 84% of patients treated with naftifine compared to 10% of patients treated with placebo (P<0.001).
Parish et al.[93] (2011) Naftifine 2% cream QD for 2 weeks vs naftifine 1% cream QD for 4 weeks vs placebo for 2 weeks vs placebo for 4 weeks	DB, MC, PC, RCT Patients 12 years of age and older with a clinical diagnosis of *T. pedis*	N=709 6 weeks	Primary: Complete cure Secondary: Mycological cure, treatment effectiveness, clinical cure, and clinical success	Primary: At week six, a greater proportion of patients treated with naftifine 2% achieved complete cure compared to patients treated with placebo (18 vs 7%; P<0.010). The complete cure rates were not statistically significantly different between naftifine 2% and placebo at weeks two (P=0.100) and four (P=0.234). At week six, a greater proportion of patients treated with naftifine 1% achieved complete cure compared to patients treated with placebo (16 vs 3%; P<0.001). The complete cure rates were not statistically significantly different between naftifine 1% and placebo at weeks two (P=0.097) and four (P=0.143). Secondary: Compared to placebo, a greater proportion of patients treated with naftifine 2% achieved mycological cure at week two (28 vs 19%; P<0.049), at week four (54 vs 20%; P<0.001), and at week six (67 vs 21%; P<0.001). Similarly, compared to placebo, a greater proportion of patients treated with naftifine 1% achieved mycological cure at week two (32 vs 19%; P<0.028), at week four (53 vs 9%; P<0.001), and at week six (71 vs 22%; P<0.001). Compared to placebo, a greater proportion of patients treated with naftifine 2% achieved treatment effectiveness at week four (35 vs 10%; P<0.001) and at week six (57 vs 20%; P<0.001). Treatment effectiveness was not statistically significantly different between naftifine 2% and placebo at week two (P=0.460). Compared to placebo, a greater proportion of patients treated with naftifine 1% achieved treatment effectiveness at week two (18 vs 6%; P<0.011), at week four (36 vs 6%; P<0.001), and at week six (59 vs 14%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At week six, a greater proportion of patients treated with naftifine 2% achieved clinical cure compared to patients treated with placebo (22 vs 11%; P<0.040). The clinical cure rates were not statistically significantly different between naftifine 2% and placebo at week two (P=0.213) and at week four (P=0.987). At week six, a greater proportion of patients treated with naftifine 1% achieved clinical cure compared to patients treated with placebo (22 vs 8%; P<0.008). The clinical cure rates were not statistically significantly different between naftifine 1% and placebo at week two (P=0.193) and at week four (P=0.564). Compared to placebo, a greater proportion of patients treated with naftifine 2% achieved clinical success at week four (57 vs 35%; P<0.001) and at week six (78 vs 49%; P<0.001). Clinical success rates was not statistically significantly different between naftifine 2% and placebo at week two (P=0.482). Compared to placebo, a greater proportion of patients treated with naftifine 1% achieved clinical success at week two (44 vs 27%; P<0.007) and at week six (84 vs 44%; P<0.001). Clinical success rates were not statistically significantly different between naftifine 1% and placebo at week four (P<0.078).
Ramelet et al.[94] (1987) Oxiconazole cream applied QAM and placebo QPM vs oxiconazole cream applied BID	DB, MC, RCT Patients 8 to 80 years of age with confirmed dermatomycoses or erythrasma	N=138 7 to 60 days	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: At the conclusion of the study, 69 and 70 patients treated with oxiconazole QD and BID, respectively, achieved cure. The cure rates were 92.0 and 93.3% for patients treated with oxiconazole QD and BID, respectively; no significant difference found between treatment groups. Secondary: Adverse effects were negligible. Three patients reported adverse events which included irritation with erythema and pruritus near the infected area and burning sensations.
Pariser et al.[95] (1994) Oxiconazole 1% lotion applied BID	DB, MC, PC, RCT Patients 12 to 82 years of age with confirmed tinea	N=332 6 weeks	Primary: Mycological cure, clinical cure, overall cure, and global response	Primary: At the end of the study, 67 and 31% of patients treated with oxiconazole and placebo, respectively, experienced mycological cure. At the end of the study, >80 and 50% of patients treated with oxiconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo QAM, then oxiconazole 1% lotion applied QPM vs placebo	pedis		score Secondary: Adverse events	and placebo, respectively, experienced good to excellent improvement in clinical signs and symptoms of tinea pedis as well as global response. A significant improvement was observed in patients treated with oxiconazole compared to placebo relative to overall cure. Secondary: Adverse effects reported were similar across study groups. Commonly reported adverse events included burning, stinging, dyshidrotic eczema, pain, scaling on dorsum of feet, and tingling.
Van Esso et al.[96] (1995) Sertaconazole 2% cream applied QD vs placebo	MC, OL Patients 2 to 16 years of age with tinea corporis, tinea cruris, or tinea pedis	N=16 2 weeks	Primary: Symptoms, clinical cure Secondary: Adverse effects	Primary: The number of patients experiencing symptoms of tinea infections decreased throughout the treatment duration of two weeks; exact percentages were not provided. All of the patients treated with sertaconazole achieved clinical cure after four weeks since start of treatment; 31% achieved cure at week one and 75% achieved cure at week two. Secondary: No local or systemic adverse effects were observed.
Sharma et al.[97] (2011) Sertaconazole 2% cream applied BID for 2 weeks vs miconazole 2% cream applied BID for 2 weeks	DB, MC, PG, RCT Patients 18 to 70 years of age with a clinical diagnosis of cutaneous dermatophytosis	N=260 2 weeks	Primary: Physician global assessment of clinical response regarding complete clinical cure Secondary: Clinical evaluation of the disease condition	Primary: Overall global assessment showed that clinical cure was achieved in 62.3% of patients receiving sertaconazole and in 44.6% of patients receiving miconazole (P<0.05). Secondary: After one week, 76.3% of patients receiving sertaconazole reported improvement in their pruritus symptoms to be ‘better’ or ‘much better’ compared to 49.2% of patients in the miconazole group (P<0.05). After two weeks, clinical cure of pruritus was reported by 45.9% of patients receiving sertaconazole compared to 36.7% of patients receiving miconazole group (P=NS). After one week, 79.5% of patients in the sertaconazole group reported ‘better’ to ‘much better’ relief of erythema compared to 45.3% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the miconazole group (P<0.05). After two weeks, 51.6% of patients receiving sertaconazole reported clinical cure of erythema compared to 30.5% of patients receiving miconazole (P<0.05). After one week, 79.5% of patients reported improvement in desquamation and reported it to be 'better' or 'much better' following therapy with sertaconazole compared to 46.9% of patients in the miconazole group. After two weeks, 45.1% of patients receiving sertaconazole reported clinical cure of desquamation compared to 22.7% of patients receiving miconazole (P=NS). After two weeks of therapy, changes in mean scores of erythema/itching, burning/weeping and scaling/pustules were significantly lower with sertaconazole (73.3%) than with miconazole (69.6%; P<0.05). There was a significant improvement in the mean total score at the end of week two by 74.1% in the sertaconazole group compared to 69.3% in the miconazole group. Both treatments were well tolerated. Only 4.5% of patients receiving sertaconazole reported adverse events compared to 8.2% of patients receiving miconazole. The most common adverse events were dry skin, erythema, burning, itching, irritation, and hyperpigmentation.
Ghaninejad et al.[98] (2009) Sertaconazole 2% cream applied BID for 4 weeks vs miconazole 2% cream applied BID for 4 weeks	DB, RCT Patients ≥18 years of age with a clinical diagnosis of cutaneous dermatophytosis	N=100 43 days	Primary: Cure, adverse events Secondary: Not reported	Primary: At day 15 in the ITT population, cure rates were 20.0 and 23.6% in the miconazole and sertaconazole groups, respectively (P=0.66). In the PP population, cure rates were 2.2 and 13.0% in the miconazole and sertaconazole groups, respectively (P<0.01). At day 29 in the ITT population, cure rates were 66.7 and 69.1% in the miconazole and sertaconazole groups, respectively (P=0.80). In the PP population, cure rates were 73.2 and 82.6% in the miconazole and sertaconazole groups, respectively (P=0.36). At day 43 in the ITT population, cure rates were 88.9 and 76.4% in the miconazole and sertaconazole groups, respectively (P=0.09). In the PP population, cure rates were 100.0 and 100.0% in the miconazole and sertaconazole groups, respectively (P=1.0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were reported by 22 patients in the sertaconazole group and 15 patients in the miconazole group (P=0.28). Their symptoms did not require cessation of therapy. The most commonly reported adverse event was pruritus. Secondary: Not reported
Borelli et al.[99] (2010) Sertaconazole 2% cream applied BID for 4 weeks	OL, MC, RCT (subgroup analysis) Patients 18 to 70 years of age with tinea pedis interdigitalis of dermatophyte origin	N=92 4 weeks	Primary: Eradication of the pathogen and reduction in total clinical score of at least two points Secondary: Reduction in sign and symptoms, adverse events	Primary: After four weeks, 89.9% of patients had eradication of the pathogen and 97.8% had reduction in total clinical score of at least two points. Overall, 88.8% of patients achieved both primary end points for successful treatment. Secondary: After four weeks, 63.7% of patients were free of erythema, 33.0% of patients were free of desquamation, and 91.2% of patients were free of itch. Most patients had either absent or mild symptoms by the end of the study. Adverse events were reported by 8.7% of patients during the study and none were considered serious.
Rotta et al.[100] (2013) Amorolfine* vs bifonazole* vs butenafine vs	MA Patients with mycologically determined diagnosis of dermatophytosis, excluding onychomycosis and tinea capitis	N=7,629 (65 trials) 5 to 42 days	Primary: Mycologic cure at the end of treatment, sustained cure rate Secondary: Not reported	Primary: No statistically significant difference was found between any antifungal for the mycologic cure at the end of treatment. There was no statistically significant difference between placebo and the amorolfine (OR, 3.04; 95% CrI, 0.14 to 65.66), bifonazole (OR, 3.77; 95% CrI, 0.60 to 23.67), flutrimazole (OR, 5.70; 95% CrI, 0.86 to 31.11), ketoconazole (OR, 9.40; 95% CrI, 0.89 to 99.46), and oxiconazole (OR, 3.86; 95% CrI, 0.83 to 18.04) for the mycologic cure at the end of treatment outcome. For all comparisons with placebo (except oxiconazole vs placebo), the results were determined with indirect comparisons due to the lack of head-to-head RCTs. For the sustained cure outcome, treatment with butenafine was more effective compared to the azoles clotrimazole (OR, 2.76; 95% CrI, 1.20 to 6.36), oxiconazole (OR, 4.26; 95% CrI, 1.40 to 12.93), and sertaconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ciclopirox vs clotrimazole vs econazole vs fenticonazole* vs flutrimazole* vs isoconazole* vs ketoconazole vs miconazole vs naftifine vs oxiconazole				(OR, 3.44; 95% CrI, 1.04 to 11.34), respectively. Treatment with the same azoles clotrimazole (OR, 0.36; 95% CrI, 0.20 to 0.67), oxiconazole (OR, 0.24; 95% CrI, 0.09 to 0.62), and sertaconazole (OR, 0.29; 95% CrI, 0.10 to 0.87) was significantly inferior compared to terbinafine. Treatment with ciclopirox was significantly inferior to treatment with terbinafine (OR, 0.45; 95% CrI, 0.22 to 0.93). Treatment with naftifine was more effective compared to oxiconazole (OR, 3.13; 95% CrI, 1.09 to 8.95). Compared to placebo, treatment with amorolfine (OR, 10.77; 95% CrI, 1.00 to 116.38), ketoconazole (OR, 3.90; 95% CrI, 0.77 to 19.70), and tioconazole (OR, 3.24; 95% CrI, 0.14 to 76.18) had no statistically significant difference for sustained cure outcome. For all comparisons with placebo, the results were determined with indirect comparisons due to the lack of head-to-head RCTs. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sertaconazole vs terbinafine vs tioconazole vs placebo				
Rotta et al.[101] (2012) Amorolfine* vs bifonazole* vs butenafine vs ciclopiroxolamine vs clotrimazole	MA, SR Patients with dermatophytosis, including cutaneous candidiasis and that of *T. pedis, T. corporis, T. cruris* and *T. versicolor;* patients with onychomycosis or *T. capitis* were excluded	N=15,795 (104 trials) 1 to 6 weeks	Primary: Mycologic cure at the end of treatment, sustained cure rate Secondary: Not reported	Primary: Data from 26 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, and tioconazole) was more effective in achieving mycological cure at the end of treatment compared to placebo (OR, 10.25; 95% CI, 6.88 to 15.27; I^2=71%). Data from 20 RCTs showed that treatment with allylamines (naftifine and terbinafine) was more effective in achieving mycological cure at the end of treatment compared to placebo (OR, 6.15; 95% CI, 3.47 to 10.91; I^2=75%). Data from 12 PC RCTs showed that treatment with butenafine and ciclopiroxolamine was more effective in achieving mycological cure at the end of treatment compared to placebo (OR, 6.63; 95% CI, 4.12 to 10.67; I^2=67%). Data from 15 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, fenticonazole, miconazole, and oxiconazole) was not statistically different from treatment with allylamines (naftifine and terbinafine) in achieving mycological cure at the end of treatment (OR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs econazole vs fenticonazole* vs flutrimazole* vs isoconazole* vs ketoconazole vs miconazole vs naftifine vs oxiconazole vs sertaconazole vs				0.78; 95% CI, 0.48 to 1.24; I^2=45%). Data from 10 RCTs showed that treatment with azoles (bifonazole, clotrimazole, and fenticonazole) was not statistically different from treatment with antifungals other than allylamines in achieving mycological cure at the end of treatment (OR, 0.64; 95% CI, 0.40 to 1.01; I^2=7%). Data from 13 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, and tioconazole) was more effective in achieving sustained cure compared to placebo (OR, 7.25; 95% CI, 5.15 to 10.20; I^2=5%). Data from 25 RCTs showed that treatment with allylamines (naftifine and terbinafine) was more effective in achieving sustained cure compared to placebo (OR, 12.67; 95% CI, 8.99 to 17.84; I^2=42%). Data from 12 PC RCTs showed that treatment with butenafine and ciclopiroxolamine was more effective in achieving sustained cure compared to placebo (OR, 6.63; 95% CI, 4.12 to 10.67; I^2=67%). Data from 15 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, fenticonazole, miconazole, and oxiconazole) was more effective in achieving sustained cure compared to treatment with allylamines (naftifine and terbinafine) (OR, 0.55; 95% CI, 0.33 to 0.89; I^2=60%); however, no statistically significant difference was observed when one study accounting for high heterogenicity was hypothetically removed, decreasing the I^2 to 50%. Data from 10 RCTs showed that treatment with azoles (bifonazole, clotrimazole, and fenticonazole) was not statistically different from treatment with antifungals other than allylamines in achieving sustained cure (OR, 0.79; 95% CI, 0.50 to 1.26; I^2=0%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
terbinafine vs tioconazole vs placebo				
Miscellaneous				
Grigoriu et al.[102] (1983) Econazole 1% cream applied BID vs tioconazole 1% cream applied BID	DB, RCT Patients with confirmed fungal skin infection or erythrasma	N=61 Mean 38 to 40 days	Primary: Clinical response, mycological response, combined clinical and mycological cure Secondary: Adverse effects	Primary: In 28 days or less, 46.7 and 41.7% of patients treated with tioconazole and econazole, respectively, achieved symptomatic improvement. After 14 days of treatment, 23 and 25 patients treated with tioconazole and econazole, respectively, were cured. Combined clinical and mycological cure was achieved in 93.1 and 93.5% of patients treated with tioconazole and econazole, respectively. There was no significant difference in rate of improvement, mycologically or clinically, between the two treatment groups. Overall response rate was 90% observed in both treatment groups. Secondary: Reported adverse event included mild intermittent pruritus, which was identified in a patient treated with econazole.
Concannon et al.[103] (2001) Miconazole 0.25% in zinc oxide-petrolatum base applied to rash at each diaper change and after infant's bath	DB, PC, PG, RCT Patients 2 to 13 months of age with acute diaper dermatitis	N=188 7 days	Primary: Number of rash sites, mean total rash score Secondary: Adverse events	Primary: On days five and seven, patients treated with miconazole-zinc oxide-petrolatum had fewer rash sites and lower mean total rash scores than patient receiving zinc oxide-petrolatum alone (P<0.001). By day seven, patients treated with miconazole-zinc oxide-petrolatum had a greater number of mild or no cases of diaper dermatitis compared to the zinc oxide-petrolatum group (94 vs 72%, respectively; P<0.001). For patients with mild diaper dermatitis at baseline, there was a significant difference between treatment groups in mean total rash scores favoring the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zinc oxide-petrolatum base applied to rash at each diaper change and after infant's bath				miconazole-zinc oxide-petrolatum study group (0.78 vs 1.65, respectively; P=0.031) on day seven. For patients with moderate diaper dermatitis at baseline, there was a significant difference between treatment groups in mean total rash scores favoring the miconazole-zinc oxide-petrolatum study group on days three (P=0.006), five (P<0.001), and seven (P<0.001). For patients with severe diaper dermatitis at baseline, there was no significant difference between treatment groups in mean total rash scores due to the limited study size. For patients with Candida-positive rash cultures, there was a significant difference between treatment groups in mean total rash scores favoring the miconazole-zinc oxide-petrolatum study group on days three, five, and seven (P<0.001). In this patient population, microbiologic response was greater in patients treated with miconazole-zinc oxide-petrolatum (P<0.001). Secondary: No serious adverse events were noted with either treatment group.
Spraker et al.[104] (2006) Miconazole 0.25% in zinc oxide-petrolatum ointment applied to rash at each diaper change and after infant's bath vs zinc oxide-petrolatum ointment applied	DB, PC, PG, RCT Patients with diaper dermatitis complicated by candidiasis with a severity score of 3 or higher	N=236 7 days	Primary: Clinical cure, microbiologic cure, overall rate of cure, and diaper dermatitis index score Secondary: Adverse events	Primary: On day 14, patients treated with miconazole-zinc oxide-petrolatum had a higher clinical cure compared to patients treated with zinc oxide/petrolatum (38 vs 11%, respectively; P<0.001). On day 14, patients treated with miconazole-zinc oxide-petrolatum had a higher microbiologic cure compared to patients treated with zinc oxide/petrolatum (50 vs 23%, respectively). On day 14, patients treated with miconazole-zinc oxide-petrolatum had a higher overall rate of cure compared to patients treated with zinc oxide/petrolatum (23 vs 20%, respectively; P=0.005). From days three through 14, patients treated with miconazole-zinc oxide-petrolatum had a lower diaper dermatitis severity index score compared to patients treated with zinc oxide-petrolatum (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to rash at each diaper change and after infant's bath				Secondary: There was no statistical difference in the percentage of patients with adverse events between the study groups (P=0.585).
Hart et al.[105] (1999) Allylamines vs azoles vs ciclopirox vs tolnaftate vs undecenoic acid vs tea tree oil vs placebo	MA Patients with confirmed superficial fungal infection of the skin and toenails	72 trials	Primary: Relative risk of failure to cure for topical antifungal agents Secondary: Not reported	Primary: According to a MA of 17 trials comparing topical azoles to placebo, the pooled relative risk of failure to cure was 0.54 (95% CI, 0.42 to 0.68). According to a MA of 12 trials comparing allylamines to placebo, the pooled relative risk of failure to cure was 0.30 (95% CI, 0.24 to 0.38). According to a MA of 12 trials comparing azoles to allylamines given QD or BID for greater than or equal to four weeks, the pooled risk for failure to cure was 0.88 (95% CI, 0.78 to 0.99) with study results favoring the allylamines. It is important to note that there was a significance difference in both the clinical efficacy of the azoles and duration of use as well as the relative risk estimates reported by English and foreign language papers. No difference was detected between individual azoles and allylamines. According to a MA of three trials comparing tolnaftate to placebo, the pooled risk for failure to cure was 0.46 (95% CI, 0.17 to 1.22). Data showed that tolnaftate was not as effective as haloprogin or clotrimazole. According to a MA of four trials comparing undecenoic acid to placebo or active control, the pooled risk for failure to cure was 0.28 (95% CI, 0.11 to 0.74). In nail trials, ciclopirox was shown to be significantly more effective than placebo with the pooled risk for failure to cure of 0.14 (95% CI, 0.06 to 0.32) and more effective than clotrimazole though not significantly, with the pooled risk for failure to cure of 0.89 (95% CI, 0.72 to 1.10). One trial showed that both clotrimazole solution and tea tree oil achieved a cure rate of 10% after six months. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Crawford et al.[106] (2007) Allylamines vs azoles vs ciclopiroxolamine vs griseofulvin* vs haloprogin* vs tea tree oil vs tolnaftate vs undecenoates vs placebo	MA Patients with fungal infections of the skin and toenails	67 trials Duration varied	Primary: Pooled relative risks of failure to cure for topical antifungal agents Secondary: Not reported	Primary: Among the PC trials, the pooled relative risks of failure to cure for skin infections were as follows for the topical antifungal agents: allylamines 0.33 (95% CI, 0.24 to 0.44), azoles 0.30 (95% CI, 0.20 to 0.45), ciclopiroxolamine 0.27 (95% CI, 0.11 to 0.66), tolnaftate 0.19 (95% CI, 0.08 to 0.44), butenafine 0.33 (95%, CI 0.24 to 0.45), undecenoates 0.29 (95% CI, 0.12 to 0.70). In the MA of 11 trials comparing allylamines and azoles, the pooled relative risks of failure to cure for skin infections was 0.63 (95% CI, 0.42 to 0.94) in favor of allylamines. Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, QHS=at bedtime, QPM=every evening, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, CrI=credible interval, DB=double-blind, DLSO=distal and lateral subungual onychomycosis, HIV=human immunodeficiency virus, ITT=intention-to-treat, LSO=lateral subungual onychomycosis, MA=meta-analysis, MC=multicenter, OL=open-label, OPC=oropharyngeal candidiasis, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, SB=single blinded, SC=single center, SR=systematic review, TCS=total clinical score, TDSS=total dandruff severity score, TOC=test of cure, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Lipsky et al. evaluated the National Ambulatory Medical Care Survey and Bureau of Census data and identified a 15% reduction in physician's office visits for vaginitis care between 1990 and 1994 (P<0.05).[93]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 13. Relative Cost of the Skin and Mucous Membrane Antifungals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Butenafine	cream	Mentax®	$-$$$	N/A
Butoconazole	vaginal cream	Gynazole-1®	$$$	N/A
Ciclopirox	cream, gel, shampoo, solution, suspension	Ciclodan®*, Loprox®*, Penlac®*	$$$-$$$$$	$$$
Clotrimazole	cream, solution, troche	N/A	N/A	$$
Econazole	cream	N/A	N/A	$
Ketoconazole	cream, foam, shampoo	Nizoral®*, Ketodan®*, Extina®*	$$-$$$$$	$
Miconazole	vaginal suppository	N/A	N/A	$
Naftifine	cream, gel	Naftin®	$$$$	N/A
Nystatin	cream, ointment, powder	N/A	N/A	$
Oxiconazole	cream, lotion	Oxistat®	$$$$$	N/A
Sertaconazole	cream	Ertaczo®	$$$$	N/A
Sulconazole	cream, solution	Exelderm®	$$$-$$$$	N/A
Terconazole	vaginal cream,	Terazol 3®*, Terazol 7®*,	$$-$$$	$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	vaginal suppository	Zazole®*		
Combination Products				
Benzoic acid and salicylic acid	ointment	Bensal HP®	$$-$$$$$	N/A
Clotrimazole and betamethasone	cream, lotion	Lotrisone®*	$$-$$$	$$$
Miconazole, zinc oxide, and white petrolatum	ointment	Vusion®	$$$$$	N/A
Nystatin and triamcinolone	cream, ointment	N/A	N/A	$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The skin and mucous membrane antifungals are approved for the treatment of candidiasis, dermatitis, onychomycosis and dermatophyte infections.[1-21] Many of the products are available in a generic formulation.

Clotrimazole troches are approved for the treatment oropharyngeal candidiasis. The Infectious Diseases Society of America guidelines recommend the use of clotrimazole troches or oral nystatin as initial therapy for patients with mild oropharyngeal candidiasis. Oral fluconazole is recommended for patients with moderate to severe disease.[25]

There are several antifungals available that effectively treat vulvovaginal candidiasis and no agent or regimen has been shown to be more effective than another. Patients with uncomplicated vulvovaginal candidiasis can be treated with vaginal antifungals for one to three days (short-course therapy). Patients with complicated vulvovaginal candidiasis require a longer duration of therapy with vaginal antifungals (seven to 14 days) or multiple doses of oral fluconazole. Prolonged maintenance therapy with oral fluconazole is recommended for recurrent vulvovaginal candidiasis; however, the use of intermittent vaginal antifungals is also acceptable. Guidelines do not give preference to one vaginal antifungal agent over another for the treatment of vulvovaginal candidiasis.[25-29] Clinical trials have demonstrated similar efficacy among the imidazole antifungals for the treatment of vulvovaginal candidiasis; however, the imidazoles have been shown to be more effective than nystatin.[26,27,42-53]

Ciclopirox and ketoconazole are approved for the treatment of seborrheic dermatitis. The Finnish Medical Society Duodecim guidelines recommend the use of salicylic acid to soften scales. To decrease fungal growth, the scalp should be treated with ketoconazole shampoo or selenium sulfide shampoo, as well as imidazole creams.[33] Treatment with ciclopirox and ketoconazole significantly improved clinical cure rates compared to placebo.[57-61,63,64]

Miconazole-zinc oxide-white petrolatum is approved for the treatment of diaper dermatitis.[20] It is recommended that the underlying cause of diaper dermatitis be identified and treated. Topical antifungals should be used to treat diaper dermatitis complicated by *Candida albicans*. Injured skin should also be protected with a barrier cream or paste, such as zinc oxide.[107] Studies have demonstrated greater clinical cure rates with miconazole-zinc oxide-white petrolatum than zinc oxide-white petrolatum.[103,104] There were no studies found in the medical literature that directly compared the miconazole-zinc oxide-white petrolatum combination product with the coadministration of miconazole and zinc oxide and white petrolatum as separate formulations.

Ciclopirox 8% solution is approved for the treatment of onychomycosis.[6] Oral antifungals are more effective than topical agents for the treatment of onychomycosis. Topical monotherapy is recommended when the matrix area is not involved. Oral monotherapy or the combination of oral and topical therapy is recommended when at least 50% of the distal nail plate is involved, when the nail matrix area is involved, or if mycological criteria are known.[31] Ciclopirox 8% solution has been shown to improve clinical and mycological cure rates in clinical trials.[54-56] Data from a meta-analysis demonstrated that mycological cure rates ranged from 46.7 to 85.7%, clinical cure rates

ranged from 0 to 56.9%, and clinical response rates ranged from 36.7 to 86.0% when ciclopirox was used in various dosing regimens.[54]

For the treatment of dermatophyte infections, studies have demonstrated similar efficacy among the various topical antifungals.[70,75,79,81,82,84-90,98] A recent mixed-treatment comparison meta-analysis of randomized controlled trials that included patients with dermatophytosis (excluding onychomycosis and tinea capitis) found no significant difference among the antifungals with respect to mycologic cure at the end of treatment. Butenafine, naftifine, and terbinafine were the most effective therapies for maintaining cured status. Since the efficacy difference was not very large between antifungal classes, the authors recommended cost-effectiveness studies to compare the various treatment strategies.[100] Clotrimazole-betamethasone was found to be more effective than monotherapy with clotrimazole or betamethasone.[77,78] There were no studies found in the medical literature that directly compared the clotrimazole-betamethasone combination product with the coadministration of clotrimazole and betamethasone as separate formulations.

There is insufficient evidence to support that one brand skin and mucous membrane antifungal is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antifungals within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antifungal is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Oct 24]. Available from: http://online.factsandcomparisons.com.
2. Lexi-Comp Online [database on the internet], Hudson (OH): Lexi-Comp, Inc.; 2013 [cited 2013 Oct 24]. Available from: http://www.lexi.com.
3. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Oct 24]. Available from: http://www.thomsonhc.com/.
4. Mentax® [package insert on the internet]. Morgantown (WV): Mylan Pharmaceuticals, Inc.; 2009 Feb [cited 2013 Oct 19]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=167ecefd-4553-41b8-8160-81a48dbca076.
5. Gynazole-1® [package insert on the internet]. St. Louis (MO): Ther-Rx Corporation; 2012 Sep [cited 2013 Oct 19]. Available from: http://www.gynazole-1.com/site/pdf/PI.pdf.
6. Ciclodan® [package insert on the internet]. Fairfield (NJ): Medmetriks Pharmaceuticals, Inc; 2011 Jan [cited 2013 Oct 23]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=246676e5-60a0-41dc-b665-30d5e670b426#nlm34067-9.
7. Loprox® cream, Loprox® suspension, and Loprox® gel [package insert on the internet]. Scottsdale (AZ): Medicis, The Dermatology Company; 2013 June [cited 2013 Oct 23]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018748s024,019824s023,020519s016lbl.pdf.
8. Loprox® shampoo [package insert on the internet]. Scottsdale (AZ): Medicis, The Dermatology Company; 2013 May [cited 2013 Oct 23]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021159s020lbl.pdf.
9. Penlac® [package insert on the internet]. Bridgewater (NJ): Dermik Laboratories; 2006 July [cited 2013 Oct 23]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=3f82e6b5-c6b6-4d96-8295-948fec7e7fdb.
10. Nizoral® shampoo [package insert on the internet]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2012 Aug [cited 2013 Oct 23]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=efbc6388-90ce-11de-b92c-8b7156d89593.
11. Naftin® cream [package insert on the internet]. Greensboro (NC): Merz Pharmaceuticals; 2012 Jan [cited 2013 Oct 23]. Available from: http://naftin.com/wp-content/uploads/NAFTIN-Cream-2-PI.pdf.
12. Naftin® gel [package insert on the internet]. Greensboro (NC): Merz Pharmaceuticals; 2013 Jun [cited 2013 Oct 23]. Available from: http://naftin.com/wp-content/uploads/NAFTIN-Gel-2-PI.pdf.
13. Oxistat® cream and Oxistat® lotion [package insert on the internet]. Melville (NY): PharmaDerm; 2012 Jan [cited 2013 Oct 23]. Available from: http://www.oxistat.com/oxistat/pdf/oxistat_combo_pi.pdf.
14. Ertaczo® [package insert on the internet]. Bridgewater (NJ): Valeant Pharmaceuticals North America; 2012 July [cited 2013 Oct 23]. Available from: http://ertaczo.com/Portals/0/pdf/ERT_PI.pdf#zoom=125.
15. Exelderm® solution [package insert on the internet]. Jacksonville (FL): Ranbaxy; 2010 May [cited 2013 Oct 23]. Available from: http://www.exelderm.com/images/ExeldermSolutionPI.pdf.
16. Exelderm® cream [package insert on the internet]. Jacksonville, FL: Ranbaxy; 2010 May [cited 2013 Oct 23]. Available from: http://www.exelderm.com/images/ExeldermCreamPI.pdf.
17. Terazol® cream and suppository [package insert on the internet]. Raritan (NJ): Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2010 July [cited 2013 Oct 23]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=61eab575-94e4-41cb-8045-af73424bb316#nlm34067-9.
18. Bensal HP® [package insert on the internet]. Easley (SC): 7 Oaks Pharmaceutical Corp; 2010 [cited 2013 Oct 24]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=4b8ccee9-0f26-416d-a6e5-1261408df899.
19. Lotrisone® cream and Lotrisone® lotion [package insert on the internet]. Kenilworth (NJ): Schering Corporation; 2009 May [cited 2013 Oct 24]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020010s021lbl.pdf.
20. Vusion® [package insert on the internet]. Research Triangle Park (NC): Stiefel Laboratories, Inc.; 2011 May [cited 2013 Oct 24]. Available from: https://www.gsksource.com/gskprm/htdocs/documents/VUSION-OINTMENT-PI-PIL.PDF.
21. Nystatin and triamcinolone [package insert on the internet]. Brampton (Ontario): Taro Pharmaceuticals Inc.; 2004 Sep [cited 2013 Oct 24]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=2fd97fc5-cae5-43dd-a3c7-c9a03876153e#.

22. Kauffman CA. Overview of candida infections. In: Marr KA (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2013 Nov 28]. Available from: http://www.utdol.com/utd/index.do.
23. Weston WL, Howe W. Overview of dermatitis. In: Dellavalle RP (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Nov 28]. Available from: http://www.utdol.com/utd/index.do.
24. Goldstein AO, Goldstein BG. Dermatophyte (tinea) infections. In: Dellavalle RP, Levy ML, Rosen T (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Nov 28]. Available from: http://www.utdol.com/utd/index.do.
25. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009 Mar 1;48(5):503-35.
26. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep. 2010;59(RR-12):1-110.
27. British Association for Sexual Health and HIV: Clinical Effectiveness Group. United Kingdom National Guideline on the Management of Vulvovaginal Candidiasis [guideline on the internet]. Macclesfield (UK): British Association for Sexual Health and HIV; 2007 [cited 2013 Oct 1]. Available from: http://www.bashh.org/documents/1798.pdf.
28. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: Vaginitis. Obstet Gynecol. 2006 May;107(5):1195-206.
29. European (International Union Against Sexually Transmitted Infections/World Health Organization). Guideline on the Management of Vaginal Discharge [guideline on the internet]. London (UK): European (International Union Against Sexually Transmitted Infections/World Health Organization); 2011 [cited 2013 Oct 1]. Available from: http://www.iusti.org/regions/europe/pdf/2011/Euro_Guidelines_Vaginal_Discharge_2011.Intl_Jrev.pdf.
30. Finnish Medical Society Duodecim. "Seborrheic dermatitis." In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007 Apr 19 [Various].
31. Lecha M, Effendy I, Feuilhade de Chauvin M, Di Chiacchio N, Baran R; Taskforce on Onychomycosis Education. Taskforce on Onychomycosis Education. Treatment options-development of consensus guidelines. J Eur Acad Dermatol Venereol. 2005 Sep;19 Suppl 1:25-33.
32. Roberts DT, Taylor WD, Boyle J, British Association of Dermatologists. Guidelines for treatment of onychomycosis. Br J Dermatol. Br J Dermatol. 2003 Mar;148(3):402-10.
33. Kakourou T, Uksal U, European Society for Pediatric Dermatology. Guidelines for the management of tinea capitis in children. Pediatr Dermatol. 2010 May-Jun;27(3):226-8.
34. Higgins EM, Fuller LC, Smith CH. Guidelines for the management of tinea capitis. British Association of Dermatologists. Br J Dermatol. 2000 Jul;143(1):53-8.
35. Bagatell FK, Bogaert H, Cullen S. Evaluation of a new antifungal cream ciclopirox olamine 1% in the treatment of cutaneous candidiasis. Clin Ther. 1985;8(1):41-8.
36. Rajan VS, Thirumoorthy T. Treatment of cutaneous candidiasis: a double blind parallel group comparison of sulconazole nitrate 1% cream and clotrimazole 1% cream. Australas J Dermatol. 1983 Apr;24(1):33-6.
37. Tanenbaum L, Anderson C, Rosenberg M, Dorr A. A new treatment for cutaneous candidiasis: sulconazole nitrate cream 1%. Int J Dermatol. 1983 Jun;22(5):318-20.
38. Beveridge GW, Fairburn E, Finn OA, Scott OL, Stewart TW, Summerly R. A comparison of nystatin cream with nystatin/triamcinolone acetonide combination cream in the treatment of Candidal inflammation of the flexures. Curr Med Res Opin. 1977;4(8):584-7.
39. Kirkpatrick CH, Alling DW. Treatment of chronic oral candidiasis with clotrimazole troches: a controlled clinical trial. N Engl J Med. 1978 Nov 30;299(22):1201-3.
40. Owens NJ, Nightingale CH, Schweizer RT, Schauer PK, Dekker PT, Quintiliani R. Prophylaxis of oral candidiasis with clotrimazole troches. Arch Intern Med. 1984 Feb;144(2):290-3.
41. Vazquez JA, Patton LL, Epstein JB, Ramlachan P, Mitha I, Noveljic Z, et al. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of miconazole Lauriad® efficacy and safety (SMiLES). HIV Clin Trials. 2010 Jul-Aug;11(4):186-96.
42. Droegemueller W, Adamson DG, Brown D, Cibley L, Fleury F, LePage ME, et al. Three-day treatment with butoconazole nitrate for vulvovaginal candidiasis. Obstet Gynecol. 1984 Oct;64(4):530-4.
43. Hajman AJ. Vulvovaginal candidosis: comparison of 3-day treatment with 2% butoconazole nitrate cream and 6-day treatment with 1% clotrimazole cream. J Int Med Res. 1988 Sep-Oct;16(5):367-75.

44. Brown D, Henzl MR, Kaufman RH. Butoconazole nitrate 2% for vulvovaginal candidiasis: new single-dose vaginal cream formulation vs, seven-day treatment with miconazole nitrate. J Reprod Med. 1999 Nov;44(11):933-8.
45. Kaufman RH, Henzl MR, Brown D Jr, Horner DS, Krauss RH, Mehlisch DR, et al. Comparison of three-day butoconazole treatment with seven-day miconazole treatment for vulvovaginal candidiasis. J Reprod Med. 1989 Jul;34(7):479-83.
46. Jacobson JB, Hajman AJ, Wiese J, Gandrup P, Forsström S. A new vaginal antifungal agent - butoconazole nitrate. Acta Obstet Gynecol Scand. 1985;64(3):241-4.
47. Brown D Jr, Henzl MR, LePage ME, Tsao LL, Izu AE, Walker KA, et al. Butoconazole vaginal cream in the treatment of vulvovaginal candidiasis: comparison with miconazole nitrate and placebo. J Reprod Med. 1986 Nov;31(11):1045-8.
48. Hirsch HA. Clinical evaluation of terconazole. European experience. J Reprod Med. 1989 Aug;34(8 Suppl):593-6.
49. Young GL, Jewell D. Topical treatment of vaginal candidiasis (thrush) in pregnancy. Cochrane Database Syst Rev. 2001;(4):CD000225.
50. Thomason JL, Gelbart SM, Kellett AV, Scaglione NJ, Gotwalt KT, Broekhuizen FF. Terconazole for the treatment of vulvovaginal candidiasis. J Reprod Med. 1990 Nov;35(11):992-4.
51. Corson SL, Kapikian RR, Nehring R. Terconazole and miconazole cream for treating vulvovaginal candidiasis: a comparison. J Reprod Med. 1991 Aug;36(8):561-7.
52. Thomason JL. Clinical evaluation of terconazole. United States experience. J Reprod Med. 1989 Aug;34(8 Suppl):597-601.
53. Martins HP, da Silva MC, Paiva LC, Svidzinski TI, Consolaro ME. Efficacy of fluconazole and nystatin in the treatment of vaginal Candida species. Acta Derm Venereol. 2012 Jan;92(1):78-82.
54. Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer solution 8% in the treatment of toenail onychomycosis. J Am Acad Dermatol. 2000 Oct;43(4 Suppl):S70-80.
55. Brenner MA, Harkless LB, Mendicino RW, Page JC. Ciclopirox 8% nail lacquer topical solution for the treatment of onychomycosis in patients with diabetes: a multicenter, open-label study. J Am Podiatr Med Assoc. 2007 May-Jun;97(3):195-202.
56. Shemer A, Nathansohn N, Trau H, Amichai B, Grunwald MH. Ciclopirox nail lacquer for the treatment of onychomycosis: an open non-comparative study. J Dermatol. 2010 Feb;37(2):137-9.
57. Aly R, Katz HI, Kempers SE, Lookingbill DP, Lowe N, Menter A, et al. Ciclopirox for seborrheic dermatitis of the scalp. Int J Dermatol. 2003 Sep;42 Suppl 1:19-22.
58. Vardy DA, Zvulunov A, Tchetov T, Biton A, Rosenman D. A double-blind, placebo-controlled trial of a ciclopirox olamine 1% shampoo for the treatment of scalp seborrheic dermatitis. J Dermatol. Treat. 2000;11(2):73-7.
59. Lebwohl M, Plott T. Safety and efficacy of ciclopirox 1% shampoo for the treatment of seborrheic dermatitis of the scalp in the US population: results of a double-blind, vehicle-controlled trial. Int J Dermatol. 2004 Jul;43 Suppl 1:17-20.
60. Shuster S, Meynadier J, Kerl H, Nolting S. Treatment and prophylaxis of seborrheic dermatitis of the scalp with antipityrosporal 1% ciclopirox shampoo. Arch Dermatol. 2005 Jan;141(1):47-52.
61. Green, CA, Farr PM, Shuster S. Treatment of seborrheic dermatitis with ketoconazole: II. Response to seborrheic dermatitis of the face, scalp and trunk to topical ketoconazole. Br J Dermatol. 1987 Feb;116(2):217-21.
62. Piérard-Franchimont C, Piérard GE, Arrese JE, De Doncker P. Effect of ketoconazole 1% and 2% shampoos in severe dandruff and seborrheic dermatitis: clinical, squamometric and mycological assessments. Dermatology. 2001;202(2):171-6.
63. Carr MM, Pryce DM, Ive FA. Treatment of seborrheic dermatitis with ketoconazole: I. response of seborrheic dermatitis of the scalp to topical ketoconazole. Br J Dermatol. 1987 Feb;116(2):213-6.
64. Ratnavel RC, Squire RA, Boorman GC. Clinical efficacies of shampoos containing ciclopirox olamine (1.5%) and ketoconazole (2.0%) in the treatment of seborrheic dermatitis. J Dermatolog Treat. 2007;18(2):88-96.
65. Squire RA, Goode K. A randomized, single-blind, single-center clinical trial to evaluate comparative clinical efficacy of shampoos containing ciclopirox olamine (1.5%) and salicylic acid (3%), or ketoconazole (2%, Nizoral) for the treatment of dandruff/seborrheic dermatitis. J Dermatolog Treat. 2002 Jun;13(2):51-60.
66. Koc E, Arca E, Kose O, Akar A. An open, randomized, prospective, comparative study of topical pimecrolimus 1% cream and topical ketoconazole 2% cream in the treatment of seborrheic dermatitis. J Dermatolog Treat. 2009;20(1):4-9.

67. Piérard-Franchimont C, Goffin V, Decroix J, Piérard GE. A multicenter, randomized trial of ketoconazole 2% and zinc pyrithione 1% shampoos in severe dandruff and seborrheic dermatitis. Skin Pharmacol Appl Skin Physiol. 2002 Nov-Dec;15(6):434-41.
68. Reyes BA, Beutner KR, Cullen S, et al. Butenafine, a fungicidal benzylamine derivative, used once daily for the treatment of interdigital tinea pedis. Int J Dermatol. 1998 Jun;37(6):450-3.
69. Tschen E, Elewski B, Gorsulowsky DC, Pariser DM. Treatment of interdigital tinea pedis with a four-week once- daily regimen of butenafine hydrochloride 1 % cream. J Am Acad Dermatol. 1997 Feb;36(2 Pt 1):S9-14.
70. Singal A, Pandhi D, Agrawal S, Das S. Comparative efficacy of topical 1% butenafine and 1% clotrimazole in tinea cruris and tinea corporis: a randomized, double-blind trial. J Dermatolog Treat. 2005;16(5-6):331-5.
71. Aly R, Fisher G, Katz I, Levine N, Lookingbill DP, Lowe N, et al. Ciclopirox gel in the treatment of patients with interdigital tinea pedis. Int J Dermatol. 2003 Sep;42 Suppl 1:29-35.
72. Gupta AK, Skinner AR, Cooper EA. Evaluation of the efficacy of ciclopirox 0.77% gel in the treatment of tinea pedis interdigitalis (dermophytosis complex) in a randomized, double-blind placebo-controlled trial. Int J Dermatol. 2005 Jul;44(7):590-3.
73. Aly R, Maibach HI, Bagatell FK, Dittmar W, Hänel H, Falanga V, et al. Ciclopirox olamine lotion 1%: bioequivalence to ciclopirox olamine cream 1 % and clinical efficacy in tinea pedis. Clin Ther. 1989 May-Jun;11(3):290-303.
74. Wu YC, Chuan MT, Lu YC. Efficacy of ciclopiroxolamine 1% cream in onychomycosis and tinea pedis. Mycoses. 1991 Jan-Feb;34(1-2):93-5.
75. Bogaert H, Cordero C, Ollague W, Savin RC, Shalita AR, Zaias N. Multicentre double-blind trial of ciclopirox olamine cream 1% in the treatment of tinea corporis and tinea cruris. J Int Med Res. 1986;14(4):210-6.
76. Chen C, Koch LH, Dice JE, Dempsey KK, Moskowitz AB, Barnes-Eley ML, et al. A randomized, double-blind study comparing the efficacy of selenium sulfide shampoo 1% and ciclopirox shampoo 1% as adjunctive treatments for tinea capitis in children. Pediatr Dermatol. 2010 Sep-Oct;27(5):459-62.
77. Wortzel MH. A double-blind study comparing the superiority of a combination antifungal (clotrimazole)/steroidal (betamethasone dipropionate) product. Cutis. 1982 Aug;30(2):258-61.
78. Katz HI, Bard J, Cole GW, Fischer S, McCormick GE, Medansky RS, et al. SCH 370 (Clotrimazole-betamethasone dipropionate) cream in patients with tinea cruris or tinea corporis. Cutis. 1984 Aug;34(2):183-8.
79. Kamalam A, Thambiah AS. Clotrimazole and econazole in dermatophytoses (a double blind study). Mykosen. 1980 Dec;23(12):707-10.
80. Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole vs topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. J Dermatol. 2010 Aug;37(8):699-702.
81. Sivayathorn A, Piamphongsant. Topical antimycotic agents for the treatment of superficial dermatophytoses in Thailand – a double-blind study. Mykosen. 1979 Jan;22(1):21-4.
82. Clayton YM, Connor BL. Comparison of clotrimazole cream, Whitfield's ointment and Nystatin ointment for the topical treatment of ringworm infections, pityriasis versicolor, erythrasma and candidiasis. Br J Dermatol. 1973 Sep;89(3):297-303.
83. Lassus A, Forstrom S, Salo O. A double-blind comparison of sulconazole nitrate 1 % cream with clotrimazole 1 % cream in the treatment of dermatophytoses. Br J Dermatol. 1983 Feb;108(2):195-8.
84. Tanenbaum L, Taplin D, Lavelle C, Akers WA, Rosenberg MJ, Carmargo G. Sulconazole nitrate cream 1 percent for treating tinea cruris and corporis. Cutis. 1989 Oct;44(4):344-7.
85. Tham SN. Treatment of pityriasis versicolor: comparison of sulconazole nitrate 1% solution and clotrimazole 1% solution. Australas J Dermatol. 1987 Dec;28(3):123-5.
86. Patel A, Brookman SD, Bullen MU, Marley J, Ellis DH, Williams T, et al. Topical treatment of interdigital tinea pedis: terbinafine compared to clotrimazole. Australas J Dermatol. 1999 Nov;40(4):197-200.
87. Lassus A, Forsström S. Double-blind parallel study comparing sulconazole with econazole in the treatment of dermatophytoses. Mykosen. 1984 Dec;27(12):592,595-8.
88. Bonifaz A, Saul A. Comparative study between terbinafine 1% emulsion-gel vs ketoconazole 2% cream in tinea cruris and tinea corporis. Eur J Dermatol. 2000 Mar;10(2):107-9.
89. Tanenbaum L, Anderson C, Rosenberg MJ, Howard W, McDaniel W, Neimanis A, et al. Sulconazole nitrate 1.0 percent cream: a comparison with miconazole in the treatment of tinea pedis and tinea cruris/corporis. Cutis. 1982 Jul;30(1):105-7,115,118.

90. Tanenbaum L, Anderson C, Rosenberg MJ, Akers W. 1% sulconazole cream v 2% miconazole cream in the treatment of tinea versicolor: a double blind, multicenter study. Arch Dermatol. 1984 Feb;120(2):216-9.
91. Jordon RE, Rapini RP, Rex IH Jr, Katz HI, Hickman JG, Bard JW, et al. Once-daily naftifine cream 1 % in the treatment of tinea cruris and tinea corporis. Int J Dermatol. 1990 Jul-Aug;29(6):441-2.
92. Parish LC, Parish JL, Routh HB, Avakian E, Olayinka B, Pappert EJ, et al. A double-blind, randomized, vehicle-controlled study evaluating the efficacy and safety of naftifine 2% cream in tinea cruris. J Drugs Dermatol. 2011 Oct;10(10):1142-7.
93. Parish LC, Parish JL, Routh HB, Fleischer AB Jr, Avakian EV, Plaum S, et al. A randomized, double-blind, vehicle-controlled efficacy and safety study of naftifine 2% cream in the treatment of tinea pedis. J Drugs Dermatol. 2011 Nov;10(11):1282-8.
94. Ramelet AA, Walker-Nasir E. One daily application of oxiconazole cream is sufficient for treating dermatomycoses. Dermatologica. 1987;175(6):293-5.
95. Pariser DM, Pariser RJ. Oxiconazole nitrate lotion, 1 percent: an effective treatment for tinea pedis. Cutis. 1994 Jul;54(1):43-4.
96. Van Esso D, Fajo G, Losada I, Vilallonga M, Casanovas JM, Clanxet J, et al. Sertaconazole in the treatment of pediatric patients with cutaneous dermatophyte infections. Clin Ther. 1995 Mar-Apr;17(2):264-9.
97. Sharma A, Saple DG, Surjushe A, Rao GR, Kura M, Ghosh S, et al. Efficacy and tolerability of sertaconazole nitrate 2% cream vs miconazole in patients with cutaneous dermatophytosis. Mycoses. 2011 May;54(3):217-22.
98. Ghaninejad H, Gholami K, Hashemi P, Hajibabai M, Rahbar Z, Farivar MS, et al. Sertaconazole 2% cream vs miconazole 2% cream for cutaneous mycoses: a double-blind clinical trial. Clin Exp Dermatol. 2009 Dec;34(8):e837-9.
99. Borelli C, Korting HC, Bödeker RH, Neumeister C. Safety and efficacy of sertaconazole nitrate cream 2% in the treatment of tinea pedis interdigitalis: a subgroup analysis. Cutis. 2010 Feb;85(2):107-11.
100. Rotta I, Ziegelmann PK, Otuki MF, Riveros BS, Bernardo NL, Correr CJ. Efficacy of topical antifungals in the treatment of dermatophytosis: a mixed-treatment comparison meta-analysis involving 14 treatments. JAMA Dermatol. 2013 Mar;149(3):341-9.
101. Rotta I, Sanchez A, Gonçalves PR, Otuki MF, Correr CJ. Efficacy and safety of topical antifungals in the treatment of dermatomycosis: a systematic review. Br J Dermatol. 2012 May;166(5):927-33.
102. Grigoriu D, Grigoriu A. Double-blind comparison of the efficacy, toleration, and safety of tioconazole base 1% and econazole nitrate 1% cream in the treatment of patients with fungal infections of the skin or erythrasma. Dermatologica. 1983;166 (Suppl 1):8-13.
103. Concannon P, Gisoldi E, Phillips S, Grossman R. Diaper dermatitis: a therapeutic dilemma. Results of a double-blind placebo controlled trial of miconazole nitrate 0.25%. Pediatr Dermatol. 2001 Mar-Apr;18(2):149-55.
104. Spraker MK, Gisoldi EM, Siegfried EC, Fling JA, de Espinosa ZD, Quiring JN, et al. Topical miconazole nitrate ointment in the treatment of diaper dermatitis complicated by candidiasis. Cutis. 2006 Feb;77(2):113-20.
105. Hart R, Bell-Syer SE, Crawford F, Torgerson DJ, Young P, Russell I. Systematic review of topical treatments for fungal infections of the skin and nails of the feet. BMJ. 1999 Jul 10;319(7202):79-82.
106. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001434.
107. Horri KA, Prossick TA. Overview of diaper dermatitis in infants and children. In: Levy ML, Drutz JE (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Nov 28]. Available from: http://www.utdol.com/utd/index.do.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Scabicides and Pediculicides
AHFS Class 840412
February 12, 2014

I. Overview

The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-9] Pediculosis is a transmissible infection, which is caused by three different kinds of lice depending on the location: head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*) and pubic region (*Phthirus pubis*). Pediculosis is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[10] Scabies is also a transmissible skin infection caused by the mite *Sarcoptes scabiei.* Mites burrow into the skin and lay eggs, which when hatched, will crawl to the skin's surface and begin to make new burrows. The most common clinical manifestation of scabies is itching, which is due to a hypersensitivity reaction to the mite or mite excrement.[11]

When treating scabies and lice, the goal of therapy is to eradicate the parasite. Benzyl alcohol inhibits lice from closing their respiratory spiracles, which causes the lice to asphyxiate.[3] Crotamiton has scabicidal and antipruritic actions; however, the exact mechanism of action is unknown.[4] Lindane is a central nervous system stimulant, which causes convulsions and death of the arthropod.[1,2] Malathion is an organophosphate agent, which inhibits cholinesterase activity.[5] Permethrin disrupts the sodium channel current, which leads to delayed repolarization and paralysis of the arthropod.[1,2] Spinosad causes neuronal excitation, which leads to paralysis and death.[6] The suspension also contains an unspecified amount of benzyl alcohol. Retreatment with benzyl alcohol and permethrin is required after seven to 10 days to eradicate the infestation. The newest agent in the class ivermectin, is pediculicidal but not ovicidal and it is approved as a single application product only.[7]

The skin and mucous membrane scabicides and pediculicides that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. All of the products are available in a generic formulation, with the exception of benzyl alcohol, crotamiton and ivermectin. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Scabicides and Pediculicides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Benzyl alcohol	lotion	Ulesfia®	none
Crotamiton	cream, lotion	Eurax®	none
Ivermectin	lotion	Sklice®	none
Lindane	lotion, shampoo	N/A	none†
Malathion	lotion	Ovide®*	malathion
Permethrin	cream	Elimite®*	permethrin
Spinosad	suspension	Natroba®*	spinosad

*Generic is available in at least one dosage form or strength.
†Generic lindane requires prior authorization.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane scabicides and pediculicides are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Scabicides and Pediculicides

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics: **Clinical Report - Head**	Treatment • Therapy could be initiated with permethrin 1% or pyrethrins when resistance to these products is not suspected. These agents are available over-the-counter

Clinical Guideline	Recommendation(s)
Lice[12] **(2010)**	without a prescription. • Malathion 0.5% can be used in people who are ≥24 months of age when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. • Other treatments can be considered for people who cannot afford or who wish to avoid pediculicides. Improper application of the pediculicide should be considered first as a cause of treatment failure. • Permethrin is the most studied pediculicide in the United States and is the least toxic to humans. Permethrin is less allergenic than pyrethrins and does not cause allergic reactions in individuals with plant allergies. Permethrin leaves a residue on the hair that kills nymphs emerging from the 20 to 30% of eggs not killed by the first application. However, conditioners and silicone-based additives present in almost all currently available shampoos impair permethrin adherence to the hair shaft and reduce its residual effect. Application should be repeated in seven to 10 days if live lice are seen. Many experts now recommend routine retreatment, preferably on day nine. An alternate treatment schedule on days zero, seven, and 13 to 15 has been proposed for nonovicidal products. • Resistance to 1% permethrin has been reported, but the prevalence of this resistance is not known. • Pyrethrins are formulated with piperonyl butoxide. Pyrethrins are neurotoxic to lice but have extremely low mammalian toxicity. Pyrethrins are applied to dry hair and left on for 10 minutes before rinsing out. No residual pediculicidal activity remains after rinsing. In addition, none of these natural pyrethrins are totally ovicidal and 20 to 30% of the eggs remain viable after treatment, requiring a second treatment. New evidence based on the life cycle of lice suggests that retreatment at day nine is optimal. An alternate schedule of three treatments with nonovicidal products on days zero, seven, and 13 to 15 has been proposed. • Malathion is a prescription lotion that is applied to dry hair, left to air dry, then washed off after eight to 12 hours. The current United States formulation of malathion differs from the malathion products available in Europe in that it contains terpineol, dipentene, and pine needle oil, which themselves have pediculicidal properties and may delay development of resistance. Malathion has high ovicidal activity, and a single application is adequate for most patients. The product should be reapplied in seven to nine days if live lice are still seen. Due to the high alcohol concentration of the product it is highly flammable. • Benzyl alcohol 5% kills head lice by asphyxiation. Benzyl alcohol is available by prescription and is not ovicidal. It should be applied topically for 10 minutes and repeated in seven days, although as with other nonovicidal products, consideration should be given to retreating in nine days or using three treatment cycles. • Lindane is an organochloride that has central nervous system toxicity in humans. It has low ovicidal activity (30 to 50% of eggs are not killed), and resistance has been reported worldwide for many years. For these reasons, it should be used cautiously. The Food and Drug Administration (FDA) has warned that lindane shampoo should only be used for patients who cannot tolerate or whose infestation has failed to respond to first-line treatment with safer medications for the treatment of head lice.
Sanford Guide to Antimicrobial Therapy[13] **(2011)**	Lice (head/pubic) • Primary: Permethrin 1% lotion applied for 10 minutes and repeated in nine to 10 days or malathion 0.5% lotion applied for eight to 12 hours and repeated in seven to nine days. • Alternative: Ivermectin 200 µg/kg orally once repeated in two weeks. • Due to potential neurotoxicity and risk of aplastic anemia, lindane is not recommended.

Clinical Guideline	Recommendation(s)
	Scabies • Primary: Permethrin 5% cream. Apply to entire skin from chin down to and including toes. Leave on eight to 14 hours. Repeat if itching persists for more than two to four weeks after treatment or new pustules occur. • Alternative: Ivermectin 200 µg/kg orally for dose and permethrin (as above). • Less effective: Crotamiton 10% cream, applied for 24 hours, rinsed off, then reapplied for 24 hours.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines[14] (2010)**	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir 200 mg orally five times daily for seven to 10 days, famciclovir 250 mg orally three times daily for seven to 10 days or valacyclovir 1,000 mg orally twice daily for seven to 10 days. Treatment can be extended if healing is incomplete after 10 days of therapy. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • The safety and efficacy of suppressive therapy have been documented among patients receiving daily therapy with acyclovir for as long as six years and with famciclovir or valacyclovir for one year. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy. • Recommended regimens for suppressive therapy of genital herpes include acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily, valacyclovir 500 mg orally once daily or valacyclovir 1,000 mg orally once daily. • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are

Clinical Guideline	Recommendation(s)

	important to consider when deciding on prolonged treatment.
	• Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms being.
	• Recommended regimens for episodic treatment of genital herpes include acyclovir 400 mg orally three times daily for five days, acyclovir 800 mg orally twice daily for five days, acyclovir 800 mg orally three times daily for two days, famciclovir 125 mg orally twice daily for five days, famciclovir 1,000 mg orally twice daily for one day, famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days, valacyclovir 500 mg orally twice daily for three days or valacyclovir 1,000 mg orally once daily for five days.
	• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.
	• The sex partners of patients who have genital herpes can benefit from evaluation and counseling.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with human immunodeficiency virus (HIV) include acyclovir 400 to 800 mg orally twice daily, famciclovir 500 mg orally twice daily or valacyclovir 500 mg orally twice daily.
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV include acyclovir 400 mg orally three times daily for five to 10 days, famciclovir 500 mg orally twice daily for five to 10 days or valacyclovir 1,000 mg orally twice daily for five to 10 days.
	• The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established.
	• Infants exposed to HSV during birth should be followed carefully in consultation with a pediatric infectious disease specialist.
	
	<u>Pediculosis pubis (pubic lice infestation)</u>
	• Recommended regimens:
	  ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  ○ Ivermectin 250 µg/kg orally and repeated in two weeks.
	
	<u>Scabies</u>
	• Recommended regimens:
	  ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  ○ Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Alternative regimens:
	  ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	
	<u>Bacterial vaginosis</u>
	• Recommended regimens for nonpregnant women include:
	  ○ Metronidazole 500 mg orally twice a day for seven days.

Clinical Guideline	Recommendation(s)
	○ Metronidazole 0.75% gel 5 g intravaginally for five days. ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens for nonpregnant women include: ○ Tinidazole 2 g orally once daily for two days. ○ Tinidazole 1 g orally once daily for five days. ○ Clindamycin 300 mg orally twice daily for seven days. ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days. • Additional regimens include metronidazole (750 mg extended-release tablets once daily for seven days), or a single dose of clindamycin intravaginal cream, although data on these alternative regimens are limited. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • The topically applied azole drugs are more effective than nystatin. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: ○ Butoconazole 2% cream 5 g intravaginally for three days. ○ Butoconazole 2% cream 5 g single intravaginal application. ○ Clotrimazole 1% cream 5 g intravaginally for seven to 14 days. ○ Clotrimazole 2% cream 5 g intravaginally for three days. Miconazole 2% cream 5 g intravaginally for seven days. ○ Miconazole 4% cream 5 g intravaginally for three days. ○ Miconazole 100 mg vaginal suppository for seven days. ○ Miconazole 200 mg vaginal suppository for three days. ○ Miconazole 1,200 mg vaginal suppository, for one day. ○ Nystatin 100,000-unit vaginal tablet, one tablet for 14 days. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally for seven days. ○ Terconazole 0.8% cream 5 g intravaginally for three days. ○ Terconazole 80 mg vaginal suppository for three days. ○ Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent (four or more episodes in one year) or severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with uncontrolled diabetes, debilitation or immunosuppression. • Treatment: Each individual episode of recurrent vulvovaginal candidiasis caused by *Candida albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Maintenance regimens: Oral fluconazole weekly for six months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.

Clinical Guideline	Recommendation(s)

	<u>Severe vulvovaginal candidiasis</u>
	• Severe vulvovaginitis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	<u>Non-albicans vulvovaginal candidiasis</u>
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. Options include longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for two weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.
	
	<u>Genital warts</u>
	• Treatment of genital warts should be guided by the preference of the patient, the available resources, and the experience of the health-care provider.
	• No definitive evidence suggests that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that influence selection of treatment include wart size, wart number, location of the wart, wart morphology, patient preference, convenience, adverse effects, and provider experience.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens (patient-applied):
	  o Podofilox 0.5% solution or gel.
	  o Imiquimod 5% cream.
	  o Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  o Cryotherapy with liquid nitrogen or cryoprobe.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  o Surgical removal
	• Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.
	
	<u>Cervical warts</u>
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.

Clinical Guideline	Recommendation(s)

	Vaginal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90%.
	
	Urethral meatus warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	
	Anal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  ○ Surgical removal.

Centers for Disease Control and Prevention: **Treatment of Head Lice**[15] **(2013)**	• Treatment for head lice is recommended for persons diagnosed with an active infestation. All household members and other close contacts should be checked; those persons with evidence of an active infestation should be treated.
	• Some experts believe prophylactic treatment is prudent for persons who share the same bed with actively-infested individuals. All infested persons (household members and close contacts) and their bedmates should be treated at the same time.
	• Retreatment of head lice usually is recommended because no approved pediculicide is completely ovicidal. To be most effective, retreatment should occur after all eggs have hatched and before new eggs are produced. The retreatment schedule can vary depending on whether the pediculicide used is ovicidal.
	  ○ When treating head lice, non-pharmacologic measures can be combined with recommended medicine; however, such measures generally are not required to eliminate a head lice infestation.
	
	Over-the-counter medications
	  ○ Pyrethrin or permethrin-containing products are approved by the FDA for the treatment of head lice and are available over-the-counter.
	  ○ Pyrethrins only kill live lice, not unhatched eggs (nits). A second treatment is recommended on day nine to kill newly hatched lice before they produce new eggs.
	  ○ Permethrin is a synthetic pyrethroid similar to naturally occurring pyrethrins. Permethrin kills live lice but not unhatched eggs. Permethrin may continue to kill newly hatched lice for several days after treatment. A second treatment often is necessary on day nine to kill newly hatched lice before they produce new eggs.
	
	Prescription medications
	• Malathion is pediculicidal and partially ovicidal. A second treatment is recommended if live lice still are present seven to nine days after treatment.
	• Benzyl alcohol lotion 5% kills live lice but does not kill unhatched lice eggs. A second treatment is required nine days after the first treatment to kill any newly hatched lice before they can produce new eggs.
	• Ivermectin is not ovicidal, but appears to prevent nymphs (newly hatched lice) from surviving. It is effective when given as a single application on dry hair without nit combing. Retreatment should not occur before discussions with the health care provider.
	• Spinosad kills live lice and unhatched eggs and as a result, retreatment is usually not needed and nit combing is not required. Treatment should not be

Clinical Guideline	Recommendation(s)
	repeated if live (crawling) lice are seen seven days after the first treatment. • For second-line treatment only: Lindane is an organochloride. The American Academy of Pediatrics no longer recommends using this agent for the treatment of lice. Incorrect use of lindane can be neurotoxic; its use should be restricted to patients for whom prior treatments have failed or who cannot tolerate safer medications. Lindane should not be used to treat premature infants, persons with human immunodeficiency virus, a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. Retreatment with lindane should be avoided.
Centers for Disease Control and Prevention: **Treatment of Scabies[16] (2013)**	Suggested general guidelines • Lotion or cream should be applied to all areas of the body from the neck down to the feet and toes. When treating infants and young children, scabicide lotion or cream also should be applied to their entire head and neck because scabies can affect their face, scalp, and neck, as well as the rest of their body. The lotion or cream should be applied to a clean body and left on for the recommended time before washing it off. Clean clothing should be worn after treatment. Medications • Permethrin is the drug of choice for the treatment of scabies and is approved in persons at least two months of age. Permethrin kills scabies mite and eggs. Two (or more) applications may be necessary to eliminate all mites, particularly when treating crusted (Norwegian) scabies. • Crotamiton is approved for the treatment of scabies in adults. Crotamiton is not approved for use in children. This agent is frequently associated with treatment failure. • Lindane is not recommended as a first-line therapy. Incorrect use of lindane can be toxic to the brain and other parts of the nervous system; its use should be restricted to patients who have failed recommended therapies or who cannot tolerate recommended treatments. Lindane should not be used to treat premature infants, persons with a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. • Oral ivermectin may be safe and effective for the treatment of scabies; however, ivermectin is not approved for this use. Oral ivermectin has been reported effective in the treatment of crusted scabies; its use should be considered for patients who have failed treatment with or who cannot tolerate topical medications for the treatment of scabies. The dosage of ivermectin is 200 µg/kg orally. Two or more doses at least seven days apart may be necessary to eliminate a scabies infestation. The safety of ivermectin in children weighing less than 15 kg and in pregnant women has not been established.
Centers for Disease Control and Prevention: **Treatment of Pubic Lice[17] (2013)**	Medications • A lice-killing lotion containing 1% permethrin or a mousse containing pyrethrins and piperonyl butoxide can be used to treat pubic lice. These products are available over-the-counter without a prescription and are safe and effective when used according to instructions on the package. • Lindane shampoo is a prescription medication that can kill lice and lice eggs. However, lindane is not recommended as a first-line therapy. Lindane can be toxic to the brain and other parts of the nervous system; its use should be restricted to patients who have failed treatment with recommended therapies. Lindane should not be used to treat premature infants, persons with a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. • Malathion lotion is a prescription medication that can kill lice and some lice

Clinical Guideline	Recommendation(s)
	eggs but has not been approved by the FDA for this indication. • Oral ivermectin has been used successfully to treat lice; but only has not been approved by FDA for treatment of lice. Of note, in 2012, a topical formulation of ivermectin was approved for the treatment of head lice infestations.
British Association of Sexual Health and Human Immunodeficiency Virus: **United Kingdom National Guideline on the Management of *Phthirus pubis* Infestation[18] (2007)**	General considerations • A number of treatments are available. The recommendation of some agents is based on successful results when treating head lice; there is no evidence to give an efficacy rate for public lice. • Lotions are likely to be more effective than shampoos, and should be applied to all body hair including the beard and moustache if necessary. • A second application after three to seven days is advised. Recommended regimens • Malathion 0.5%: Apply to dry hair and wash out after at least two, and preferably, 12 hours (overnight). • Permethrin 1% cream rinse: Apply to damp hair and wash out after 10 minutes. • Infestation of eyelashes can be treated with permethrin 1% lotion, keeping the eyes closed during the 10 minute application.
British Association of Sexual Health and Human Immunodeficiency Virus: **United Kingdom National Guideline on the Management of Scabies Infestation[19] (2007)**	• The recommended treatment regimens include permethrin 5% cream or malathion 0.5% lotion. • Crotamiton is ineffective compared to the recommended options. • Itch may persist for several weeks. Application of crotamiton cream may give symptomatic relief, and antihistamines may also be helpful.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane scabicides and pediculicides are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Scabicides and Pediculicides[1-9]

Indication	Benzyl Alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad
Lice							
Treatment of head lice infestation	✔		✔			✔ †	✔
Treatment of patients infected with head lice and their ova of the scalp hair					✔		
Treatment of infestations of head lice, crab lice, and their eggs only in patients who cannot tolerate other approved therapies, or have failed treatment with other approved therapies				✔ ‡			
Scabies							
Treatment of infestations of scabies						✔ §	
Treatment of infestations of scabies and for symptomatic treatment of pruritic skin		✔					
Treatment of infestations of scabies only in patients who cannot tolerate other approved therapies, or have failed treatment with other approved therapies				✔ *			

*Lotion formulation.
†Liquid formulation.
‡Shampoo formulation.
§Cream formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane scabicides and pediculicides are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Scabicides and Pediculicides[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Benzyl alcohol	Not reported	Not reported	Not reported	Not reported	Not reported
Crotamiton	Not reported	Not reported	Not reported	Not reported	Not reported
Ivermectin	Not reported	Not reported	Not reported	Not reported	Not reported
Lindane	10	Not reported	Not reported	Not reported	18
Malathion	<10	Not reported	Not reported	Not reported	Not reported
Permethrin	<2	Not reported	Not reported	Not reported	Not reported
Spinosad	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

There are no significant drug interactions with the scabicides and pediculicides.[1-9] Lindane should be used with caution with any drug that is known to lower the seizure threshold. These include antipsychotics, antidepressants, theophylline, cyclosporine, mycophenolate, tacrolimus, penicillins, imipenem, fluoroquinolones, chloroquine, isoniazid, meperidine, radiographic contrast media, centrally active anticholinesterases and methocarbamol.[8]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane scabicides and pediculicides are listed in Table 5. The boxed warning for lindane is listed in Table 6. Malathion is an organophosphate agent. Inadvertent transdermal absorption has occurred from agricultural use. Acute toxicity was manifested by excessive cholinergic activity (i.e., increased sweating, salivary and gastric secretion, gastrointestinal and uterine motility, and bradycardia).[5]

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Scabicides and Pediculicides[1-9]

Adverse Events	Benzyl Alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad
Central Nervous System							
Ataxia	-	-	-	✔	-	-	-
Dizziness	-	-	-	✔	-	-	-
Headache	-	-	-	✔	-	-	-
Pain	-	-	-	✔	-	-	-
Restlessness	-	-	-	✔	-	-	-
Seizures	-	-	-	✔	-	-	-
Dermatological							
Allergic sensitivity reaction	-	✔	-	-	-	-	-
Alopecia	-	-	-	✔	-	-	0.1 to 1
Application site anesthesia	2	-	-	-	-	-	-
Application site hypoesthesia	2	-	-	-	-	-	-
Dandruff	<1	-	-	-	-	-	-
Dermatitis	<1	✔	<1	✔	-	-	-
Dryness	<1	-	<1	-	-	-	0.1 to 1
Erythema	10	-	-	-	-	1 to 10	3
Excoriation	<1	-	-	-	-	-	-
Exfoliation	<1	-	-	-	-	-	0.1 to 1
Irritation	2	✔	-	-	✔	-	1
Mild transient burning/stinging	-	-	<1	✔	-	1 to 10	-
Numbness	-	-	-	-	-	1 to 10	-
Pruritus	12	✔	-	✔	-	1 to 10	-
Rash	<1	✔	-	-	-	1 to 10	-
Thermal burn	<1	-	-	-	-	-	-
Urticaria	-	-	-	✔	-	-	-
Warm sensation	-	✔	-	-	-	-	-
Gastrointestinal							
Nausea	-	-	-	✔	-	-	-
Vomiting	-	-	-	✔	-	-	-
Other							
Aplastic anemia	-	-	-	✔	-	-	-

Adverse Events	Benzyl Alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad
Cardiac arrhythmia	-	-	-	✔	-	-	-
Conjunctivitis (if eye contact)	-	-	<1	-	✔	-	-
Edema	-	-	-	-	-	1 to 10	-
Hematuria	-	-	-	✔	-	-	-
Hepatitis	-	-	-	✔	-	-	-
Ocular edema	-	-	-	-	-	-	2
Ocular irritation/hyperemia	6	-	<1	-	-	-	2
Pain	1	-	-	-	-	-	-
Paresthesia	<1	-	-	✔	-	-	-
Pulmonary edema	-	-	-	✔	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6. Boxed Warning for Lindane[8]

WARNING
Only use lindane in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of scabies. **Neurologic toxicity:** Seizures and deaths have been reported following lindane use with repeat or prolonged application, but also in rare cases following a single application used according to directions. Exercise caution when using lindane in infants, children, the elderly, and individuals with other skin conditions (e.g., atopic dermatitis, psoriasis) and in those who weigh less than 110 lbs (50 kg) as they may be at risk of serious neurotoxicity. **Contraindications:** Lindane is contraindicated in premature infants and individuals with known uncontrolled seizure disorders. **Proper use:** Instruct patients on the proper use of lindane, the amount to apply, how long to leave it on, and avoiding retreatment. Inform patients that itching occurs after the successful killing of scabies and is not necessarily an indication for retreatment with lindane.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane scabicides and pediculicides are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Scabicides and Pediculicides[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Benzyl alcohol	Head lice: Lotion: apply to dry hair, using enough to completely saturate the scalp and hair; rinse off with water after 10 minutes; repeat treatment in seven days	Head lice ≥6 months of age: Lotion: apply to dry hair, using enough to completely saturate the scalp and hair; rinse off with water after 10 minutes; repeat treatment in seven days	Lotion: 5%
Crotamiton	Scabies: Cream, lotion: prior to application, patients should bathe or shower; shake the lotion well before using; thereafter, a thin layer of the cream or lotion should be thoroughly massaged into all skin surfaces from the chin down to the toes including all skin folds and creases; crotamiton is left on the skin and a second application is advisable 24 hours later; the patient should take a cleansing bath 24 to 48 hours after the last application to remove any remaining drug; patients can be retreated after seven days if live mites appear or if no clinical improvement is observed	Safety and efficacy in children have not been established.	Cream: 10% Lotion: 10%
Ivermectin	Head lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp; leave lotion in place for 10 minutes and then rinse off with water	Head lice ≥6 months of age: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp; leave lotion in place for 10 minutes and then rinse off with water	Lotion: 0.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Lindane	Head lice: Shampoo: apply shampoo directly to dry hair without adding water; work thoroughly into the hair and allow it to remain in place for four minutes only; special attention should be given to the fine hairs along the neck; after four minutes, add small quantities of water to hair until a good lather forms; immediately rinse all lather away; avoid unnecessary contact of lather with other body surfaces; do not retreat Scabies: Lotion: apply a thin layer of lindane lotion over all skin from the neck down; one ounce is sufficient for an average adult; do not prescribe more than two ounces for larger adults; apply only once; wash off in eight to 12 hours; do not retreat	Head lice: Shampoo: apply shampoo directly to dry hair without adding water; work thoroughly into the hair and allow it to remain in place for four minutes only; special attention should be given to the fine hairs along the neck; after four minutes, add small quantities of water to hair until a good lather forms; immediately rinse all lather away; avoid unnecessary contact of lather with other body surfaces; do not retreat Scabies: Lotion: apply a thin layer of lindane lotion over all skin from the neck down; one ounce is sufficient for an average adult; apply only once; wash off in eight to 12 hours; do not retreat	Lotion: 1% Shampoo: 1%
Malathion	Head lice: Lotion: apply on dry hair in an amount just sufficient to thoroughly wet the hair and scalp; allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered; after eight to 12 hours, the hair should be shampooed; rinse and use a fine-toothed (nit) comb to remove dead lice and eggs; if lice are still present after seven to nine days, repeat with a second application of lotion	Head lice: Lotion: apply on dry hair in an amount just sufficient to thoroughly wet the hair and scalp; allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered; after eight to 12 hours, the hair should be shampooed; rinse and use a fine-toothed (nit) comb to remove dead lice and eggs; if lice are still present after seven to nine days, repeat with a second application of lotion	Lotion: 0.5%
Permethrin	Scabies: Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application; leave on six to 14 hours and then remove by washing off; repeat dose 14 days later if demonstrable living mites	Scabies >2 months of age: Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application; leave on six to 14 hours and then remove by washing off; repeat dose 14 days later if demonstrable living mites	Cream: 5%
Spinosad	Head lice: Apply a sufficient amount to adequately cover scalp and hair; rinse off with water after 10 minutes; if live lice are seen seven days after the first treatment, a second treatment should be applied	Head lice ≥4 years of age: Apply a sufficient amount to adequately cover scalp and hair; rinse off with water after 10 minutes; if live lice are seen seven days after the first treatment, a second treatment should be applied	Suspension: 0.9%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane scabicides and pediculicides are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Skin and Mucous Membrane Scabicides and Pediculicides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Head, Body or Pubic Lice				
Barker et al.[20] (2010) Benzyl alcohol 5% lotion applied three times, at weekly intervals, (on day 0, day 7 and day 14) vs pyrethrins and piperonyl butoxide aerosol mousse applied twice (on day 0 and day 7) vs tea tree oil and lavender oil solution applied three times, at weekly intervals, (on day 0, day 7 and day 14) Nit combining was not allowed.	RCT, SB Primary school-aged children four to 12 years of age and their siblings with live head lice in their hair or on their scalp	N=132 8 or 15 days (one day after the last treatment)	Primary: Louse free rate assessed one day after the last treatment Secondary: Louse free rate on day one (one day after the first application)	Primary: In the ITT population, 97.6% of patients receiving tea tree oil and lavender oil solution and 97.6% of patients receiving benzyl alcohol were louse-free one day after the last treatment compared to 25.0% of patients receiving pyrethrins and piperonyl butoxide (both, P<0.0001). In the PP population, 97.6% of patients receiving tea tree oil and lavender oil solution and 100% of patients receiving benzyl alcohol were louse-free one day after the last treatment compared to 33.3% of patients receiving pyrethrins and piperonyl butoxide (both, P<0.0001). Secondary: In the ITT population, 90.3% of patients receiving tea tree oil and lavender oil solution and 69.4% of patients receiving benzyl alcohol were louse-free on day one compared to 43.3% of patients receiving pyrethrins and piperonyl butoxide (P=0.001 and P=0.0329, respectively). The difference in the louse-free rates for tea tree oil and lavender oil solution and benzyl alcohol was not significant (P=0.1009). In the PP population, 90.0% of patients receiving tea tree oil and lavender oil solution and 72.4% of patients receiving benzyl alcohol were louse-free on day one compared to 57.1% of patients receiving pyrethrins and piperonyl butoxide (P=0.0196 and P=0.2986, respectively). The most commonly reported adverse events with tea tree oil and lavender oil solution were stinging, flaky scalp/dry scalp and erythema. The most common adverse event with benzyl alcohol was flaky scalp/dry scalp. In the pyrethrins/piperonyl butoxide group, flaky scalp/dry scalp and erythema were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Meinking et al.[21] (2010) Phase II Trials Benzyl alcohol 2.5 to 10% lotion applied on day 0 and day 7 (BAL) vs placebo or active control (RID®) Phase III Trials Benzyl alcohol 5% lotion applied on day 0 and day 7 (BAL) vs placebo OL ES Trial Benzyl alcohol 5% lotion applied on day 0 and day 7 (BAL)	AC, PC, RCT, SB (3 Phase II trials) and DB, PC, RCT (2 Phase III trials) and EL, OL (1 trial) Phase II Trials Patients two to 70 years of age with head lice Phase III Trials and EL, OL Trial Children six months of age and older with head lice	N=459 (6 trials) Up to 21 days	Phase II Trials Primary: Treatment success seven days after final treatment Secondary: Not reported Phase III Trials Primary: Treatment success 14 days after final treatment Secondary: Treatment failure assessed one day after the second treatment ES OL Trial Primary: Treatment success 14 days after final treatment Secondary: Treatment failure assessed one day after the second treatment	Phase II Trials Primary: In the Phase IIa study, the BAL 5%, BAL 10% and RID® treatment groups had fewer live lice in comparison with the placebo group (P=0.004). The kill rate (ratio of total lice minus live lice/total lice) was >80% in the patients who received any of the active treatments and <20% in patients who received placebo (P<0.001). No significant differences were observed among the groups at day 15; however, the placebo group was treated with the active treatment at the day eight visit. The efficacy outcome one week later showed 70% overall success with BAL 5%, BAL 10%, and RID®, while the vehicle group demonstrated 53% success after one week treatment. In the Phase IIb study, all patients treated achieved 100% treatment success one week after treatment regardless of treatment duration. In the Phase IIc study, BAL 5% was more effective than BAL 2.5%, although not statistically significant, with treatment success rates of 90.5% and 81%, respectively (P=0.663). Secondary: Not reported Phase III Trials Primary: BAL 5% demonstrated greater treatment success 14 days after treatment in all subgroups compared to placebo (P<0.001). Secondary: In study 1, 3.3% of the BAL 5% ITT group were treatment failures, compared to 83.6% in the placebo group (P<0.001). In study 2, 14.3% of BAL 5% ITT patients were treatment failures, compared to 60.7% of patients treated with vehicle alone (P<0.001). ES OL Trial Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				An overall 75.0% treatment success was demonstrated with BAL at the end of study (14 days after the second treatment). Secondary: Treatment success measured one day after the second treatment (day eight) showed 92.2% success.
Brandenberg et al.[22] (1986) Lindane 1% shampoo vs permethrin 1% creme rinse	RCT Patients with head lice	N=573 2 weeks	Primary: Efficacy Secondary: Tolerance	Primary: Of the 257 patients treated with 1% permethrin cream rinse, 99% were lice free at 14 days; of the 251 patients treated with 1% lindane shampoo, 85% were lice free at 14 days (P<0.001). Secondary: For both treatments, adverse experiences were infrequent, mild, and usually difficult to distinguish from the symptoms of head lice infestation.
Bowerman et al.[23] (1987) Lindane shampoo vs permethrin 1% creme rinse	RCT Patients with head lice	N=1,040 2 weeks	Primary: Efficacy Secondary: Adverse effects	Primary: One patient in each of the 296 family groups was designated as the index patient. Among index patients 98% treated with permethrin and 76% treated with lindane were louse-free 2 weeks after treatment (P<0.001). Comparable results were found with nonindex patients as well. Secondary: Mild dermal reactions occurred in 1.2% of permethrin-treated patients and 2.6% of lindane-treated patients. There were no reports of central nervous system adverse effects or conjunctivitis.
Kalter et al.[24] (1987) Lindane 1% shampoo vs permethrin 1% creme rinse	RCT Men with the diagnosis of pediculosis pubis	N=53 10 days	Primary: Efficacy Secondary: Tolerability	Primary: In the lindane group, 10 (40%) of 25 patients were infested at the final assessment. In the permethrin group, 12 (43%) of 28 patients were infested at the final assessment. The difference was not statistically significant. Secondary: Both treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Roberts et al.[25] (2000) Malathion lotion vs wet combing	RCT Children three to 14 years of age with head lice	N=81 2 weeks	Primary: Efficacy Secondary: Not reported	Primary: The cure rate was 38% for wet combing and 78% for malathion. Children assigned wet combing were 2.8 times more likely than those assigned to malathion to have lice at the end of treatment (P=0.0006). Secondary: Not reported
Chosidow et al.[26] (2010) Malathion 0.5% lotion applied on day 1 and day 8 vs ivermectin 400 µg/kg on day 1 and day 8 Patients who still had a head lice infestation on day 15 received the alternative treatment.	DB, MC, RCT Patients two years of age and older and ≥15 kg with live lice and previously failed treatment despite topical application of a pyrethroid-based or malathion insecticide two to six weeks before enrollment	N=812 Up to 29 days	Primary: Absence of live lice on day 15 Secondary: Absence of live head lice on days two and eight and days 22 and 29 for patients who entered the extension stage; treatment preference	Primary: In the ITT population, 95.2% of patients receiving ivermectin were lice-free on day 15, as compared to 85.0% of those receiving malathion (P<0.001). In the PP population, 97.1% of patients in the ivermectin group were lice-free on day 15, as compared to 89.8% of those in the malathion group (P=0.002). Secondary: On day 15, 39 patients (eight in the ivermectin group and 31 in the malathion group) had persistent infestation and entered the extension phase. At day 29, 100% of patients receiving malathion and 96.8% of patients receiving ivermectin no longer had head lice. A total of 78.3% of the patients preferred tablets, 13.0% preferred lotion, and 8.7% had no preference. A total of 1.8% of patients in the ivermectin group and 1.2% of patients in the malathion group discontinued treatment due to an adverse event.
Meinking et al.[27] (2004) Malathion 0.5% lotion applied for 20 minutes vs permethrin 1%	RCT, SB Patients six to 70 years of age with head lice	N=66 15 days	Primary: Efficacy Secondary: Not reported	Primary: On day eight, live lice were found on eight of the 41 malathion patients (19.5%) and nine of the 22 permethrin patients (40.9%; P=0.08). For patients who required re-treatment on day eight, 88% in the malathion group and 33% in the permethrin group were lice-free on day 15 (P=0.05). At the end of the study, 98% of malathion-treated patients were lice-free compared to 55% of permethrin-treated patients (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
creme rinse applied for 10 minutes				Secondary: Not reported
Meinking et al.[28] (2007) Malathion 0.5% gel for 30, 60 and 90 minute application period vs malathion 0.5% lotion for an eight to 12 hour application period vs permethrin 1% creme rinse for a 10-minute application period	AC, RCT, SB Patients with head lice	N=172 23 days	Primary: Treatment success Secondary: Retreatment requirements and adverse events	Primary: In the ITT population, the treatment success rates were 98% for the 30-minute malathion gel (P<0.0001), 93% for the 60-minute malathion gel (P=0.001), 86% for the 90-minute malathion gel (P=0.01), 97% for malathion lotion (P=0.0006), and 45% for permethrin. In the PP population, there were no significant differences in treatment success rates between the malathion gel groups and the malathion lotion group. Secondary: The proportions of patients requiring retreatment on day eight was greater for those treated with permethrin than for those treated with malathion gels or malathion lotion. The incidence of adverse events among the treatment groups was not significantly different.
Taplin et al.[29] (1986) Permethrin 1% creme rinse vs lindane 1% shampoo vs	DB, PC, RCT Patients with head lice	N=93 2 weeks	Primary: Efficacy Secondary: Safety	Primary: At 14 days after treatment, 97% of patients treated with permethrin were free of lice compared to 6% of placebo-treated patients (P<0.001) and 43% of the lindane-treated patients. Permethrin was 70% ovicidal compared to 14% for placebo (P<0.001) and 45% for lindane. The differences between lindane and the other groups (permethrin and placebo), were not subject to statistical analysis since lindane-treated patients were not included in the pre-study blinded randomization of treatments. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				No adverse experiences were noted during this study.
Carson et al.[30] (1988) Permethrin 1% creme rinse vs pyrethrins and piperonyl butoxide	RCT Patients four years of age and older with head lice	N=58 2 weeks	Primary: Efficacy (cure rate) Secondary: Tolerability	Primary: Seven days after the initial visit, permethrin was determined to be significantly better than pyrethrins with piperonyl butoxide for eradicating the lice infestation. Of the 27 patients receiving permethrin, 26 were lice free vs 14 of the 31 piperonyl butoxide and pyrethrin-treated patients (P<0.005). At day 14, there was no statistically significant difference (P>0.01) in the treatments (27 of 27 permethrin-treated vs 29 of 31 pyrethrins with piperonyl butoxide-treated patients were lice free). Secondary: Both treatments were well tolerated, and no subject experienced adverse reactions.
DiNapoli et al.[31] (1988) Permethrin 1% creme rinse vs pyrethrins and piperonyl butoxide	RCT Patients with head lice	N=435 2 weeks	Primary: Efficacy Secondary: Adverse effects	Primary: Seven days after the treatment, 98% of the permethrin-treated and 85% of the pyrethrins combined with piperonyl butoxide-treated patients were free of lice. At 14 days, prior to nit removal, 96% of the permethrin-treated and 62% of the pyrethrins combined with piperonyl butoxide-treated patients were still lice free. Secondary: Seventeen (7%) permethrin-treated and 32 (16%) pyrethrins combined with piperonyl butoxide-treated patients were reported to have adverse experiences.
Hipolito et al.[32] (2001) Permethrin 1% creme rinse vs trimethoprim/ sulfamethoxazole vs	MC, RCT Children two to 13 years of age with head lice	N=115 1 month	Primary: Efficacy Secondary: Adverse effects	Primary: At the two-week follow-up visit, successful treatment for groups one, two, and three was 79.5, 83.0, and 95.0%, respectively. At the four-week follow-up, successful treatment was 72.0, 78.0, and 92.5% for groups one, two, and three, respectively. The absolute risk reduction for recurrence comparing group one vs group two was 6%, group two vs group three was 14%, and group one vs group three was 20%. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
permethrin 1% creme rinse 1% plus trimethoprim/ sulfamethoxazole				No major adverse complications were seen in any treatment group. There were three trimethoprim/sulfamethoxazole-related rashes. Of the 115 patients, eight had minor adverse reactions to the treatment.
Stough et al.[33] (2009) Spinosad 0.9% topical suspension without nit combing vs permethrin 1% topical solution with nit combing vs spinosad 0.9% topical suspension with nit combing	2 AC, MC, PG, RCT, SB Patients six months of age and older with head lice	N=1,038 14 days (up to 21 days for patients who received a second course of treatment)	Primary: Efficacy (cure rate) Secondary: Proportion of patients requiring one or two treatments	Primary: Treatment with spinosad without nit combing resulted in a significantly greater proportion of lice-free patients 14 days after treatment compared to permethrin with nit combining (P<0.001 for both trials). Results were similar when data from all of the patients (primary and nonprimary) were analyzed regardless of how many treatments were received. Both treatments were well tolerated, and no severe adverse events were reported. The most common adverse events were eye and scalp irritation. Overall, spinosad-treated patients had fewer adverse events; however, only application site erythema was significantly more frequent with permethrin-treated patients (P=0.007). Secondary: Overall, the majority of spinosad-treated patients (with or without nit combining) required only one treatment application for complete eradication of lice, whereas the majority of permethrin-treated patients required two treatments. In trial one, 94.2 and 68.1% of spinosad without nit combining- and permethrin with nit combing-treated patients required only one treatment (P value not reported). The corresponding numbers in trial two were 93.1 and 62.4%, respectively (P value not reported). After two treatments, 55.7 and 64.3% of spinosad without nit combing-treated patients were lice-free in both trials, compared to 33.3 and 27.1% of permethrin with nit combing-treated patients (P values not reported).
Pariser et al.[34] (2012) Ivermectin lotion 0.5% vs	2 DB, MC, PC, RCT Patients six months of age and older with head lice who agreed	N=765 15 days	Primary: Number of index patients who were louse-free by day two and remained louse-free through	Primary: Significantly more patients treated with ivermectin were free of live lice at the first post-application observation on day two and at the subsequent observations through day 15 (P<0.001 for all). The combined ITT analysis showed that significantly more patients in the ivermectin group were lice-free on day two (94.9 vs 31.3%), day eight (85.2 vs 20.8%) and day 15 (73.8 vs 17.6%) compared to the vehicle group (P<0.001 for each day).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vehicle	not to use any other louse treatment, comb out nits, or cut or chemically treat hair		days eight and 15 (ITT population) Secondary: Number of index patients plus all enrolled household members who were louse-free by day two and remained louse-free through days eight and 15 (extended ITT population) and safety	Secondary: Results were consistent when cure rates in the extended ITT populations were analyzed (95.5 vs 35.3% at day two, 88.6 vs 26.2% at day eight and 78.7 vs 22.2% at day 15; P<0.001 for all comparisons). Pruritus, excoriation and erythema were the most common adverse events, occurring in >1% in the vehicle group and <1% in the ivermectin group. There was one severe adverse event (pain in an extremity with vehicle) and no serious adverse events. All other adverse events were mild to moderate. The frequency and severity of adverse events were similar in the two study groups and across age groups. Ocular irritation was noted in seven patients in the ivermectin group and five in the vehicle-control group on day two.
Nofal et al.[35] (2010) Malathion lotion 0.5% vs oral ivermectin in a single oral dose of 200 µg/kg	AC, RCT Children with head lice who were attending an outpatient clinic	N=80 29 days	Primary: Presence of live lice and any side effects at day eight, 15 and 29 Secondary: Not reported	Primary: At day eight (after a single dose) there was a trend towards a higher cure rate in the malathion group compared to the ivermectin group, however, the difference was not statistically significant (87.5 vs 77.5%; P>0.05). The cure rate increased in both treatment groups after nonresponders were given a second dose (day 15), but the difference remained nonsignificant (95.0 vs 92.5% for malathion and ivermectin, respectively; P>0.05). By day 29, cure rates remained similar between the malathion and ivermectin treatment groups (80 vs 75%, respectively; P>0.05). Secondary: Not reported
Scabies				
Haustein et al.[36] (1989) Lindane 1% and 0.3%	OL Patients with scabies	N=194 3 weeks	Primary: Efficacy Secondary: Side effects	Primary: Cure rates were 92% for lindane, 100% for permethrin and 100% for benzyl benzoate. Lindane was less effective than the other treatments (P<0.025). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs permethrin 5 and 2.5% vs benzyl benzoate 20 and 10%				Benzyl benzoate had more immediate (22%) and late (42%) adverse effects.
Schultz et al.[37] (1990) Lindane 1% lotion vs permethrin 5% cream	MC, RCT Patients with scabies	N=467 28 days	Primary: Clinical cure Secondary: Pruritus and adverse events	Primary: Complete resolution occurred in 91% of patients treated with permethrin (P=0.18) and in 86% of patients treated with lindane (P=0.30). Secondary: Pruritus was reported in 13.9 and 24.8% of patients treated with permethrin and lindane at the end of the study period, respectively (95% CI, 0.37 to 0.86). The most frequent adverse effects were new or increased pruritus and mild, transient burning or stinging.
Zargari et al.[38] (2006) Lindane 1% cream vs permethrin 5% cream	DB, RCT Patients older than 5 years of age with scabies	N=99 4 weeks	Primary: Efficacy and pruritus; adverse events Secondary: Not reported	Primary: At the two-week post-treatment follow-up, permethrin was effective in 84.6% of treated patients compared to 48.9% of lindane-treated patients (P<0.05). At the four-week post-treatment follow-up, one patient in the permethrin group who showed no response at the first follow-up and was subsequently treated with lindane still had severe itching. In contrast, all 15 patients not responding to lindane who were then treated with permethrin showed improvement in itching and skin lesions. The better response to permethrin was partially related to its properties in reducing pruritus. Only three patients (two in permethrin group and one in lindane group) experienced irritation after application of the drug, but none had allergic reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Taplin et al.[39] (1986) Lindane 1% lotion vs permethrin 5% cream	RCT Patients with scabies	N=23 1 month	Primary: Efficacy Secondary: Not reported	Primary: Only 13% of patients treated with 1% lindane lotion were free of scabies two weeks after a single treatment and 65% of patients were cured at one month. Forty-eight percent of patients treated with permethrin cream were cured in two weeks and 91% were cured at one month (P<0.025). Secondary: Not reported
Amer et al.[40] (1992) Lindane 1% vs permethrin 5% vs crotamiton 10%	RCT Patients with microscopically confirmed detection of mites from at least one body site with no significant impetiginization	N=150 28 days	Primary: Clinical cure Secondary: Adverse effects	Primary: After four weeks of observation, the cure rates for the three treatment arms were as follows: permethrin 98%, crotamiton 88%, and lindane 84%. Secondary: No reported systemic, neurologic or local irritations, or adverse effects to the medications used in the trial.
Chouela et al.[41] (1999) Lindane 1% solution vs ivermectin 150-200 µg/kg	DB, PG, PRO, RCT Patients with scabies	N=53 1 month	Primary: Clinical healing Secondary: Adverse effects	Primary: At day 15, 74% of patients in the group receiving ivermectin showed healing of their scabies (95% CI, 48.8 to 90.8) compared to 54% of patients in the group treated with lindane (95% CI, 32.8 to 74.4). At 29 days, both treatments resulted in equivalent therapeutic efficacy. Ninety-five percent were healed with ivermectin (95% CI, 74.0 to 99.9) and 96% were healed with lindane (95% CI, 78.9 to 99.9%). Secondary: Adverse effects from the treatments were few, mild and transient.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Madan et al.[42] (2001) Lindane 1% lotion vs ivermectin 200 µg/kg	RCT Patients with scabies	N=200 1 month	Primary: Efficacy Secondary: Adverse effects	Primary: After a period of four weeks, 82.60% of the patients in the ivermectin group showed marked improvement; only 44.44% of the patients in the lindane group showed a similar response. Secondary: One severe headache from ivermectin was noted.
Taplin et al.[43] (1990) Permethrin 5% cream vs crotamiton 10% cream	DB, RCT Treatment of scabies in children two months to five years of age	N=47 28 days	Primary: Clinical cure Secondary: Pruritus	Primary: After 14 days, 30% of the children were cured with permethrin 5% cream compared to 13% of children treated with crotamiton (P=0.001). After 28 days, 89% of children treated with permethrin 5% cream compared to 60% of children treated with crotamiton were cured (P=0.002) After 14 days, 47 and 79% of patients in the permethrin group and crotamiton group were experiencing pruritus, respectively. After 28 days, 11 and 24% of patients in the permethrin group and crotamiton group were experiencing pruritus, respectively. In the permethrin group, 27% of patients (≤12 months of age) were not completely cured at 28 days. In the corresponding age group treated with crotamiton, 56% of patients were treatment failures. In children age one to five years the failure rates were 6% for permethrin and 32% for crotamiton. Five patients who were treated with permethrin but were not completely cured were dramatically improved compared to their baseline evaluations. At the end of 28 days they had a 73% reduction in the number of active lesions. In contrast, 10 of the 19 treatment failures in the crotamiton group became clinically worse after therapy, and the remaining nine were only marginally improved.
Usha et al.[44] (2000) Permethrin 5% cream	RCT Patients with scabies and their family contacts	N=85 2 months	Primary: Efficacy Secondary: Not reported	Primary: A single dose of ivermectin provided a cure rate of 70%, which increased to 95% with two doses at a two-week interval. A single application of permethrin was effective in 97.8% of patients. One

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ivermectin 200 µg/kg	older than five years of age			patient responded to two applications at a two-week interval. Permethrin-treated patients recovered earlier. Secondary: Not reported
Goldust et al.[45] (2012) Permethrin cream 5% vs ivermectin in a single oral dose of 200 µg/kg body weight	AC, RCT Patients aged two to 84 years of age with a diagnosis of scabies and family contacts	N=242 4 weeks	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: Two weeks following treatment, a similar proportion of patients treated with permethrin cream or oral ivermectin experienced a cure (92.5 vs 85.9%; P=0.42). Twenty six patients who had not improved were crossed over to the other treatment group. When crossed over, seven patients in the permethrin 5% group who experienced treatment failure continued to have severe itching when treated with ivermectin. In contrast, all 17 patients not responding to ivermectin who were then treated with permethrin showed improvement in itching and skin lesions. Secondary: Not reported
Chhaiya et al.[46] (2012) Permethrin cream 5% vs ivermectin in a single oral dose of 200 µg/kg body weight vs ivermectin lotion 1%	AC, OL, PG, RCT Patients five to 80 years of age with clinically-diagnosed scabies and presence of typical scabei lesions like papules, nodules or vesicles at classical sites	N=315 4 weeks	Primary: Efficacy (cure rate) Secondary: Complete relief of pruritus	Primary: Significantly fewer patients treated with oral ivermectin compared to ivermectin lotion or permethrin cream were cured at one week (30.0 vs 69.3 and 74.8%, respectively; P<0.05) and two weeks (63 vs 100 and 99%, respectively; P<0.05). There was no statistically significant difference in cure rates between the three treatments by three or four weeks following treatment (P>0.05 for both). Secondary: Patients treated with ivermectin lotion and permethrin cream experienced significantly higher pruritus cure rates compared to oral ivermectin at two (P<0.05) and three weeks (P<0.05). By week four, 95, 99 and 98% of patients treated with oral ivermectin, ivermectin lotion and permethrin cream, respectively, were cured of pruritus (P>0.05).

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, ITT=intent-to-treat, MC=multicenter, OL=open-label, PC=placebo controlled, PG=parallel-group, PP=per-protocol, PRO=prospective, RCT=randomized controlled trial, SB=single-blind

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Skin and Mucous Membrane Scabicides and Pediculicides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Benzyl alcohol	lotion	Ulesfia®	$$$$	N/A
Crotamiton	cream, lotion	Eurax®	$$$	N/A
Ivermectin	Lotion	Sklice®	$$$$$	N/A
Lindane	lotion, shampoo	N/A	N/A	$$$$
Malathion	lotion	Ovide®*	$$$$	$$$$
Permethrin	cream	Elimite®*	$	$
Spinosad	suspension	Natroba®*	$$$$$	$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-9] All of the products are available in a generic formulation, with the exception of benzyl alcohol, crotamiton and ivermectin.

Permethrin products are recommended as first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States.[12,15,47] The topical insecticides exert their pediculicidal and scabicidal effects

through their neurotoxic actions on lice. Benzyl alcohol acts via asphyxiation of the parasite rather than neuro excitation, theoretically lowering the risk of resistance.[3] Ivermectin and spinosad are two newer agents approved for the treatment of head lice.[6,7] Spinosad is not extensively metabolized, and therefore it is still present, and able to exert its effect when the lice eggs hatch and the nervous system develops. This may prevent the need for a second administration if no live lice are observed several days following the initial application.[6] Ivermectin has been approved for one-time use.[7] Lindane is reserved as second-line therapy and carries a Black Box Warning describing risk of neurotoxicity associated with its use. Other available agents offer alternative options should a resistant case occur, or if a patient fails first-line product.[15,47]

Overall, the comparative success rates of topical pediculicides have been shown to be approximately 57 to 99% with permethrin, 45 to 95% with piperonyl butoxide and pyrethrins, 60 to 88% with lindane and 78% with malathion. The newer agents which include benzyl alcohol, ivermectin and spinosad, have shown cure rates of 75%, 71 to 75% and 93 to 94%, respectively, although there is limited published literature confirming these results.[7,33] Permethrin is recommended as first-line therapy and lindane as second-line in the guidelines by the Centers for Disease Control (CDC) and the American Academy of Pediatrics.[15,47] Crotamiton also has a role as an antipruritic for those with scabies.[15] All patients treated for scabies should expect the rash and itching to continue for approximately two weeks after treatment.48 The CDC recommends permethrin for pediculosis pubis.[17]

Therefore, all brand skin and mucous membrane scabicides and pediculicides within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Lindane possesses an extensive adverse effect profile compared to the other brands and generics in the class (if applicable).

XI. Recommendations

No brand skin and mucous membrane scabicide or pediculicide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Lindane should not be placed in preferred status regardless of cost.

XII. References

1. Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Nov]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Nov 13]. Available from: http://www.thomsonhc.com/.
3. Ulesfia® [package insert]. Atlanta (GA): Shionogi Pharma Inc.; 2012 Jul.
4. Eurax® [package insert]. Jacksonville (FL): Ranbaxy; 2009 Jul.
5. Ovide® [package insert]. Hawthome (NY): Taro Phrmaceuticals U.S.A., Inc.; 2011 Nov.
6. Natroba® [package insert]. Carmel (IN): ParaPro LLC.; 2011 May.
7. Sklice® [package insert]. Swiftwater (PA): Sanofi Pasteur Inc.; 2012 Feb.
8. Lindane® [package insert]. Morton Grove (IL): Morton Grove Pharmaceuticals Inc.; 2005 Jun.
9. Permethrin: drug information. In: Rose BD, ed. UpToDate [database on the Internet]. Waltham, MA: UpToDate; 2013 [cited 2013 Nov 13]. Available from: http://www.uptodate.com/contents/permethrin-drug-information?source=search_result&search=Nix&selectedTitle=1%7E150.
10. Goldstein AO, Goldstein BG. Pediculosis capitis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Nov 13]. Available from: http://www.utdol.com/utd/index.do.
11. Goldstein BG, Goldstein AO. Scabies. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Nov 10]. Available from: http://www.utdol.com/utd/index.do.
12. Frankowski BL, Bocchini JA Jr; Council on School Health and Committee on Infectious Diseases. Head lice. Pediatrics. 2010 Aug;126(2):392-403. [cited 2013 Jun 13]. Available at: http://pediatrics.aappublications.org/content/early/2010/07/26/peds.2010-1308.
13. Gilbert D, Moellering R, Eliopoulos G, Chambers, H, Saag M, eds. The Sanford Guide to Antimicrobial Therapy 2011 (41st edition). Sperryville, VA: Antimicrobial Therapy, Inc., 2011.
14. Centers for Disease Control and Prevention. Ectoparasitic infections. In: Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR 2010;59 (No. RR-12):1-110. [cited 2013 Nov 13]. Available at: http://www.cdc.gov/std/treatment/2010/ectoparasitic.htm.
15. Treatment of Head Lice. Centers for Disease Control and Prevention. 2013 [cited 2013 Dec 12]. Available at: http://www.cdc.gov/parasites/lice/head/treatment.html.
16. Treatment of Scabies. Centers for Disease Control and Prevention. 2010 [cited 2013 Dec 12]. Available at: http://www.cdc.gov/parasites/scabies/health_professionals/meds.html.
17. Treatment of Pubic "Crab" Lice. Centers for Disease Control and Prevention. 2010 [cited 2013 Dec 12]. Available at: http://www.cdc.gov/parasites/lice/pubic/treatment.html.
18. British Association of Sexual Health and HIV: United Kingdom National Guideline on the Management of *Phthirus pubis* Infestation (2007). Available at: http://www.bashh.org/documents/28/28.pdf. Accessed December 2013.
19. British Association of Sexual Health and HIV: United Kingdom National Guideline on the Management of Scabies Infestation (2007). Available at: http://www.bashh.org/documents/27/27.pdf. Accessed December 2013.
20. Barker SC, Altman PM. A randomized, assessor blind, parallel group comparative efficacy trial of three products for the treatment of head lice in children-melaleuca oil and lavender oil, pyrethrins and piperonyl butoxide, and a "suffocation" product. BMC Dermatol. 2010;10:6.
21. Meinking TL, Villar ME, Vicaria M, Eyerdam DH, Paquet D, Mertz-Rivera K, et al. The clinical trials supporting benzyl alcohol lotion 5% (Ulesfia): a safe and effective topical treatment for head lice (pediculosis humanus capitis). Pediatr Dermatol. 2010;27(1):19-24.
22. Brandenburg K, Deinard AS, DiNapoli J, Englender SJ, Orthoefer J, Wagner D. 1% permethrin cream rinse vs 1% lindane shampoo in treating pediculosis capitis. Am J Dis Child. 1986;140:894-6.
23. Bowerman JG, Gomez MP, Austin RD, Wold DE. Comparative study of permethrin 1% creme rinse and lindane shampoo for the treatment of head lice. Pediatr Infect Dis J. 1987;6:252-5.
24. Kalter DC, Sperber J, Rosen T, Matarasso S. Treatment of pediculosis pubis. Clinical comparison of efficacy and tolerance of 1% lindane shampoo vs 1% permethrin creme rinse. Arch Dermatol. 1987;123:1315-9.
25. Roberts RJ, Casey D, Morgan DA, Petrovic M. Comparison of wet combing with malathion for treatment of head lice in the UK: a pragmatic randomized controlled trial. Lancet. 2000;356:540-4.
26. Chosidow O, Giraudeau B, Cottrell J, Izri A, Hofmann R, Mann SG, et al. Oral ivermectin vs malathion lotion for difficult-to-treat head lice. N Engl J Med. 2010;362(10):896-905.
27. Meinking TL, Vicaria M, Eyerdam DH, Villar ME, Reyna S, Suarez G. Efficacy of a reduced application time of Ovide lotion (malathion) compared to nix crème rinse (1% permethrin) for the treatment of head lice.

Pediatric Dermatology. 2004; 21(6);670-4.
28. Meinking T, Vicaria M, Eyerdam D, Villar ME, Reyna S, Suarez G. A Randomized, investigator-blinded, time-ranging study of the comparative efficacy of 0.5% malathion gel vs Ovide® Lotion (0.5% malathion) or Nix® Creme Rinse (1% Permethrin) used as labeled, for the treatment of head lice. Pediatr Dermatol. 2007;24(4):405-11.
29. Taplin D, Meinking TL, Castillero PM, Sanchez R. Permethrin 1% creme rinse for the treatment of Pediculus humanus var capitis infestation. Pediatr Dermatol. 1986;3:344-8.
30. Carson DS, Tribble PW, Weart CW. Pyrethrins combined with piperonyl butoxide (RID) vs 1% permethrin (NIX) in the treatment of head lice. Am J Dis Child. 1988;142:768-9.
31. DiNapoli JB, Austin RD, Englender SJ, Gomez MP, Barrett JF. Eradication of head lice with a single treatment. Am J Public Health. 1988;78:978-80.
32. Hipolito RB, Mallorca FG, Zuniga-Macaraig ZO, Apolinario PC, Wheeler-Sherman J. Head lice infestation: single drug vs combination therapy with one percent permethrin and trimethoprim/sulfamethoxazole. Pediatrics. 2001;107:E30.
33. Stough D, Shellabarger MS, Quiring J, Gabrielsen AA. Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). Pediatrics 2009;124:e389-95.
34. Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. N Engl J Med. 2012 Nov;367(18):1687-93.
35. Nofal A. Oral ivermectin for head lice: a comparison with 0.5 % topical malathion lotion. J Dtsch Dermatol Ges. 2010 Dec;8(12):985-8.
36. Haustein UF, Hlawa B. Treatment of scabies with permethrin vs lindane and benzyl benzoate. Acta Derm Venereol. 1989;69:348-51.
37. Schultz MW, Gomez M, Hansen RC, Mills J, Menter A, Rodgers H, et al. Comparative study of 5% permethrin cream and 1% lindane lotion for the treatment of scabies. Arch Dermatol. 1990;126:167-70.
38. Zargari O, Golchai J, Sobhani A, Dehpour AR, Sadr-Ashkevari S, Alizadeh N, et al. Comparison of the efficacy of topical 1% lindane vs 5% permethrin in scabies: A randomized, double-blind study. Indian J Dermatol Venereol Leprol. 2006;72;33-6.
39. Taplin D, Meinking TL, Porcelain SL, Castilero PM, Chen JA. Permethrin 5% dermal cream: a new treatment for scabies. J Am Acad Dermatol. 1986;15:995-1001.
40. Amer M, el-Garib I. Permethrin vs crotamiton and lindane in the treatment of scabies. Int J Dermatol. 1992;31:357-8.
41. Chouela EN, Abeldaño AM, Pellerano G, La Forgia M, Papale RM, Garsd A, et al. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. Arch Dermatol. 1999;135:651-5.
42. Madan V, Jaskiran K, Gupta U, Gupta DK. Oral ivermectin in scabies patients: a comparison with 1% topical lindane lotion. J Dermatol. 2001;28:481-4.
43. Taplin D, Meinking TL, Chen JA, Sanchez R. Comparison of crotamiton 10% cream (Eurax) and permethrin 5% cream (Elimite) for the treatment of scabies in children. Pediatr Dermatol. 1990;7:67-73.
44. Usha V, Gopalakrishnan Nair TV. A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. J Am Acad Dermatol. 2000;42(2 Pt 1):236-40.
45. Goldust M, Rezaee E, Hemayat S. Treatment of scabies: Comparison of permethrin 5% vs ivermectin. Dermatol. 2012 Jun;39(6):545-7.
46. Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. Indian J Dermatol Venereol Leprol. 2012 Sep;78(5):605-10.
47. Downs AM, Stafford KA, Harvey I, Coles GC. Evidence for double resistance to permethrin and malathion in head lice. Br J Dermatol. Sep 1999;141(3):508-11.
48. Wendel K, Rompalo A. Scabies and pediculosis pubis: an update of treatment regimens and general review. Clin Infect Dis. 2002;35(Suppl 2):S146-51.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Local Anti-infectives, Miscellaneous
AHFS Class 840492
February 12, 2014

I. Overview

The skin and mucous membrane miscellaneous local anti-infectives are approved for the treatment of vaginal infections, antiseptic cleansing, and prevention/treatment of burn wounds.[1-9] Vulvovaginal candidiasis is a common infection and is most often caused by *Candida albicans*.[10] Bacterial vaginosis is caused by a reduction of the normal hydrogen peroxide-producing *Lactobacillus* species in the vagina, an increase in vaginal pH and an overgrowth of anaerobic bacteria.[11] Sulfanilamide blocks certain metabolic processes essential for the growth of susceptible organisms.[7] Acetic acid and oxyquinoline is used as adjunctive therapy when restoration and maintenance of vaginal acidity is desired, such as in bacterial vaginosis.[1,2,9] Hexachlorophene is a bacteriostatic cleansing agent, which cleanses the skin thoroughly and has bacteriostatic action against *Staphylococci* and other gram-positive bacteria. It is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. Hexachlorophene may also be used to control an outbreak of gram-positive infections where other infection control procedures have been unsuccessful.[3]

Burn patients are predisposed to infections due to a loss of the protective barrier function of the skin, which leads to the entry of microorganisms. *Streptococci* and *Staphylococci* are the main organisms involved in burn wound infections; however, the incidence of *Pseudomonas* and fungal infections are increasing due to the use of broad-spectrum antibiotics.[12,13] Topical antimicrobial therapy remains one of the most important components of wound care in hospitalized burn patients. The goal of prophylactic topical antimicrobial therapy is to control microbial colonization and prevent infections. Mafenide, silver nitrate and silver sulfadiazine are used for the prevention and treatment of burn wound infections and all three have a broad spectrum of activity. Mafenide is a sulfonamide, which exerts bacteriostatic action by preventing bacterial folic acid synthesis.[4,5] Silver nitrate inhibits the growth of bacteria, which is due to the precipitation of bacterial proteins by liberated silver ions. It also coagulates cellular proteins to form an eschar, which is why it has been used for the destruction of exuberant granulations. Silver sulfadiazine is formed by combining sulfadiazine with silver nitrate, which exhibits both bactericidal and bacteriostatic actions.[1,2]

The skin and mucous membrane miscellaneous local anti-infectives that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Products indicated solely for the treatment of acne and/or rosacea are not covered by Alabama Medicaid. Therefore, these products are not included in this review. Several of the products are available in a generic formulation. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Local Anti-infectives, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Hexachlorophene	liquid	pHisoHex®	pHisoHex®
Mafenide	cream, packet	Sulfamylon®*	mafenide
Silver nitrate	solution	N/A	silver nitrate
Silver sulfadiazine	cream	Silvadene®*, SSD®*	silver sulfadiazine
Sulfanilamide	vaginal cream	AVC®	none
Combination Products			
Acetic acid and oxyquinoline	vaginal jelly	N/A	acetic acid and oxyquinoline

*Generic is available in at least one dosage form or strength.
†No current clinical significant information was identified.
N/A=Not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane miscellaneous local anti-infectives are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines[11] (2010)**	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir 200 mg orally five times daily for seven to 10 days, famciclovir 250 mg orally three times daily for seven to 10 days or valacyclovir 1,000 mg orally twice daily for seven to 10 days. Treatment can be extended if healing is incomplete after 10 days of therapy. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • The safety and efficacy of suppressive therapy have been documented among patients receiving daily therapy with acyclovir for as long as six years and with famciclovir or valacyclovir for one year. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy. • Recommended regimens for suppressive therapy of genital herpes include acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily, valacyclovir 500 mg orally once daily or valacyclovir 1,000 mg orally once daily. • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment.

Clinical Guideline	Recommendation(s)

	• Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms being.
	• Recommended regimens for episodic treatment of genital herpes include acyclovir 400 mg orally three times daily for five days, acyclovir 800 mg orally twice daily for five days, acyclovir 800 mg orally three times daily for two days, famciclovir 125 mg orally twice daily for five days, famciclovir 1,000 mg orally twice daily for one day, famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days, valacyclovir 500 mg orally twice daily for three days or valacyclovir 1,000 mg orally once daily for five days.
	• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.
	• The sex partners of patients who have genital herpes can benefit from evaluation and counseling.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with human immunodeficiency virus (HIV) include acyclovir 400 to 800 mg orally twice daily, famciclovir 500 mg orally twice daily or valacyclovir 500 mg orally twice daily.
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV include acyclovir 400 mg orally three times daily for five to 10 days, famciclovir 500 mg orally twice daily for five to 10 days or valacyclovir 1,000 mg orally twice daily for five to 10 days.
	• The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established.
	• Infants exposed to HSV during birth should be followed carefully in consultation with a pediatric infectious disease specialist.
	
	<u>Pediculosis pubis (pubic lice infestation)</u>
	• Recommended regimens:
	  ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  ○ Ivermectin 250 µg/kg orally and repeated in two weeks.
	
	<u>Scabies</u>
	• Recommended regimens:
	  ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  ○ Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Alternative regimens:
	  ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	
	<u>Bacterial vaginosis</u>
	• Recommended regimens for nonpregnant women include:
	  ○ Metronidazole 500 mg orally twice a day for seven days.

Clinical Guideline	Recommendation(s)
	○ Metronidazole 0.75% gel 5 g intravaginally for five days. ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens for nonpregnant women include: ○ Tinidazole 2 g orally once daily for two days. ○ Tinidazole 1 g orally once daily for five days. ○ Clindamycin 300 mg orally twice daily for seven days. ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days. • Additional regimens include metronidazole (750 mg extended-release tablets once daily for seven days), or a single dose of clindamycin intravaginal cream, although data on these alternative regimens are limited. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • The topically applied azole drugs are more effective than nystatin. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: ○ Butoconazole 2% cream 5 g intravaginally for three days. ○ Butoconazole 2% cream 5 g single intravaginal application. ○ Clotrimazole 1% cream 5 g intravaginally for seven to 14 days. ○ Clotrimazole 2% cream 5 g intravaginally for three days. Miconazole 2% cream 5 g intravaginally for seven days. ○ Miconazole 4% cream 5 g intravaginally for three days. ○ Miconazole 100 mg vaginal suppository for seven days. ○ Miconazole 200 mg vaginal suppository for three days. ○ Miconazole 1,200 mg vaginal suppository, for one day. ○ Nystatin 100,000-unit vaginal tablet, one tablet for 14 days. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally for seven days. ○ Terconazole 0.8% cream 5 g intravaginally for three days. ○ Terconazole 80 mg vaginal suppository for three days. ○ Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent (four or more episodes in one year) or severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with uncontrolled diabetes, debilitation or immunosuppression. • Treatment: Each individual episode of recurrent vulvovaginal candidiasis caused by *Candida albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Maintenance regimens: Oral fluconazole weekly for six months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.

Clinical Guideline	Recommendation(s)

	<u>Severe vulvovaginal candidiasis</u>
	• Severe vulvovaginitis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	<u>Non-albicans vulvovaginal candidiasis</u>
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. Options include longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for two weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.
	
	<u>Genital warts</u>
	• Treatment of genital warts should be guided by the preference of the patient, the available resources, and the experience of the health-care provider.
	• No definitive evidence suggests that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that influence selection of treatment include wart size, wart number, location of the wart, wart morphology, patient preference, convenience, adverse effects, and provider experience.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens (patient-applied):
	  o Podofilox 0.5% solution or gel.
	  o Imiquimod 5% cream.
	  o Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  o Cryotherapy with liquid nitrogen or cryoprobe.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  o Surgical removal
	• Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.
	
	<u>Cervical warts</u>
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.

Clinical Guideline	Recommendation(s)

	Vaginal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90%.
	
	Urethral meatus warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	
	Anal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  ○ Surgical removal.

American College of Obstetricians and Gynecologists: **Clinical Management Guidelines for Obstetrician-Gynecologists: Vaginitis[14] (2006)**	Bacterial vaginosis
	• Nonpregnant women with bacterial vaginosis can be treated with vaginal clindamycin, oral clindamycin, vaginal metronidazole, or oral metronidazole products. These agents seem to have comparable clinical efficacy and safety.
	• Oral metronidazole may be associated with significant gastrointestinal symptoms. Disulfiram-like reactions may occur with both oral and topical metronidazole.
	
	Uncomplicated vulvovaginal candidiasis
	• Women with uncomplicated vulvovaginal candidiasis can be treated successfully with any of the following options:
	  ○ Butoconazole 2% sustained-release cream 5 g daily for one day.
	  ○ Clotrimazole 1% cream 5 g daily for seven days.
	  ○ Clotrimazole 2% cream 5 g daily for three days.
	  ○ Clotrimazole 100 mg vaginal suppository daily for seven days.
	  ○ Clotrimazole 200 mg vaginal suppository daily for three days.
	  ○ Clotrimazole 500 mg vaginal suppository daily for one day.
	  ○ Fluconazole 150 mg oral tablet daily for one day.
	  ○ Miconazole 2% cream 5 g daily for seven days.
	  ○ Miconazole 100 mg vaginal suppository daily for seven days.
	  ○ Miconazole 200 mg vaginal suppository for three days.
	  ○ Miconazole 1,200 mg vaginal suppository daily for one day.
	  ○ Nystatin 100,000 units vaginal tablets daily for 14 days.
	  ○ Terconazole 0.4% cream 5 g daily for seven days.
	  ○ Terconazole 0.8% cream 5 g daily for three days.
	  ○ Tioconazole 2% cream 5 g daily for three days.
	  ○ Tioconazole 6.5% cream 5 g daily for one day.
	• Because all listed antifungal treatments seem to have comparable safety and efficacy, the choice of therapy should be individualized to the specific patient; factors such as ease of use, history of response or adverse reactions to prior treatments, and patient preference can all be taken into consideration.
	
	Complicated vulvovaginal candidiasis
	• Patients with complicated vulvovaginal candidiasis require more aggressive treatment to achieve relief of symptoms.
	• After initial intensive therapy for seven to 14 days to achieve mycologic remission, prolonged antifungal treatment with fluconazole, 150 mg weekly for six months, will successfully control more than 90% of symptomatic episodes and will lead to a prolonged protective effect in approximately 50%

Clinical Guideline	Recommendation(s)
	of women. • Although daily oral ketoconazole was previously described as an effective suppressive therapy in women with recurrent vulvovaginal candidiasis, weekly fluconazole has a lower risk of liver toxicity and should be used instead of ketoconazole. • For patients who are unable or unwilling to take fluconazole, prolonged maintenance therapy with intermittent topical agents, such as clotrimazole, 500 mg weekly or 200 mg twice a week, are acceptable options. <u>Non-albicans vulvovaginal candidiasis</u> • A standard course of topical imidazole therapy may be effective in up to 50% of such cases. • Therapy with vaginal boric acid, 600 mg capsules daily for a minimum of 14 days, seems to be effective for azole failures.

European (International Union Against Sexually Transmitted Infections/ World Health Organization): **Guideline on the Management of Vaginal Discharge[15] (2011)**	<u>Bacterial vaginosis</u>
	• Recommended regimens for bacterial vaginosis:
	  ○ Metronidazole 400 to 500 mg twice daily for five to seven days.
	  ○ Metronidazole 2 g in a single dose.
	  ○ Intravaginal metronidazole 0.75% gel once daily for five days.
	  ○ Tinidazole 2 g in a single dose.
	• Alternative regimens for bacterial vaginosis:
	  ○ Intravaginal metronidazole 0.75% gel once a day for five days.
	  ○ Intravaginal clindamycin 2% cream once daily for seven days.
	  ○ Clindamycin 300 mg twice daily for seven day.
	• Clindamycin and metronidazole have equal efficacy, comparing oral and vaginal formulations, both after one week and after one month of therapy. Approximately 58 to 88% will be cured after five days treatment with metronidazole or clindamycin. In most studies, clindamycin tended to have less adverse effects than metronidazole.
	• Vaginal application of metronidazole is as effective as oral administration.
	• Eradication at one month after vaginal clindamycin cream were 66 to 83% vs 68 to 87% for oral metronidazole.
	• Oral metronidazole, vaginal metronidazole 0.75% cream and vaginal clindamycin 2% cream have similar efficacy and side effect profile. Compared to oral clindamycin, vaginal clindamycin administration is associated with similar efficacy with fewer side effects.
	
	<u>Vaginal candidiasis</u>
	• Intravaginal and oral therapies are equally effective for vaginal candidiasis.
	• Treatment with azoles results in relief of symptoms and negative cultures among 80 to 90% of patients after either oral or topical treatment; only topical preparations should be used during pregnancy.
	• Recommended regimens for vaginal candidiasis:
	  ○ Fluconazole 150 mg orally as a single dose.
	  ○ Itraconazole 200 mg twice daily for one day.
	  ○ Clotrimazole vaginal tablet 500 mg once or 200 mg once daily for three days.
	  ○ Miconazole vaginal ovule 1,200 mg as a single dose or 400 mg once daily for three days.
	  ○ Econazole vaginal pessary 150 mg as a single dose.
	• Standard single dose treatments are as effective as longer courses.
	• In a severely symptomatic attack, symptomatic benefit is with fluconazole 150 mg treatment repeated after three days.

British Association for Sexual Health and	• Recommended regimens for bacterial vaginosis: ○ Metronidazole 400 mg twice daily for five to seven days.

Clinical Guideline	Recommendation(s)
Human Immunodeficiency Virus: **National Guideline for the Management of Bacterial Vaginosis[16] (2012)**	○ Metronidazole 2 g in a single dose. ○ Intravaginal metronidazole 0.75% gel once daily for five days. ○ Intravaginal clindamycin 2% cream once daily for seven days. • Alternative regimens for bacterial vaginosis: ○ Tinidazole 2 g in a single dose. ○ Clindamycin 300 mg twice daily for seven days. • All these treatments have been shown to achieve cure rates of 70 to 80% after four weeks in controlled trials using placebo or comparison with oral metronidazole. Oral metronidazole treatment is established and usually well tolerated. Dosage and duration used in trials have varied from 400 mg twice daily for five days to 500 mg twice daily for seven days. The 2 g immediate dose may be slightly less effective at four week follow up. • Intravaginal metronidazole gel and clindamycin cream have similar efficacy. Metronidazole is less active against lactobacilli than clindamycin. Clindamycin is more active than metronidazole against most of the bacteria associated with bacterial vaginosis. • Oral clindamycin has only been evaluated in one study with short-term follow up, and in pregnant women. • Tinidazole has similar in vitro antibacterial activity and efficacy compared to metronidazole.
Centers for Disease Control and Prevention: **Guideline for Hand Hygiene in Health-Care Settings[17] (2002)**	• Alcohol-based products are more effective for standard handwashing or hand antisepsis than soap or antimicrobial soaps. • Alcohol-based hand rubs are more effective at reducing bacteria on hands, cause less irritation, require less time, and more accessible compared to soap and water. • No recommendation can be made regarding the routine use of non-alcohol-based hand rubs for hand hygiene in health-care settings. • Studies of hexachlorophene as a hygienic hand wash and surgical scrub demonstrated only modest efficacy after a single hand wash. • Hexachlorophene has residual activity for several hours after use and gradually reduces bacterial counts on hands after multiple uses (i.e., it has a cumulative effect). • With repeated use of 3% hexachlorophene preparations, the drug is absorbed through the skin. • Because hexachlorophene is absorbed into the blood after repeated use, it is seldom used as a surgical scrub. • Current guidelines recommend against the routine bathing of neonates with hexachlorophene because of its potential neurotoxic effects. • Hexachlorophene is classified by the Food and Drug Administration Tentative Final Monograph as not generally recognized as safe and effective for use as an antiseptic hand wash. • Hexachlorophene should not be used to bathe patients with burns or extensive areas of susceptible, sensitive skin.
New Zealand Guidelines Group: **Management of Burns and Scalds in Primary Care[18] (2007)**	<u>First aid - initial coverings</u> • Following cooling, polyvinyl chloride film may be used as a temporary cover prior to hospital assessment. • Topical creams should not be applied as they may interfere with subsequent assessment. <u>Management of superficial and mid dermal burns or scalds</u> • Preventing infection: ○ Products with antimicrobial action (such as silver sulfadiazine cream) should be used on all burns for the first 72 hours after burn injury. If infection is suspected, longer-term use of silver sulfadiazine may be

Clinical Guideline	Recommendation(s)

	indicated.
	  ○ Burn wounds with signs of mild cellulitis can be treated with topical silver sulfadiazine and/or oral antibiotics.
	• Wound healing:
	  ○ Use dressings that encourage re-epithelialization by moist wound healing.
	  ○ The prolonged use of silver sulfadiazine cream (more than seven days) may delay healing and should be avoided in non-infected burns.
	  ○ Following initial silver sulfadiazine cream or antimicrobial dressing, a technique that promotes moist wound healing (such as a hydrocolloid dressing) is recommended.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane miscellaneous local anti-infectives are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[1-9]

Indication	Single Entity Agents					Combination Product
	Hexachlorophene	Mafenide	Silver Nitrate	Silver Sulfadiazine	Sulfanilamide	Acetic Acid and Oxyquinoline
Skin Cleanser						
Bacteriostatic skin cleanser	✔					
For use as a surgical scrub	✔					
Vaginal Indications						
Restoration and maintenance of vaginal acidity						✔
Treatment of vulvovaginitis caused by *Candida albicans*					✔	
Wound Care						
Adjunct for the prevention and treatment of wound sepsis in patients with second- and third-degree burns				✔		
Adjunctive therapy of patients with second- and third-degree burns		✔ ‡				
Adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressing over meshed autografts on excised burn wounds		✔ †				
Adjunctive therapy in the prevention of burn wound infections			✔			
Reduction of exuberant granulations			✔			
To control an outbreak of gram-positive infections where other infection control procedures have been unsuccessful	✔					

‡Cream formulation.
†Solution formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane miscellaneous local anti-infectives are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Hexachlorophene	Well absorbed	Not reported	Not reported	Not reported	6.1 to 44.2
Mafenide	Not reported	Not reported	Not reported	Renal	Not reported
Silver nitrate	Minimal	Not reported	Not reported	Not reported	Not reported
Silver sulfadiazine	Not reported	Not reported	Not reported	Renal (60)	10
Sulfanilamide	Not reported	Not reported	Not reported	Not reported	Not reported
Combination Product					
Acetic acid and oxyquinoline	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane miscellaneous local anti-infectives, no significant drug interactions have been reported.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane miscellaneous local anti-infectives are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[1-9]

Adverse Events	Single Entity Agents					Combination Product
	Hexachlorophene	Mafenide	Silver Nitrate	Silver Sulfadiazine	Sulfanilamide	Acetic Acid and Oxyquinoline
Central Nervous System						
Irritability	<1	-	-	-	-	-
Seizure	<1	-	-	-	-	-
Dermatologic						
Burning	-	✔	✔	-	<1	✔
Dermatitis	<1	✔	-	-	-	-
Discoloration of skin	-	-	✔	✔	-	-
Discomfort	-	-	-	-	<1	-
Dryness	<1	✔	-	-	-	-
Edema	-	✔	-	-	-	-
Erythema	<1	✔	-	-	-	-
Erythema multiforme	-	-	-	✔	-	-
Excoriation	-	✔	-	-	-	-
Facial edema	-	✔	-	-	-	-
Hives	-	✔	-	-	-	-
Irritation	-	✔	✔	-	-	-
Maceration	-	✔	-	-	-	-
Photosensitivity	<1	-	-	✔	-	-
Pruritus	-	✔	-	✔	-	-
Rash	-	✔	-	✔	-	-
Sensitivity reaction	-	✔	-	-	-	-
Stinging	-	-	-	-	-	✔
Urticaria	-	✔	-	-	-	-
Endocrine and Metabolic						
Hyperchloremia	-	✔	-	-	-	-
Hyponatremia	-	-	✔	-	-	-
Metabolic acidosis	-	✔	-	-	-	-
Hematologic						
Agranulocytosis	-	-	-	✔	-	-
Aplastic anemia	-	-	-	✔	-	-

Adverse Events	Single Entity Agents					Combination Product
	Hexachlorophene	Mafenide	Silver Nitrate	Silver Sulfadiazine	Sulfanilamide	Acetic Acid and Oxyquinoline
Bleeding	-	✔	-	-	-	-
Bone marrow suppression	-	✔	-	-	-	-
Eosinophilia	-	✔	-	-	-	-
Hemolytic anemia	-	✔	-	✔	-	-
Leukopenia	-	-	-	✔	-	-
Methemoglobinemia	-	-	✔	-	-	-
Porphyria	-	✔	-	-	-	-
Respiratory						
Dyspnea	-	✔	-	-	-	-
Hyperventilation	-	✔	-	-	-	-
Tachypnea	-	✔	-	-	-	-
Other						
Allergic reactions	-	-	-	✔	-	-
Hepatitis	-	-	-	✔	-	-
Hypersensitivity	-	✔	-	-	-	-
Interstitial nephritis	-	-	-	✔	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane miscellaneous local anti-infectives are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Hexachlorophene	Skin cleanser: Liquid: apply 5 mL cleanser and water to area to be cleansed; lather and rinse under running water	Skin cleanser: Liquid: apply 5 mL cleanser and water to area to be cleansed; lather and rinse under running water	Liquid: 3%
Mafenide	Adjunctive therapy for burn wounds: Cream, packet: apply to the affected area one to two times daily	Adjunctive therapy for burn wounds: Cream, packet: apply to the affected area one to two times daily	Cream: 8.5% Packet: 50 g
Silver nitrate	Adjunctive therapy for burn wounds: Solution: apply a cotton applicator dipped in solution on the affected area one to three times a week for two to three weeks	Adjunctive therapy for burn wounds: Solution: apply a cotton applicator dipped in solution on the affected area one to three times a week for two to three weeks	Solution: 0.5%
Silver sulfadiazine	Adjunctive therapy for burn wounds: Cream: apply to the affected area one to two times daily	Adjunctive therapy for burn wounds: Cream: apply to the affected area one to two times daily	Cream: 1%
Sulfanilamide	Vulvovaginitis Cream: one applicator full intravaginally one to two times daily	Safety and efficacy in children have not been established.	Cream: 15%
Combination Product			
Acetic acid and oxyquinoline	Restoration and maintenance of vaginal acidity: Vaginal jelly: one applicator full administered intravaginally in the morning and evening; the duration of treatment may be determined by the patient's response to therapy	Safety and efficacy in children have not been established.	Vaginal Jelly: 0.9%-0.025%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane miscellaneous local anti-infectives are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Burn Wound Care				
Heinle et al.[19] (2001) Mafenide 5% solution administered until autograft vascularization was observed vs historical control treated with similar protocol but without mafenide	RETRO Patients with necrotizing fasciitis admitted to the burn unit after undergoing debridement and grafting	N=74 6 years	Primary: First time successful wound closure, mean débridements, mean wound closure procedures, mortality rate Secondary: Not reported	Primary: The mafenide group exhibited a higher percentage of first-time successful wound closures compared to the control group (P=0.039). There was no significant difference in the mean number of débridements performed in each patient between the mafenide (3.7) and the control groups (5.4). There was no significant difference in the mean number of wound closure procedures performed between the two groups. There was no significant difference in the mortality between the two groups (P=0.158). Secondary: Not reported
Kucan et al.[20] (1993) Mafenide 5% topical solution	PRO Patients with burn wounds requiring topical antibacterial therapy	N=669 7 years	Primary: Burn wound biopsy, infection, sepsis, adverse effects Secondary: Not reported	Primary: Eighteen percent of the patients receiving mafenide 5% topical solution had at least one positive burn wound biopsy. Forty-two patients exhibited systemic signs of sepsis. Use of mafenide 5% topical solution was not associated with acid-base disturbances. Discontinuation of therapy because of the patient's pain was necessary in less than 1% of patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MacMillan et al.[21] (1967) Mafenide acetate 10% applied once daily with replenishment as needed vs silver nitrate 0.5% dressings changed twice daily and saturated every two hours vs gentamicin ointment applied as an occlusive dressing and changed every two to three days vs control group treated with occlusive dressings and no topical drugs Patients also received systemic antibiotic and	OL Patients with second-and third-degree burn wounds requiring topical antibacterial therapy	N=52 Variable duration	Primary: Bacterial flora of the burn wounds and complications Secondary: Not reported	Primary: Of 13 patients treated with mafenide, two died of pneumonia (15%). One patient in this group developed *Pseudomonas* septicemia, but recovered. Of 18 patients treated with silver nitrate, two (11%) died, both of whom developed *Pseudomonas* septicemia. Of 10 patients treated with gentamicin, none died, but two developed septicemia, one due to *Pseudomonas* and one due to *Aerobacter* and *Klebsiella*. In a control group of 11 patients treated with occlusive dressings and no topical drugs, four (36%) died, three from *Pseudomonas aeruginosa* septicemia and one from *Paracolobactrum aerogenoides* septicemia. It was documented that 100% of the patients with no topical drug treatment had wound colonization with *Paracolobactrum aerogenoides*, whereas 25% receiving mafenide, 42% of those receiving silver nitrate, and 75% receiving gentamicin, respectively, demonstrated this species. Mafenide was found to be at least as effective in containing burn wound sepsis as silver nitrate and gentamicin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gamma globulin therapy.				
Pegg et al.[22] (1979) Mafenide vs silver sulfadiazine vs control	OL Patients >12 years of age with burn injuries requiring admission	N=645 9 years of follow-up	Primary: Wound infection and complications Secondary: Not reported	Primary: There were 78 patients with clinical wound infections. Patients treated with silver sulfadiazine had significantly fewer positive cultures than the control group (No growth [P<0.001], *Pseudomonas* [P<0.01], Staphylococcus [P<0.01], *Proteus* [P<0.01], *Klebsiella* [P<0.01], *Escherichia coli* [P<0.01], *Candia albicans* [P<0.01]). Patients treated with mafenide has significantly fewer positive cultures than the control group (*Streptococcus* [P<0.01], *Proteus* [P<0.025], *Klebsiella* [P<0.01], *Escherichia coli* [P<0.01], *Candia* albicans [P<0.01]). Silver sulfadiazine was more effective than mafenide in reducing the clinical infection rate of *Pseudomonas* and *Staphylococcus*. Both treatment groups were comparable in reducing *Escherichia coli* and *Candida albicans*; however, pneumonias were increased in the treatment groups. There was no difference in the number of patients requiring grafting between the groups. There was no difference in the average days in the hospital between the groups. Mortality was reduced in the silver sulfadiazine group compared to control (P<0.01). Secondary: Not reported
Livingston et al.[23] (1990) Silver nitrate 0.5%	RCT Patients admitted to the adult burn unit with thermal injury	N=52 Variable follow-up	Primary: Prevention of autogenous skin-graft loss due to infection	Primary: Graft loss of 10% or more occurred in 33 % of patients. Graft loss of 10% or more occurred in 12% of patients with small burns (<20% total body surface area).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs neomycin (1 g/L) and bacitracin (50,000 units/L) (NB) vs ringers lactate	who required skin grafting		Secondary: Not reported	Graft loss of 10% or more occurred in 67% of patients with large burns (>40% total body surface area). There was no difference in the incidence of graft loss between the treatments. In patients with 20 to 40 % total body surface area burns, the use of either antimicrobial (silver nitrate or neomycin/bacitracin) resulted in a 7% graft loss rate compared to a 67% graft loss rate in the ringers lactate group (P<0.05). The rate of graft loss in the silver nitrate group was significantly lower than in the ringers lactate group (P=0.02). There was no difference in the rate of graft loss between the neomycin/bacitracin and ringers lactate treatment groups (P=0.10) Infection in the area of graft loss was caused by antibiotic-resistant organisms or yeast in 50% of the ringers lactate group and the entire neomycin plus bacitracin group. No graft infections were caused by resistant organisms or yeast in the silver nitrate group. Secondary: Not reported
Khorasani et al.[24] (2009) Silver sulfadiazine 1% cream applied twice daily vs aloe vera cream applied twice daily Each patient had one burn treated with silver sulfadiazine and one burn treated	DB, RCT Patients with second degree burns at two sites on different parts of the body and <40% total burn surface are burns	N=30 21 days	Primary: Time to wound healing and average wound size Secondary: Not reported	Primary; The mean times for healing were 18.73 days for SSD cream and 15.90 days for aloe cream (P<0.0001). The sites treated with aloe healed ~3 days sooner than the sites treated with silver sulfadiazine in all the patients. There was a significant difference in the average wound size among the treatment groups 10, 13, and 16 days after treatment, which favored aloe cream (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with aloe cream.				
Muangman et al.[25] (2010) Silver sulfadiazine 1% applied daily vs Aquacel® Ag (Hydrofiber® dressing and 1.2% ionic silver) applied every three days	RCT Patients with superficial second-degree burns covering <15% total body surface area	N=70 Up to 21 days	Primary: Time to wound healing Secondary: Pain during dressing changes	Primary: Time-to-wound closure was significantly shorter in the Aquacel® Ag group compared to the silver sulfadiazine group (10.0 vs 13.7 days, respectively; P<0.02). Secondary: The average pain scores in the Aquacel® Ag group were significantly lower than in the silver sulfadiazine group on days one, three and seven (4.1, 2.1, and 0.9 vs 6.1, 5.2, and 3.3, respectively; P<0.02).
Barret et al.[26] (2000) Silver sulfadiazine 1% applied twice daily vs Biobrane® (bilaminar temporary skin substitute) applied twice daily	AC, RCT Patients ≤17 years of age with second-degree noninfected burns admitted within 24 hours of the burn, with total body surface area burned 2 to 29%	N=20 3 days	Primary: Pain relief, length of stay, wound healing time, pain and anxiolytic medication use Secondary: Not reported	Primary: Patients treated with Biobrane® had a significantly shorter length of stay, wound healing time, and decreased requirement of pain medications compared to patients in the silver sulfadiazine group (P<0.05). While patients in the Biobrane® treatment group experienced significant pain relief compared to baseline (P<0.001), patients treated with silver sulfadiazine maintained constant high pain scores during their hospital stay. No differences between groups were noted in terms of anxiolytic medication use, infection rate, or autographing needs. Secondary: Not reported
Glat et al.[27] (2009) Silver sulfadiazine 1% cream applied every two to three days	RCT Patients two months to 18 years of age with superficial or mid-dermal burns covering <40% of	N=24 Up to 21 days	Primary: Time to full reepithelialization, pain during dressing changes, number of dressing changes, and	Primary: No significant difference was found between the treatment groups in the time to re-epithelialization (P=0.949). Pain ratings were significantly less in the SilvaSorb® group compared to the silver sulfadiazine group (2.33 vs 5.33; P<0.0001). More patients in the SilvaSorb group (50%) experienced less pain (in the range 1 to 4)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs SilvaSorb® gel applied every two to three days	total body surface area		patient satisfaction Secondary: Not reported	compared to the silver sulfadiazine group (17%). There was no significant difference in the number of dressing changes among the treatment groups (P=0.449). Patients receiving silver sulfadiazine had lower satisfaction scores compared to patients in the SilvaSorb® group (P=0.004). Secondary: Not reported
Muangman et al.[28] (2009) Silver sulfadiazine 1% applied daily vs Urgotul SSD® (hydrocolloid dressing material impregnated with silver sulfadiazine) applied every 2 days	RCT Patients >17 years of age with partial thickness burns covering <15% total body surface area	N=68 Up to 21 days	Primary: Pain relief and time of wound healing Secondary: Rate of wound infections	Primary: Patients treated with Urgotul SSD® had significantly lower pain scores (P=0.02), follow-up times (P=0.03) and time of burn wound closure (P=0.04) compared to silver sulfadiazine. Patients treated with Urgotul SSD® had decreased requirements for pain medications (P=0.04) compared to patients receiving silver sulfadiazine. Secondary: Two patients developed wound infection; one patient in the Urgotul SSD® group and one patient in the silver sulfadiazine group. There was no growth of organism in either patient.
Gravante et al.[29] (2009) Silver sulfadiazine vs nanocrystalline silver	MA Patients with burn wounds	N=285 (5 trials) Up to 21 days	Primary: Differences in the infection rate of burns Secondary: Differences in pain and length of hospitalizations	Primary: The nanocrystalline silver group had a significantly lower incidence of infections compared to the silver sulfadiazine group (9.5 vs 27.8%; P<0.001). Secondary: When data were available, decreased pain scores were observed with nanocrystalline silver compared to silver sulfadiazine (P<0.0001). There were contrasting results for length of hospitalizations among the studies.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Miscellaneous Wound Care				
Dire et al.[30] (1995) Bacitracin zinc, applied to the wound three times a day vs bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound three times a day vs silver sulfadiazine, applied to the wound three times a day vs petrolatum, applied to the wound three times a day	DB, PC, PRO, RCT Patients with uncomplicated soft tissue wound admitted to the emergency department within 12 hours of injury	N=426	Primary: Wound infection rates Secondary: Not reported	Primary: Wound infection rates were 17.6% for petrolatum, 5.5% for bacitracin (NNT=8), 4.5% for bacitracin, neomycin sulfate, and polymyxin B (NNT=8), and 12.1% for silver sulfadiazine (NNT=18; P=0.0034). Sixty percent of the infections were stitch abscesses and were treated with local care only. There was no difference in rates of more serious infections between groups. One patient developed a hypersensitivity reaction to bacitracin, neomycin sulfate, and polymyxin B. Secondary: Not reported
Skin Cleanser or Surgical Scrub				
Smylie et al.[31] (1973) Period 1: Hexachlorophene	OL Operating team consisting of surgeons, nurses,	Period 1: 154 operations Period 2: 228 operations	Primary: Reduction of postoperative CFUs	Primary: During periods 1, 2, and 3, there was no difference between hexachlorophene and chlorhexidine (P>0.1). There was no difference between the two hexachlorophene treatment periods (P>0.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3% Period 2: chlorhexidine 4% Period 3: hexachlorophene 3% Period 4: povidone-iodine	and assistants	Period 3: 262 operations Period 4: 222 operations	Secondary: Not reported	Combining the two baseline measurement periods for hexachlorophene treatment and comparing that with period 2, chlorhexidine appeared to be a better treatment, although of only marginal significance (P=0.05). The major difference was for period 4 with povidone-iodine treatment, which gave counts above five significantly more often than did the other periods (P<0.001). The members of the team found chlorhexidine to be more acceptable for use than either povidone-iodine or hexachlorophene. Secondary: Not reported
Bodey et al.[32] (1976) Hexachlorophene 3% vs P-300® (tribromsalan and triclosan)	AC, RCT Patients with acute leukemia hospitalized in isolation units	N=26 ≤14 weeks	Primary: Reduction of CFUs Secondary: Not reported	Primary: Bathing with either P-300® or hexachlorophene resulted in a major reduction in the number of CFUs on each body site. After one week of bathing, the median number of CFUs was reduced to 0 to 100 per body site in the P-300® group and to 0 to 50 in the hexachlorophene treatment group. Secondary: Not reported

Study design abbreviations: AC=active-control, DB=double-blind, MA=meta-analysis, NNT=number needed to treat, OL=open-label, PC=placebo-controlled, PRO=prospective, RCT=randomized trial, RETRO=retrospective
Miscellaneous abbreviations: CFUs=colony-forming units

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Hexachlorophene	liquid	pHisoHex®	$$$$	N/A
Mafenide	cream, packet	Sulfamylon®*	$$-$$$$$	N/A
Silver nitrate	solution	N/A	N/A	$
Silver sulfadiazine	cream	Silvadene®*, SSD®*	$	$
Sulfanilamide	vaginal cream	AVC®	$$$$	N/A
Combination Products				
Acetic acid and oxyquinoline	vaginal jelly	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
†No current clinical significant information was identified.
N/A=Not available

X. Conclusions

The skin and mucous membrane miscellaneous local anti-infectives are approved for the treatment of vaginal infections, antiseptic cleansing, and prevention/treatment of burn wounds.[1-9] Several of the products are available in a generic formulation.

Guidelines do not provide recommendations regarding the use of sulfanilamide or acetic acid and oxyquinoline (with or without ricinoleic acid) for the treatment of vaginal infections.[11,14,16] There were no published studies found in the medical literature with these agents. According to the prescribing information, sulfanilamide has been shown to be significantly more effective than placebo following 15 to 30 days of treatment.[7]

Hexachlorophene is approved for use as a surgical scrub and a bacteriostatic skin cleanser. The Centers for Disease Control and Prevention (CDC) guidelines on hand hygiene in health care settings recommend alcohol-based products for standard handwashing or hand antisepsis compared to soap or antimicrobial soaps as they are more effective. Studies of hexachlorophene as a hygienic hand wash and surgical scrub have demonstrated modest efficacy after a single hand wash. Hexachlorophene has residual activity for several hours after use and gradually reduces bacterial counts on hands after multiple uses. However, with repeated use, the drug is absorbed through the skin. As a result, it is seldom used as a surgical scrub. Hexachlorophene should not be used to bathe patients with burns or extensive areas of susceptible, sensitive skin. The CDC recommends against the routine bathing of neonates with hexachlorophene because of its potential neurotoxic effects.[17]

Topical antimicrobial therapy remains one of the most important components of wound care in hospitalized burn patients. Mafenide, silver nitrate and silver sulfadiazine are effective for the prevention and treatment of burn wounds. Silver sulfadiazine is the most frequently used agent because of its low toxicity and ease of use. Mafenide rapidly penetrates burn eschar; however, the application must be limited because of systemic toxicity associated with prolonged use.[33] Mafenide is a strong carbonic anhydrase inhibitor, which can lead to acid-base abnormalities. Pain or burning following mafenide application is the most frequently reported adverse event. Silver nitrate does not penetrate the eschar due to precipitation upon contact with exudates. Therefore, it is only used for prevention of infection and is not effective in treating wound infections. Silver nitrate may be an effective treatment option for patients with an allergy to sulfonamides. There are very few studies that directly compared the efficacy and safety of the miscellaneous local anti-infectives for the prevention/treatment of burn wounds.[18-28] MacMillan et al. reported similar efficacy with mafenide and silver nitrate in patients with second-and third-degree burn wounds who required topical antibacterial therapy.[20] Pegg et al. demonstrated similar efficacy with mafenide and silver sulfadiazine in patients with burn injuries requiring admission.[22]

There is insufficient evidence to support that one brand skin and mucous membrane miscellaneous local anti-infective is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane miscellaneous local anti-infectives within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane miscellaneous local anti-infective is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Nov]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Nov 13]. Available from: http://www.thomsonhc.com/.
3. pHisoHex® [package insert]. Bridgewater (NJ): Sanofi-aventis U.S. LLC; 2012 Jan.
4. Sulfamylon® cream [package insert]. Rockford (IL): UDL Laboratories, Inc.; 2007 Aug.
5. Sulfamylon® packets [package insert]. Rockford (IL): UDL Laboratories, Inc.; 2008 Apr.
6. Silvadene® [package insert]. Bristol (TN): Monarch Pharmaceuticals, Inc.; 2013 Mar.
7. AVC® [package insert]. Philadelphia (PA): Azur Pharma, Inc.; 2011 Sept.
8. Silver nitrate [package insert on the internet]. Sellersville (PA): Teva Pharmaceuticals USA; 2004 Jan [cited 2013 Dec]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=6956c883-fc1b-49be-97bc-e642e0aa907d.
9. Fem pH® [package insert on the internet]. Salt Lake City (UT): Pharmics, Inc.; 2013 May [cited 2013 Dec]. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=77237c50-aeb5-44a0-a1e6-ce1551b49f75.
10. Sobel JD. Candida vulvovaginitis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Dec 12]. Available from: http://www.utdol.com/utd/index.do.
11. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
12. Madoff Lawrence C, Pereyra Florencia. Chapter e15. Infectious Complications of Burns and Bites (Chapter). Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine. 17th ed. 2008 Available from: http://www.accessmedicine.com/content.aspx?aID=2885387.
13. Mozingo DW, Cioffi WG, Pruitt BA. Burns. In: Bongard FS, Sue DY, eds. Current Critical Care Diagnosis & Treatment. 2nd ed. New York: McGraw-Hill; 2003.
14. ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: Vaginitis. Obstet Gynecol. 2006;107:1195-206.
15. European (International Union Against Sexually Transmitted Infections/World Health Organization). Guideline on the Management of Vaginal Discharge [guideline on the internet]. London (UK): European (International Union Against Sexually Transmitted Infections/World Health Organization); 2011 [cited 2013 Oct 1]. Available from: http://www.iusti.org/regions/europe/pdf/2011/Euro_Guidelines_Vaginal_Discharge_2011.Intl_Jrev.pdf.
16. British Association for Sexual Health and HIV: Clinical Effectiveness Group. UK National Guideline for the Management of Bacterial Vaginosis [guideline on the internet]. Cheshire (UK): British Association for Sexual Health and HIV; 2012 [cited 2013 Oct 1]. Available from: http://www.bashh.org/documents/4413.pdf.
17. Centers for Disease Control and Prevention. Guideline for Hand Hygiene in Health-Care Settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. MMWR 2002;51(No. RR-16):1-56. Available at: http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf. Accessed December 2013.
18. New Zealand Guidelines Group (NZGG). Management of burns and scalds in primary care. Wellington (NZ): Accident Compensation Corporation (ACC); 2007 Jun. 116 p. Available at: http://www.acc.co.nz/PRD_EXT_CSMP/groups/external_communications/documents/guide/dis_ctrb094689.pdf. Accessed December 2013.
19. Heinle EC, Dougherty WR, Garner WL, Reilly DA. The use of 5% mafenide acetate solution in the postgraft treatment of necrotizing fasciitis. J Burn Care Rehabil. 2001;22(1):35-40.
20. Kucan JO, Smoot EC. Five percent mafenide acetate solution in the treatment of thermal injuries. J Burn Care Rehabil. 1993;14:158-63.
21. MacMillan BG, Hill EO, Altemeier WA. Use of topical silver nitrate, mafenide, and gentamicin in the burn patient. A comparative study. Arch Surg. 1967;95:472-81.
22. Pegg SP, Ramsay K, Meldrum L, Laundy M. Clinical comparison of maphenide and silver sulphadiazine. Scand J Plast Reconstr Surg. 1979;13(1):95-101.
23. Livingston DH, Cryer HG, Miller FB, Malangoni MA, Polk HC Jr, Weiner LJ. A randomized prospective study of topical antimicrobial agents on skin grafts after thermal injury. Plast Reconstr Surg. 1990;86(6):1059-64.

24. Khorasani G, Hosseinimehr SJ, Azadbakht M, Zamani A, Mahdavi MR. Aloe vs silver sulfadiazine creams for second-degree burns: a randomized controlled study. Surg Today. 2009;39(7):587-91.
25. Muangman P, Pundee C, Opasanon S, Muangman S. A prospective, randomized trial of silver containing hydrofiber dressing vs 1% silver sulfadiazine for the treatment of partial thickness burns. Int Wound J. 2010;7(4):271-6.
26. Barret JP, Dziewulski P, Ramzy PI, Wolf SE, Desai MH, Herndon DN. Biobrane vs 1% silver sulfadiazine in second-degree pediatric burns. Plast Reconstr Surg. 2000;105(1):62-5.
27. Glat PM, Kubat WD, Hsu JF, Copty T, Burkey BA, Davis W, et al. Randomized clinical study of SilvaSorb gel in comparison to Silvadene silver sulfadiazine cream in the management of partial-thickness burns. J Burn Care Res. 2009;30(2):262-7.
28. Muangman P, Muangman S, Opasanon S, Keorochana K, Chuntrasakul C. Benefit of hydrocolloid SSD dressing in the outpatient management of partial thickness burns. J Med Assoc Thai. 2009;92(10):1300-5.
29. Gravante G, Caruso R, Sorge R, Nicoli F, Gentile P, Cervelli V. Nanocrystalline silver: a systematic review of randomized trials conducted on burned patients and an evidence-based assessment of potential advantages over older silver formulations. Ann Plast Surg. 2009;63(2):201-5.
30. Dire DJ, Coppola M, Dwyer DA, Lorette JJ, Karr JL. Prospective evaluation of topical antibiotics for preventing infections in uncomplicated soft-tissue wounds repaired in the ED. Acad Emerg Med. 1995 Jan;2(1):4-10.
31. Smylie H, Logie J, Smith G. From Phisohex to Hibiscrub. Br Med J. 1973;4(5892):586-9.
32. Bodey GP, Edersole R, Hong H. Randomized trial of a hexachlorophene preparation and P-300 bacteriostatic soaps. J Invest Dermatol. 1976;67(4):532-7.
33. Monafo WW. The initial management of burns. N Engl J Med. 1996;335:1581-6.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Anti-inflammatory Agents
AHFS Class 840600
February 12, 2014

I. Overview

The skin and mucous membrane anti-inflammatory agents are approved for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.[1-28] While systemic corticosteroids are more effective for dermatologic inflammatory conditions, they are generally reserved for more widespread and advanced conditions. Topical treatment is preferred in most cases, with limited or localized involvement, to help minimize systemic adverse events.

The mechanism of action of corticosteroids is complex and not completely understood. After entering the cell through passive diffusion, they bind to specific receptors. It is estimated that there are between 5,000 and 100,000 receptors per cell.[29] Therefore, these agents have the potential to elicit a wide variety of biologic responses. Corticosteroids reduce inflammation, possess antimitotic activity and induce cutaneous vasoconstriction.[30]

The topical corticosteroids are classified based on their relative potency: super high potency (Class I), high potency (Classes II to III), medium potency (Classes IV to V) and low potency (Classes VI to VII).[30] The super high potency agents are used to treat severe dermatoses over non-facial and non-intertriginous areas.[30] Medium to high potency agents are often used for the treatment of mild to moderate non-facial and non-intertriginous dermatoses. Low to medium potency agents are used when large areas need to be treated due to the potential for systemic absorption. Only low potency agents should be used on the eyelids and genital areas.[30]

The efficacy and safety of topical corticosteroids depends on a variety of factors, including potency, type and location of lesions being treated, vehicle used, application method and patient factors (e.g., age). The topical corticosteroids are available in a variety of vehicles, including cream, foam, gel, lotion, ointment, paste, shampoo, solution, spray and tape.[30] Ointments are semiocclusive and are considered the most potent vehicle; however, they are greasy and difficult to use on hairy areas. Creams are less potent than ointments, but are stronger than lotions. They can be easily washed off with water and are the most cosmetically appealing vehicle for applying topical medications. Lotions are considered the least potent of all of the vehicles, but are easier to apply to large or hairy areas. Solutions are often used as bath soaks and for wet dressings. Gels are greaseless and dry as a thin film after application. Foams spread easily and are often easier to apply than other vehicles, especially to hairy areas. Unlike other vehicles, foams require a special delivery system due to the pressurized nature of the product.[30]

The skin and mucous membrane anti-inflammatory agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The relative potency ratings of the topical corticosteroids are listed in Table 2. There is at least one topical corticosteroid available in a generic formulation in each potency category. Hydrocortisone is also available over-the-counter. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Anti-Inflammatory Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Alclometasone	cream, ointment	N/A	alclometasone
Amcinonide	cream, lotion, ointment	N/A	amcinonide
Betamethasone dipropionate	cream, gel, lotion, ointment	N/A	betamethasone dipropionate
Betamethasone valerate	cream, foam, lotion, ointment	Luxiq®*	betamethasone valerate
Clobetasol	cream, foam, gel, lotion, ointment, shampoo, solution, spray	Clobex®*, Cormax®*, Olux®*, Olux-E®*, Temovate®*, Temovate Emollient®*	clobetasol
Clocortolone	cream	Cloderm®	none
Desonide	cream, foam, gel, lotion,	Desonate®, Verdeso®,	desonide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	ointment	Lokara®*	
Desoximetasone	cream, gel, ointment, spray	Topicort®*	desoximetasone
Diflorasone	cream, ointment	ApexiCon E®	diflorasone
Dimethyl sulfoxide	solution^	Rimso-50®	none
Fluocinolone	cream, oil, ointment, shampoo, solution	Capex Shampoo®, Derma-Smoothe/FS®*, Synalar®*	fluocinolone, Capex Shampoo®
Fluocinonide	cream, gel, ointment, solution	Vanos®	fluocinonide
Flurandrenolide	tape	Cordran®	none
Fluticasone	cream, lotion, ointment	Cutivate®*	fluticasone
Halcinonide	cream, ointment	Halog®	none
Halobetasol	cream, ointment	Ultravate®*	halobetasol
Hydrocortisone	cream, lotion, ointment, rectal cream, rectal enema, solution	Anusol-HC®*, Cortenema®*, Proctocort®*, ProctoCream-HC®*, Texacort®	hydrocortisone
Hydrocortisone acetate	rectal foam	Cortifoam®	none
Hydrocortisone butyrate	cream, ointment, solution	N/A	hydrocortisone butyrate
Hydrocortisone probutate	cream	Pandel®	none
Hydrocortisone valerate	cream, ointment	N/A	hydrocortisone valerate
Mometasone	cream, ointment, solution	Elocon®*	mometasone
Prednicarbate	cream, ointment	Dermatop®*	prednicarbate
Triamcinolone	aerosol, cream, dental paste, lotion, ointment	Kenalog®, Oralone®*, Trianex®	triamcinolone
Combination Products			
Betamethasone dipropionate and propylene glycol	cream, lotion, ointment	Diprolene®*, Diprolene AF®*	betamethasone dipropionate and propylene glycol
Halobetasol and ammonium lactate	combination package	Halonate®, Halonate PAC®, Ultravate PAC®	none
Halobetasol and lactic acid	combination package	Ultravate X®	none
Hydrocortisone, mineral oil, and white petrolatum	ointment	N/A	hydrocortisone, mineral oil, and white petrolatum
Hydrocortisone acetate and aloe vera	gel	N/A	hydrocortisone acetate and aloe vera
Hydrocortisone acetate and lidocaine	cream	N/A	hydrocortisone acetate and lidocaine
Hydrocortisone acetate and pramoxine	rectal cream, rectal foam	PramCort®, ProCort®, ProctoFoam-HC®	none
Hydrocortisone acetate and urea	cream	N/A	hydrocortisone acetate and urea
Mometasone and ammonium lactate	combination package	Momexin®	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
N/A=Not available
PDL=Preferred Drug List

Table 2. Relative Potency Ratings of the Skin and Mucous Membrane Anti-inflammatory Agents[30]

Group	Generic Name(s)	Strength	Formulations
I	betamethasone dipropionate and propylene glycol	0.05%	gel, lotion, ointment
I	clobetasol	0.05%	cream, foam, gel, lotion, ointment, shampoo, solution, spray
I	fluocinonide	0.1%	cream
I	flurandrenolide	4 µg/cm^2	tape
I	halobetasol	0.05%	cream, ointment
II	amcinonide	0.1%	ointment
II	betamethasone dipropionate	0.05%	cream, ointment
II	desoximetasone	0.05%	gel
II	desoximetasone	0.25%	cream, ointment, spray
II	diflorasone	0.05%	cream, ointment
II	fluocinonide	0.05%	cream, gel, ointment, solution
II	halcinonide	0.1%	cream, ointment
II	triamcinolone	0.5%	ointment
III	amcinonide	0.1%	cream, lotion
III	betamethasone dipropionate	0.05%	gel, lotion
III	betamethasone valerate	0.1%	ointment
III	betamethasone valerate	0.12%	foam
III	desoximetasone	0.05%	cream, ointment
III	fluticasone	0.005%	ointment
III	mometasone	0.1%	ointment
III	triamcinolone	0.5%	cream, ointment
III	triamcinolone	0.1%	ointment
IV	clocortolone	0.1%	cream
IV	fluocinolone	0.025%	ointment
IV	hydrocortisone valerate	0.2%	ointment
IV	mometasone	0.1%	cream, solution
IV	triamcinolone	0.1%	cream
IV	triamcinolone	0.2 mg	aerosol
V	betamethasone valerate	0.1%	cream
V	desonide	0.05%	gel, ointment
V	fluocinolone	0.025%	cream
V	fluticasone	0.05%	cream, lotion
V	hydrocortisone butyrate	0.1%	cream, ointment, solution
V	hydrocortisone valerate	0.2%	cream
V	hydrocortisone probutate	0.1%	cream
V	prednicarbate	0.1%	cream, ointment
V	triamcinolone	0.025%	ointment
V	triamcinolone	0.1%	lotion
VI	alclometasone	0.05%	cream, ointment
VI	betamethasone valerate	0.1%	lotion
VI	desonide	0.05%	cream, foam, lotion
VI	fluocinolone	0.01%	cream, oil, shampoo, solution
VI	triamcinolone	0.025%	cream, lotion
VII	Hydrocortisone (base)	0.5%	cream, ointment
VII	Hydrocortisone (base)	1%	cream, lotion, ointment, spray
VII	hydrocortisone (base)	2.5%	cream, lotion, ointment, solution

Group	Generic Name(s)	Strength	Formulations
VII	Hydrocortisone acetate with pramoxine 1% combination	1%	cream, foam, lotion, ointment

I=Highest Potency; VII=Lowest Potency

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane anti-inflammatory agents are summarized in Table 3.

Table 3. Treatment Guidelines Using the Skin and Mucous Membrane Anti-Inflammatory Agents

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network: **Management of Atopic Eczema in Primary Care[31] (2011)**	Emollient therapy • Patients with atopic eczema should receive ongoing treatment with emollients. Topical corticosteroid therapy • Patients should continue with emollient therapy during treatment with topical corticosteroids. • Patients with atopic eczema should be advised to apply topical corticosteroids once daily. • Twice weekly maintenance therapy with a topical corticosteroid should be considered in patients with moderate to severe atopic eczema experiencing frequent relapses. • There is no good quality evidence to assist in the choice of topical corticosteroid potency in the treatment of atopic eczema. • The choice of topical corticosteroid potency should be tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed. For delicate areas of skin, such as the face and flexures, only mild or moderately potent preparations should be used. On the face, especially in children, it is reasonable to start with a mildly potent topical corticosteroid. • Topical corticosteroids should be used with caution in the periocular region. Topical calcineurin inhibitors • Tacrolimus should be considered for short-term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids, or if there is a serious risk of important adverse effects from further topical corticosteroid use (e.g., skin atrophy). • Topical calcineurin inhibitors should not be applied to skin which appears actively infected. • Due to long-term safety issues, topical calcineurin inhibitors should not be used as first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Antihistamines • Short-term bedtime use of sedating antihistamines should be considered in patients with atopic eczema when there is sleep disturbance.
Primary Care Dermatology Society/British Association of Dermatologists: **Guidelines for the Management of Atopic Eczema[32] (2009)**	Emollients • Most patients have dry skin and require the general use of emollients. • Emollients should be applied as liberally and frequently as possible. They are best applied when the skin is moist but they can and should be applied at other times as well. Emollients should be applied every four hours or at least three to four times per day. • Continual treatment with complete emollient therapy (combinations of cream, ointment, bath oil and emollient soap substitute) will help provide maximal effect.

Clinical Guideline	Recommendation(s)
	• Intensive use of emollients will reduce the need for topical steroids. Topical Steroids • Topical steroids provide symptomatic relief and are safe in the short term. • The potency should be matched to the disease severity and the affected site. Weaker corticosteroids should be used on the face and flexures. • The weakest steroid that controls the disease effectively should be chosen. • Steroid use should be limited to a few days to a week for acute eczema and up to four to six weeks to gain initial remission for chronic eczema. • Very potent corticosteroids may rarely be indicated in resistant severe eczema on the hands and feet of adults. • Patients using moderate and potent steroids must be kept under review for both local and systemic side-effects, including the use of growth charts for children. • Topical steroids should not be used to provide an emollient effect. Emollients should not be applied shortly after application of a topical steroid. Immunomodulatory treatments • Immunomodulatory agents (e.g., tacrolimus or pimecrolimus) are an alternative to topical steroids. • They should only be considered if the patient is intolerant to or has failed with conventional corticosteroid therapy. • They do not cause skin atrophy. • The long-term adverse effects of tacrolimus and pimecrolimus are unknown. • Treatment with tacrolimus or pimecrolimus should be initiated only by physicians with experience in dermatology, after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options. Other treatments • Sedating antihistamines may be used to reduce pruritus. Non-sedating antihistamines have very limited benefit. • Third-line treatments include phototherapy and various immunosuppressive agents.
European Academy of Dermatology and Venereology: **Position Paper on Diagnosis and Treatment of Atopic Dermatitis[33] (2009)**	• Topical corticosteroids are a first-line anti-inflammatory therapy. Application two to three times monthly with emollients should suffice in mild disease. • Topical calcineurin inhibitors have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Tacrolimus 0.1% ointment is similar to an intermediately potent topical corticosteroid and an intermediately potent topical corticosteroid is more active than pimecrolimus 1% cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and pre-clinical data do not indicate an increased risk for photo carcinogenicity, though ultraviolet protection is advised. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma over a period of six years or photo carcinogenicity for topical calcineurin inhibitors. But since the continuous oral administration of the cyclosporine is associated with an increased photo carcinogenicity risk in solid organ transplant patients, ultraviolet protection e.g. with sunscreens has been advised.
National Institute for Health and Clinical Excellence:	General considerations • A stepped approach should be used for managing atopic eczema in children. Treatment should be tailored based on the severity of the atopic eczema.

Clinical Guideline	Recommendation(s)

Management of Atopic Eczema in Children From Birth Up to the Age of 12 Years[34] (2007)	• Emollients should always be used, even when the atopic eczema is clear. Treatment can be stepped up or down, according to the severity of symptoms, with the addition of the other treatments as necessary as follows:
	  o Mild atopic eczema: emollients and mild potency topical corticosteroids.
	  o Moderate atopic eczema: emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages.
	  o Severe atopic eczema: emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy.
	
	<u>Emollients</u>
	• Emollients should be used on the whole body when the atopic eczema is clear and while using all other treatments.
	
	<u>Topical corticosteroids</u>
	• Use mild potency topical corticosteroids on the face and neck, except for short-term (three to five days) use of moderate potency agents for severe flares.
	• Use moderate or potent topical corticosteroids for short periods only (seven to 14 days) for flares in sites such as axillae and groin.
	• Do not use very potent preparations in children without specialist dermatological advice.
	• Topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily.
	• In children ≥12 months of age, potent topical corticosteroids should be used for the shortest amount of time as possible; no longer than 14 days. They should not be used on the face or neck. Potent topical corticosteroids should not be used in children <12 months of age without specialist dermatological supervision.
	• Consider treating problem areas with topical corticosteroids for two consecutive days per week to prevent flares, rather than treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled.
	• A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected.
	
	<u>Topical calcineurin inhibitors</u>
	• Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.
	• Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
	• Pimecrolimus is recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged two to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
	• Treatment with tacrolimus or pimecrolimus should only be initiated by physicians (including general practitioners) with a special interest and experience in dermatology.
	• For facial atopic eczema in children that requires long-term or frequent use of

Clinical Guideline	Recommendation(s)
	mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors. Antihistamines • Oral antihistamines should not be used routinely in the management of atopic eczema in children. • A one-month trial of a nonsedating antihistamine should be offered to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every three months. • A seven to 14 day trial of an age-appropriate sedating antihistamine should be offered to children aged six months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful. Phototherapy and systemic treatments • Phototherapy or systemic treatments should be considered for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life.
American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma and Immunology/Joint Council on Allergy, Asthma and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter**[35] **(2012)**	General considerations • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. Skin hydration • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. Topical corticosteroids • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. Topical calcineurin inhibitors • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a

Clinical Guideline	Recommendation(s)
	reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. <u>Tar preparations</u> • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. <u>Antihistamines</u> • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. <u>Vitamin D</u> • Patients with atomic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. <u>Dilute bleach baths</u> • The addition of dilute bleach baths twice weekly may reduce the severity of atomic dermatitis, especially in patients with recurrent skin infections. <u>Microbes</u> • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atomic dermatitis, and patients with moderate-to-severe atomic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atomic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atomic dermatitis and might contribute to exacerbations. <u>Systemic Immunomodulating Agents</u> • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects.

Clinical Guideline	Recommendation(s)
	Phototherapy • Ultraviolet therapy can be a useful treatment for recalcitrant atomic dermatitis. Allergen immunotherapy • Select patients with atomic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for Atopic Dermatitis[36] (2004)**	Topical agents • Topical corticosteroids are the standard of care for the treatment of atopic dermatitis. • Cutaneous complications such as striae, atrophy, and telangiectasia limit the long-term use of these agents. • Despite the extensive use of topical corticosteroids, there are limited data regarding optimal corticosteroid concentrations, duration and frequency of therapy, and quantity of application; similarly, data supporting the perception that long-term corticosteroid use is not associated with extracutaneous adverse effects are lacking. • Altering the local environment by hydration and/or occlusion as well as varying the vehicle can impact the absorption and effect of the topical corticosteroid administered. • The use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies. • Emollients are a standard of care, steroid-sparing, and useful for prevention and maintenance therapy. • Pimecrolimus and tacrolimus have been shown to reduce the extent, severity, and symptoms of atopic dermatitis in adults and children. • Tar may be associated with therapeutic benefits, but is limited by compliance. • Short-term adjunctive use of topical doxepin may reduce pruritus, but adverse events may limit its usefulness. Antibiotics and antiseptics • Patients with atopic dermatitis are commonly colonized with *Staphylococcus aureus*. Systemic and topical antibiotics temporarily reduce *Staphylococcus aureus* colonization on the skin. • Topical antibiotics can be effective when infection is present; however, development of resistance is a concern. Oral antihistamines • For patients with significant sleep disruption due to itch, allergic dermatographism, or allergic rhinoconjunctivitis, sedating antihistamines may be useful. • Many patients with atopic dermatitis may also have allergic rhinoconjunctivitis, urticaria, and dermatographism and may benefit from the use of antihistamines.
British Association of Dermatologists: **Guidelines for the Management of Contact Dermatitis[37] (2009)**	• Most irritant contact dermatitis involves the hands. Gloves are therefore the mainstay of protection. • Barrier creams by themselves are of questionable value in protecting against contact with irritants. After-work creams confer some degree of protection against developing irritant contact dermatitis. • Topical corticosteroids, soap substitutes and emollients are widely accepted as the treatment of established contact dermatitis. • Second-line treatments such as psoralen plus ultraviolet A, azathioprine and cyclosporine are used for steroid-resistant chronic hand dermatitis.
American Academy of Dermatology:	• Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents.

Clinical Guideline	Recommendation(s)
Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapies[38] (2009)	• Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include vitamin D analogs, tazarotene, tacrolimus, pimecrolimus, nonmedicated topical moisturizers, salicylic acid, anthralin, coal tar and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific Food and Drug Administration (FDA)-approved indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid; however, the agent is typically used in combination with other topical therapies. • Coal tar products are often poorly tolerated by patients because of cosmetic issues, including staining of clothes and the tar odor that is present in almost all products. • Coal tar is carcinogenic in animals; however, in humans there are no convincing data proving carcinogenicity, and epidemiologic studies fail to show increased risk of skin cancer in patients who use coal tar.

British Association of Dermatologists/Primary Care Dermatology Society: **Recommendations for the Initial Management of Psoriasis[39] (2009)**	• Emollients should be used to soften scaling and reduce any irritation.
	• For localized plaque psoriasis (e.g., on the elbows or knees), one or more of the following topical preparations can be tried. The sequence of choice will vary according to the extent and pattern of psoriasis, and patient preference:
	  ○ A tar-based cream, or a tar/corticosteroid mixture.
	  ○ A moderate potency topical corticosteroid (e.g. 0.05% clobetasone butyrate); stronger agents can be used on palms and soles or on the scalp (use of topical steroids may lead to rebound exacerbation when treatment is discontinued).
	  ○ A vitamin D analog (e.g.; calcipotriol, calcitriol or tacalcitol). The latter two tend to be less irritant and are more suitable for face or flexures, but should still be used with caution.
	  ○ Calcipotriol with betamethasone dipropionate as a combination product (long-term data regarding relapse rates is not yet established).
	  ○ A vitamin A analog (tazarotene).
	  ○ A dithranol preparation, usually used as a short-contact treatment (these are effective but more difficult to use, especially if there are many small lesions).
	• For more widespread plaque psoriasis (e.g., on the trunk or the limbs), the same treatments may be appropriate.
	  ○ Dithranol is often impracticable to apply to multiple small lesions and will irritate flexures.
	  ○ Topical corticosteroids may be inappropriate for use in widespread psoriasis, particularly more potent agents if used on a long-term basis.
	• For scalp psoriasis, a tar-based shampoo should be tried first. This can be combined with salicylic acid (2 to 5% preparation), a coconut oil/tar/salicylic acid combination ointment, a potent topical corticosteroid preparation (e.g., 0.1% betamethasone valerate), calcipotriol scalp application, or more than one of these.
	• In palm and sole psoriasis, both hyperkeratosis and inflammation are usually present and may require separate treatments. Hyperkeratosis usually needs to be treated with a keratolytic agent. Topical steroids (usually potent, due to the thick skin at this site), tars and vitamin D analogs may all be useful.
	• In general, milder agents are used for flexures. These include low potency

Clinical Guideline	Recommendation(s)
	topical steroids, mild tar preparations, and tacalcitol or calcitriol (not calcipotriol, this is usually irritant in flexures). • In facial psoriasis, use mild agents: emollients, mild corticosteroids, calcitriol, tacalcitol, mild tars.
Finnish Medical Society Duodecim: **Seborrheic Dermatitis[40] (2007)**	<u>General considerations</u> • Treatment does not cure the disease. Therefore, it must be repeated when the symptoms recur, or even prophylactically. <u>Removing the thick scales and decreasing the amount of sebum</u> • The scales can be softened with a cream containing salicylic acid and sulfur (but not Vaseline) or by wetting and washing. • Seborrheic skin should be washed more often than usual. <u>Decreasing fungal growth</u> • Washing the scalp with ketoconazole shampoo or selenium sulfide shampoo. • Topical treatment with creams containing imidazole derivatives. • Antimycotic on skin creases (rarely necessary). • Sometimes ultraviolet light therapy. <u>Symptomatic topical treatment</u> • Corticosteroid liniments for the scalp (from mild to potent). • Corticosteroid creams for other parts of the body (from mild to potent). • Moisturizing emollients after washing. • Ketoconazole shampoo and corticosteroid liniments must often be combined in therapy-resistant cases.
American Gastroenterological Association: **Medical Position Statement: Diagnosis and Treatment of Hemorrhoids[41] (2004)**	• Treatment of hemorrhoids depends on their severity. • The cornerstone of medical therapy is fiber and water. • Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge, or fecal seepage. • Prolonged use of potent corticosteroid preparations may be harmful and should be avoided.
American Gastroenterological Association: **Technical Review on the Diagnosis and Treatment of Hemorrhoids[42] (2004)**	• Add dietary fiber and avoid straining at stool. • Over-the-counter topical agents and suppositories have become equally ubiquitous in the empirical treatment of hemorrhoidal symptoms, but data supporting their use are lacking. • Topical analgesics may bring relief of local pain and itching. • Corticosteroid creams may ameliorate local perianal inflammation, but no data suggest that they actually reduce hemorrhoidal swelling, bleeding, or protrusion. • Long-term use of high-potency corticosteroid creams is deleterious and should be avoided.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane anti-inflammatory agents are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Skin and Mucous Membrane Anti-Inflammatory Agents[1-28]

Generic Name(s)	Relief of Inflammatory and Pruritic Manifestations of Corticosteroid-Responsive Dermatoses*
Single Entity Agents	
Alclometasone	✔
Amcinonide	✔
Betamethasone dipropionate	✔
Betamethasone valerate	✔
Clobetasol	✔
Clocortolone	✔
Desonide	✔
Desoximetasone	✔
Diflorasone	✔
Fluocinolone	✔
Fluocinonide	✔
Flurandrenolide	✔
Fluticasone	✔
Halcinonide	✔
Halobetasol	✔
Hydrocortisone	✔ †‡
Hydrocortisone acetate	✔ †§
Hydrocortisone butyrate	✔
Hydrocortisone probutate	✔
Hydrocortisone valerate	✔
Mometasone	✔
Prednicarbate	✔
Triamcinolone	✔ ‖
Combination Products	
Betamethasone dipropionate and propylene glycol	✔
Halobetasol and ammonium lactate	✔
Halobetasol and lactic acid	✔
Hydrocortisone, mineral oil and white petrolatum	✔
Hydrocortisone acetate and aloe vera	✔ †
Hydrocortisone acetate and lidocaine	✔
Hydrocortisone acetate and pramoxine	✔
Hydrocortisone acetate and urea	✔
Mometasone and ammonium lactate	✔

*Dermatoses include anogenital and anorectal pruritus, atopic dermatitis, psoriasis, seborrheic dermatitis, and inflammatory phase of xerosis.
†Over the counter topical products are used for the temporary relief of itching associated with minor skin irritations, inflammation, and rashes.
‡Rectal enema is indicated as adjunctive therapy in the treatment of ulcerative colitis.
§Rectal foam is indicated as adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.
‖Dental paste is indicated for adjunctive treatment and for the temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane anti-inflammatory agents are listed in Table 5. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individuals components listed in the table below.

Table 5. Pharmacokinetic Parameters of the Skin and Mucous Membrane Anti-Inflammatory Agents[1-28]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Alclometasone	3	Not reported	Liver	Renal	Not reported
Amcinonide	Not reported	Not reported	Liver	Renal	Not reported
Betamethasone	12 to 14	64	Liver	Renal	Not reported
Clobetasol	Not reported	Variable	Liver	Renal, Bile	Not reported
Clocortolone	Not reported	Variable	Liver	Renal, Bile	Not reported
Desonide	Not reported	Not reported	Liver	Renal, Bile	Not reported
Desoximetasone	Variable	Variable	Liver	Renal, Feces, Bile	15 to 17
Diflorasone	1	Not reported	Liver	Renal, Bile	Not reported
Fluocinolone	Variable	>90	Not reported	Renal, Bile	Not reported
Fluocinonide	Not reported	Variable	Liver	Renal, Feces	Not reported
Flurandrenolide	Variable	Variable	Liver	Renal, Bile	Not reported
Fluticasone	Not reported	91	Liver	Renal, Feces	7.2
Halcinonide	Not reported	Note reported	Liver	Renal, Bile	Not reported
Halobetasol	3	Not reported	Not reported	Not reported	Not reported
Hydrocortisone	Not reported	90	Liver	Renal	1 to 2
Mometasone	0.7	Not reported	Liver	Renal, Feces	Not reported
Prednicarbate	Poor	Not reported	Not reported	Not reported	Not reported
Triamcinolone	Not reported	Not reported	Liver	Renal, Bile	2 to 3

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane anti-inflammatory agents, no significant drug interactions have been reported.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane anti-inflammatory agents are listed in Tables 6 and 7. Adverse drug events of the combination products not listed in the tables below would be in line with the properties of their individuals components listed in the table below.

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Anti-Inflammatory Agents (Drugs A to F)[1-28]

Adverse Events	Alclometasone	Amcinonide	Betamethasone	Clobetasol	Clocortolone	Desonide	Desoximetasone	Diflorasone	Fluocinolone
Dermatological									
Acneform eruptions	✔	✔	✔	✔	<1	✔	<1	✔	✔
Allergic contact dermatitis	✔	✔	✔	✔	-	✔	<1	✔	✔
Alopecia	-	-	-	✔	-	-	-	-	-
Asteatotic eczema	-	-	-	✔	-	-	-	-	-
Atopic dermatitis (secondary)	-	-	-	-	-	-	-	-	✔
Atrophy	-	-	-	-	-	✔	-	-	-
Burning	✔	✔	✔	✔	1 to 10	✔	<1	✔	✔
Cracking	-	-	-	✔	-	-	-	-	-
Dermatitis	-	-	-	-	-	✔	-	-	-
Dryness	✔	✔	✔	✔	1 to 10	✔	<1	✔	✔
Erythema	✔	-	✔	✔	1 to 10	✔	<1	-	✔
Folliculitis	✔	✔	✔	✔	-	✔	<1	✔	✔
Hypertrichosis	✔	✔	✔	✔	<1	-	<1	✔	✔
Hypopigmentation	✔	✔	-	✔	<1	✔	<1	✔	✔
Irritation	✔	✔	✔	✔	1 to 10	✔	<1	✔	✔
Keratosis pilaris	-	-	-	-	-	-	-	-	✔
Maceration of the skin	✔	✔	-	✔	<1	-	<1	✔	-
Miliaria	✔	✔	✔	✔	<1	✔	<1	✔	✔
Numbness	-	-	-	✔	-	-	-	-	-
Papular rash	✔	-	-	-	1 to 10	-	-	-	-
Papules	-	-	-	-	-	-	-	-	✔
Peeling of skin	-	-	-	-	-	✔	-	-	-
Perioral dermatitis	✔	-	-	✔	<1	✔	<1	✔	✔
Pruritus	✔	✔	✔	✔	1 to 10	✔	<1	✔	✔
Pustules	-	-	-	-	-	-	-	-	✔
Rash	-	-	-	-	-	✔	-	-	-
Scaly skin	-	-	-	-	-	✔	-	-	-
Shiny skin	-	-	-	-	-	-	-	-	✔
Skin atrophy	✔	✔	✔	✔	<1	✔	<1	✔	✔
Stinging	-	-	-	✔	-	✔	-	-	-
Striae	✔	✔	✔	-	<1	✔	<1	✔	✔
Telangiectasia	✔	✔	-	✔	-	✔	-	-	✔
Urticaria	-	-	-	✔	-	-	-	-	-
Vesiculation	-	-	✔	-	-	-	<1	-	-
Endocrine and Metabolic									
Adrenal suppression	-	-	-	✔	-	-	-	-	-
Cushing's Syndrome	✔	✔	✔	✔	-	✔	-	-	✔

Adverse Events	Alclometasone	Amcinonide	Betamethasone	Clobetasol	Clocortolone	Desonide	Desoximetasone	Diflorasone	Fluocinolone
Growth retardation	✔	✔	✔	-	-	✔	-	-	-
Hypothalamic-pituitary-adrenal suppression	✔	✔	✔	-	-	✔	-	-	✔
Hyperglycemia	-	✔	✔	✔	-	✔	-	-	-
Weight gain delayed	-	-	-	-	-	✔	-	-	-
Respiratory									
Asthma	-	-	-	-	-	✔	-	-	-
Cough	-	-	-	-	-	✔	-	-	-
Pharyngitis	-	-	-	✔	-	✔	-	-	-
Upper respiratory tract infection	-	-	-	✔	-	✔	-	-	-
Other									
Arthralgia	-	-	-	-	-	-	✔	-	-
Ear infection	-	-	-	-	-	-	-	-	✔
Edema	-	-	-	✔	-	-	-	-	-
Glucosuria	-	-	-	✔	-	-	-	-	-
Headache	-	-	-	-	-	✔	-	-	-
Herpes simplex	-	-	-	-	-	-	-	-	✔
Hypertension	-	-	-	-	-	✔	-	-	-
Intracranial hypertension	-	-	-	-	-	✔	-	-	✔
Irritability	-	-	-	-	-	✔	-	-	-
Muscle atrophy	-	-	-	-	-	-	-	✔	-
Secondary infection	✔	✔	-	✔	-	✔	<1	✔	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Anti-Inflammatory Agents (Drugs F to T)[1-28]

Adverse Events	Fluocinonide	Flurandrenolide	Fluticasone	Halcinonide	Halobetasol	Hydrocortisone	Mometasone	Prednicarbate	Triamcinolone
Dermatological									
Acneform eruptions	✔	✔	✔	✔	✔	✔	-	<1	✔
Allergic contact dermatitis	✔	✔	✔	✔	✔	<1	-	<1	✔
Bacterial skin infection	-	-	-	-	-	-	1 to 10	-	-
Burning	✔	✔	-	✔	1 to 4	<1	1 to 10	<1	✔
Dryness	✔	✔	1	✔	✔	2	-	-	✔
Edema	-	-	✔	-	-	-	-	<1	-
Eczema exacerbation	-	-	2	-	-	13	-	-	-
Erythema	-	-	-	-	✔	-	-	-	-
Folliculitis	✔	✔	✔	✔	-	<1	<1	<1	✔
Furunculosis	-	-	-	-	-	-	1 to 10	-	-
Hyperpigmentation	-	✔	-	-	-	-	-	-	-
Hypertrichosis	✔	✔	-	✔	-	✔	-	-	✔
Hypopigmentation	✔	-	✔	-	✔	<1	<1	<1	✔
Irritation	✔	✔	3	-	-	-	-	-	✔
Leukoderma	-	-	-	-	✔	-	-	-	-
Maceration of the skin	✔	✔	-	✔	-	-	-	-	✔

Adverse Events	Fluocinonide	Flurandrenolide	Fluticasone	Halcinonide	Halobetasol	Hydrocortisone	Mometasone	Prednicarbate	Triamcinolone
Miliaria	✔	✔	✔	✔	✔	-	-	<1	✔
Paresthesia	-	-	-	-	-	-	<1	<1	-
Perioral dermatitis	✔	✔	✔	✔	✔	-	-	<1	✔
Pruritus	✔	✔	3	✔	1 to 4	6	1 to 10	<1	✔
Pustules	-	-	✔	-	✔	-	-	-	-
Rash	-	-	-	-	✔	-	-	<1	-
Rosacea	-	-	-	-	-	-	<1	-	-
Shininess	-	-	-	-	-	-	-	3	-
Skin atrophy	✔	✔	✔	✔	✔	<1	1 to 10	1 to 10	✔
Stinging	-	-	-	-	1 to 4	2	1 to 10	-	-
Striae	✔	✔	✔	✔	✔	<1	-	<1	✔
Telangiectasia	✔	-	-	-	-	-	-	5	-
Thinness	-	-	-	-	-	-	-	3	-
Urticaria	-	-	✔	-	-	-	-	<1	-
Vesicles	-	-	-	-	✔	-	-	-	-
Endocrine and Metabolic									
Cushing's Syndrome	✔	✔	✔	✔	-	-	-	-	-
Growth retardation	✔	✔	-	✔	-	-	<1	-	-
Hypothalamic-pituitary-adrenal suppression	✔	✔	-	✔	✔	✔	<1	-	✔
Hyperglycemia	✔	-	✔	✔	-	✔	-	-	✔
Hypokalemia	-	-	-	-	-	✔	-	-	✔
Respiratory									
Nasal congestion	✔	-	-	-	-	-	-	-	-
Pharyngitis	✔	-	-	-	-	-	-	-	-
Other									
Blurred vision	-	-	✔	-	-	-	-	-	-
Cataract formation	-	-	-	-	-	-	<1	-	-
Glucosuria	✔	-	✔	-	-	-	-	-	-
Hemorrhage	-	-	✔	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	✔	-	-	-
Intracranial hypertension	✔	✔	-	✔	-	-	-	-	-
Immunosuppression	-	-	✔	-	-	-	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-	-
Moniliasis	-	-	-	-	-	-	<1	-	-
Numbness of fingers	-	-	1	-	-	-	-	-	-
Rectal bleeding	-	-	-	-	-	✔	-	-	-
Rectal pain	-	-	-	-	-	✔	-	-	-
Secondary infection	✔	✔	✔	✔	✔	✔	-	<1	✔
Sepsis	-	-	✔	-	-	-	-	-	-
Thrombocytopenia	-	-	✔	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane anti-inflammatory agents are listed in Table 8.

Table 8. Usual Dosing Regimens for the Skin and Mucous Membrane Anti-Inflammatory Agents[1-28]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Alclometasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area two to three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >1 year of age:* Cream, ointment: apply to the affected area two to three times daily	Cream: 0.05% Ointment: 0.05%
Amcinonide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area two to three times daily Lotion: apply to the affected area two to three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area two to three times daily Lotion: Apply to the affected area two to three times daily	Cream: 0.1% Lotion: 0.1% Ointment: 0.1%
Betamethasone dipropionate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, gel, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >13 years of age:* Cream, gel, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Cream: 0.05% Gel: 0.05% Lotion: 0.05% Ointment: 0.05%
Betamethasone valerate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to three times daily Foam: apply to the affected scalp area two times daily Lotion: apply a few drops to the affected area two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to three times daily Lotion: apply a few drops to the affected area two times daily	Cream: 0.1% Foam: 0.12% Lotion: 0.1% Ointment: 0.1%
Clobetasol	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, foam, gel, lotion, ointment, spray: apply to the	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >12 years of age:* Cream, foam, gel, ointment:	Cream: 0.05% Foam: 0.05%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	affected area two times daily Shampoo: apply to dry scalp once daily Solution: apply to the affected scalp area two times daily	apply to the affected area two times daily Solution: apply to the affected scalp area two times daily	Gel: 0.05% Lotion: 0.05% Ointment: 0.05% Shampoo: 0.05% Solution: 0.05% Spray: 0.05%
Clocortolone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to the affected area three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to the affected area three times daily	Cream: 0.1%
Desonide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, lotion, ointment: apply to the affected area two to three times daily Foam, gel: apply to the affected area two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >3 months of age:* Foam, gel: apply to the affected area two times daily	Cream: 0.05% Foam: 0.05% Gel: 0.05% Lotion: 0.05% Ointment: 0.05%
Desoximetasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Topical formulations: apply to the affected area two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, gel: apply to the affected area two times daily ≥10 years of age: Ointment: apply to the affected area two times daily	Cream: 0.05% 0.25% Gel: 0.05% Ointment: 0.05% 0.25% Spray: 0.25
Diflorasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to three	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Ointment: apply to the affected area one to three	Cream: 0.05% Ointment: 0.05%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	times daily	times daily	
Fluocinolone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to the affected area three to four times daily Oil (body): apply to the affected area three times daily Oil (scalp): wet or dampen hair and scalp thoroughly; apply a thin film on the scalp, massage well, and cover scalp with the supplied shower cap; leave on overnight or for a minimum of four hours before washing off; wash hair with regular shampoo and rinse thoroughly Shampoo: apply no more than approximately one ounce to the scalp area once daily, work into a lather, and allow it to remain on the scalp for approximately five minutes' the hair and scalp should then be rinsed thoroughly with water	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to the affected area two to four times daily ≥3 months of age: Oil (body): apply to the affected area two times daily ≥2 years of age: Oil (scalp):apply to the affected area two times daily	Cream: 0.01% 0.025% Oil: 0.01% Ointment: 0.025% Shampoo: 0.01% Solution: 0.01%
Fluocinonide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, gel, ointment (0.05%): apply to the affected area two to four times daily Cream (0.1%): apply to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, gel, ointment (0.05%): apply to the affected area two to four times daily ≥12 years of age: Cream (0.1%): apply to the affected area one to two times daily	Cream: 0.05% 0.1% Gel: 0.05% Ointment: 0.05% Solution: 0.05%
Flurandrenolide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Tape: apply tape to prepared skin; replace after 12 to 24 hours.	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Tape: apply tape to prepared skin; replace after 12 to 24 hours	Tape: 4 $\mu g/cm^2$
Fluticasone	Atopic dermatitis: Cream: apply to the affected area one to two times daily Corticosteroid-responsive	Atopic dermatitis: ≥3 months of age: Cream: apply to the affected area one to two times daily	Cream: 0.05% Lotion: 0.05%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	dermatoses: Cream, ointment: apply to the affected area twice daily Lotion: apply to the affected area once daily	>1 year of age: Lotion: apply to the affected area once daily Corticosteroid-responsive dermatoses: ≥3 months of age: Cream: apply to the affected area twice daily ≥1 year of age: Lotion: apply to the affected area once daily	Ointment: 0.005%
Halcinonide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area two to three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area two to three times daily	Cream: 0.1% Ointment: 0.1%
Halobetasol	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in children >12 years of age:* Cream, ointment: apply to the affected area one to two times daily	Cream: 0.05% Ointment: 0.05%
Hydrocortisone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, lotion, ointment, solution: apply to affected area two to four times daily Rectal enema:† one enema nightly for 21 days or until remission occurs	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >2 years of age:* Cream, lotion, ointment: apply to affected area two to four times daily	Cream: 1% 2.5% Lotion: 2.5% Ointment: 1% 2.5% Rectal cream: 1% 2.5% Rectal enema: 100 mg/60 mL Solution: 2.5%
Hydrocortisone acetate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Rectal foam:‡ apply one applicator full once or twice daily for two or three weeks, and every second day	Safety and efficacy of the rectal foam have not been established in children.	Rectal foam: 10%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	thereafter		
Hydrocortisone butyrate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to affected area two to three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to affected area two to three times daily	Cream: 0.1% Ointment: 0.1% Solution: 0.1%
Hydrocortisone probutate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to affected area one to two times daily	Safety and efficacy in children have not been established.	Cream: 0.1%
Hydrocortisone valerate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to affected area two to three times daily	Safety and efficacy in children have not been established.	Cream: 0.2% Ointment: 0.2%
Mometasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area once daily Solution: apply a few drops to affected area once daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* ≥2 years of age: Cream, ointment: apply a thin film to affected area of the skin once daily ≥12 years of age: Solution: apply a few drops to affected area once daily	Cream: 0.1% Ointment: 0.1% Solution: 0.1%
Prednicarbate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area twice daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* ≥1 year of age: Cream: apply to the affected area twice daily ≥10 years of age: Ointment: apply to the affected area twice daily	Cream: 0.1% Ointment: 0.1%
Triamcinolone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Aerosol: apply to the affected area three to four times daily Cream, lotion, ointment: <0.1%: apply to the affected area two to four times daily ≥0.1%: apply to the affected	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Aerosol: apply to the affected area three to four times daily Cream, lotion, ointment (<0.1%): apply to the affected area two to four times daily	Aerosol: 0.147 mg/g Cream: 0.025% 0.1% 0.5% Dental paste: 0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	area two to three times daily Dental paste:§ press a small amount (1/4 inch) to the lesion until a thin film develops up to three times daily	Dental paste:§ press a small amount (1/4 inch) to the lesion until a thin film develops up to three times daily	Lotion: 0.025% 0.1% Ointment: 0.025% 0.05% 0.1% 0.5%
Combination Products			
Betamethasone dipropionate and propylene glycol	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >13 years of age:* Cream, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Cream: 0.05% Lotion: 0.05% Ointment: 0.05%
Halobetasol and ammonium lactate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Topical formulations: apply to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >12 years of age:* Topical formulations: apply to the affected area one to two times daily	Cream/lotion: 0.05%-12% Ointment/foam: 0.05%-12% Ointment/lotion: 0.05%-12%
Halobetasol and lactic acid	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Topical formulations: apply to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >12 years of age:* Topical formulations: apply to the affected area one to two times daily	Cream/lotion: 0.05%-10% Ointment/lotion: 0.05%-10%
Hydrocortisone, mineral oil and white petrolatum	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Ointment: apply to affected area two to four times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Ointment: apply to affected area two to four times daily	Ointment: 1%
Hydrocortisone acetate and aloe vera	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Gel: apply to affected area three to four times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Gel: apply to affected area three to four times daily	Gel: 2%
Hydrocortisone acetate and lidocaine	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to the affected area twice daily	Safety and efficacy in children have not been established.	Cream: 0.5%-3%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Hydrocortisone acetate and pramoxine	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Rectal cream, rectal foam: apply to affected area three to four times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Rectal cream, rectal foam: apply to affected area three to four times daily	Rectal cream: 1%-1% 1.85%-1.15% Rectal foam: 1%-1%
Hydrocortisone acetate and urea	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to affected area two to four times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to affected area two to four times daily	Cream: 1%-10%
Mometasone and ammonium lactate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Topical formulation: apply to the affected area once daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >2 years of age:* Topical formulation: apply a thin film to affected area of the skin once daily	Cream/foam: 0.1%-12%

*Dermatoses include anogenital and anorectal pruritus, atopic dermatitis, psoriasis, seborrheic dermatitis, and inflammatory phase of xerosis.
†Rectal enema is indicated as adjunctive therapy in the treatment of ulcerative colitis.
‡Rectal foam is indicated as adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.
§Dental paste is indicated for adjunctive treatment and for the temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane anti-inflammatory agents are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Skin and Mucous Membrane Anti-Inflammatory Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atopic Dermatitis				
Kuokkanen et al.[43] (1987) Alclometasone 0.05% ointment applied BID vs hydrocortisone 1% ointment applied BID	DB, RCT Children with eczema	N=34 3 weeks	Primary: Potential for induction of cutaneous atrophy; severity of erythema, induration, pruritus; global evaluation Secondary: Not reported	Primary: At study endpoint, the percent improvement in signs and symptoms in the alclometasone and hydrocortisone treatment sides were 88 and 86%, respectively. Secondary: Not reported
Lassus et al.[44] (1984) Alclometasone 0.05% cream applied BID vs clobetasol butyrate 0.05% cream applied BID	DB, PG, RCT Children with stable or worsening AD	N=43 2 weeks	Primary: Erythema, induration, pruritus, physician global evaluation Secondary: Not reported	Primary: The average percent reduction in disease signs was similar with clobetasol (86%) and alclometasone (85%; P>0.10). Physicians deemed nine of 22 patients in the alclometasone group cleared compared to 10 of 21 patients in the clobetasol group (P>0.10). Secondary: Not reported
Bickers et al.[45] (1984) Amcinonide 0.1% cream applied BID vs	DB, PG, RCT Patients 17 to 84 years of age with acute or subacute eczematous dermatitis	N=33 2 weeks	Primary: Itching, burning, pain, erythema, edema, excoriation, vesiculation, crusting, scaling,	Primary: The amcinonide group had a greater improvement in edema compared to the halcinonide group at endpoint (P=0.04). All other primary endpoints were not significantly different between the two treatment groups (P≤0.82). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
halcinonide 0.1% cream applied BID			lichenification, plaques, pigmentation changes, secondary skin infection, fissuring Secondary: Cosmetic acceptability questionnaire	No significant difference in cosmetic acceptability was seen between the two treatment groups (P=0.92).
Guenther et al.[46] (1981) Amcinonide 0.1% cream applied BID vs halcinonide 0.1% cream applied BID	DB, PG Patients 16 to 71 years of age with eczematous dermatitis for at least one year with slow exacerbation of disease	N=29 2 weeks	Primary: Erythema, scaling, lichenification, plaques, fissuring, oozing, crusting, excoriation, pigmentation changes, itching and burning and/or pain Secondary: Investigator's overall evaluation, patient's overall evaluation and patient's acceptability evaluation	Primary: All signs and symptoms, and the total score, yielded statistically significant improvements in both treatment groups at both weeks one and two, with the exception of pigmentation changes at week one (P=0.10 to 0.001). Halcinonide-treated patients had significantly greater improvements in fissuring at week one; however, there was no apparent difference at week two. At week two, the amcinonide group had much greater improvement in burning/pain, and this was repeated in the evaluation of the number of patients experiencing complete burning/pain relief (all 11 patients treated with amcinonide reported complete relief compared to four of seven halcinonide patients). There were no major differences among other signs and symptoms between the groups at week two. Secondary: No significant difference was reported between the two treatment groups.
Breneman et al.[47] (2005) Clobetasol lotion applied BID for two weeks	AC, MC, PC, RCT, SB Patients with moderate to severe AD	N=229 4 weeks	Primary: Success rate (derived from global severity scale) Secondary:	Primary: At the end of the two-week treatment period (last observation carried forward) the proportion of subjects who achieved "success" was significantly higher in the lotion group compared to the placebo group (72.9 vs 36.4%; P=0.001). There was no difference between the active treatments (72.9 vs 74.0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clobetasol cream applied BID for two weeks vs placebo			Global severity scale (full-scale); individual disease scores of erythema, excoriation, induration/ papulation, lichenification, oozing/crusting, and dryness/ scaling; pruritus, global improvement	At all other time points, success rates for the lotion group were significantly higher than for the placebo group (P<0.05), and were non-inferior to the emollient cream group (P>0.05). After the two-week treatment-free period, success rates for both the lotion and cream groups remained significantly higher relative to those observed in the lotion placebo group. Success rates decreased by 14.5% in the clobetasol propionate lotion group as compared to an 18.0% decrease in the cream group. Secondary: At week two, the full-scale global severity scale for the lotion group was significantly lower than that for the placebo group (P=0.001); there was no difference between the two clobetasol propionate formulations. The number of subjects with reduced severity in individual disease scores was significantly higher (P<0.05) in the lotion group as compared to the placebo group; no significant differences were observed between the lotion group and the emollient cream group. Pruritus scores in both active groups were comparable. However, after two weeks of a treatment-free follow-up period, pruritus scores in the lotion group were significantly lower compared to that in the emollient cream group (P=0.014) and placebo group (P=0.002). Global improvement at the two week endpoint demonstrated that the lotion group was more effective that the placebo group (P=0.001); however, the lotion group was not significantly different from the emollient cream group. The majority of subjects in both active treatment groups showed improvement, whereas the majority of subjects in the placebo group showed no changes.
Kircik et al[48] (2013) Clobetasol 0.05% spray applied BID for 15 days	DB, MC, PG, RCT, VC Patients ≥12 years of age with moderate to severe	N=125 15 days	Primary: Proportion of patients achieving treatment success (defined as improvement from	Primary: The treatment success at day 15 did not differ significantly between treatment groups. Adverse events were reports in 18% of patients treated with clobetasol propionate foam and 8% of patients in the placebo group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	chronic hand dermatitis with an Investigator's Static Global Assessment score of 3 or 4 at baseline		baseline ≥2 Investigator's Static Global Assessment grades for the target hand at day 15) Secondary: Not reported	Not reported
Wolkerstorfer et al.[49] (1998) Clobetasone 0.05% cream applied BID vs fluticasone 0.05% cream applied daily	DB, RCT Children 3 to 8 years of age with moderately active AD	N=21 4 weeks	Primary: Modified scoring of atopic dermatitis system Secondary: Not reported	Primary: There were no significant differences between the fluticasone and the clobetasone treatment groups in scoring of atopic dermatitis system improvements (P=0.8). Secondary: Not reported
Jorizzo et al.[50] (1995) Desonide 0.05% ointment applied BID vs hydrocortisone 1% ointment applied BID	MC, PG, RCT, SB Children ≤12 years of age with mild to moderate AD	N=111 5 weeks	Primary: Global improvement, erythema, lichenification, excoriations, oozing or crusting, pruritus, induration Secondary: Not reported	Primary: The investigator's global assessment favored desonide over hydrocortisone. In the desonide group, 69% of patients showed clearing or marked improvement, compared to 41% of patients in the hydrocortisone group (P=0.003). There was a greater improvement in erythema, excoriations, oozing/crusting, and pruritus in the desonide group compared to the hydrocortisone group with improvements of 52.7 and 33.9% for erythema, 76.4 and 57.1% for excoriations, 78.2 and 60.7% for oozing/crusting, and 58.2 and 39.3% for pruritus, respectively (P<0.05). There was no significant difference between the treatment groups in lichenification and induration/papules.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Lucky et al.[51] (1997) Desonide 0.05% ointment applied BID vs hydrocortisone 2.5% ointment applied BID	RCT Pediatric patients with AD	N=15 28 days	Primary: Hypothalamic-pituitary-adrenal axis suppression Secondary: Not reported	Primary: No significant differences were seen in either early morning cortisol levels or adrenocorticotropic hormone-stimulated mean cortisol values from baseline to endpoint. Secondary: Not reported
Ashton et al.[52] (1987) Desoximetasone 0.25% cream applied BID vs desoximetasone 0.05% cream applied BID vs betamethasone valerate 0.1% cream applied BID vs hydrocortisone 1% cream applied BID	DB, MC, PG Patients ≥2 years of age with eczema	N=96 3 weeks	Primary: Erythema/redness, scaling, itching, extent of area affected Secondary: Not reported	Primary: Based on final clinician assessment scores, the difference in erythema was most significant between the desoximetasone 0.25% and hydrocortisone (P=0.006; mean P value for all treatments was P<0.05). There was no statistically significant difference in improvement from baseline to endpoint for any of the treatments. The only difference in scaling that was significant was between desoximetasone 0.25% and hydrocortisone (P=0.014). There was a greater decrease in the extent of area affected final mean score for desoximetasone 0.25% (mean, 1.5) and betamethasone (mean, 1.6) compared to hydrocortisone (mean, 3.2; P=0.02). The differences in mean change from baseline between desoximetasone 0.25% (4.3) and betamethasone (2.5) was significant (P=0.047). The difference between desoximetasone 0.25% when compared to hydrocortisone at week three was also significant (P=0.001). The mean scores for scaling were 0.8 for desoximetasone 0.25%, 1.5 for desoximetasone 0.05%, 0.8 for betamethasone, and 3.0 for hydrocortisone (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The patient mean scores for extent of affected area were 1.5 for desoximetasone 0.25%, 2.6 for desoximetasone 0.05%, 2.0 for betamethasone, and 3.8 for hydrocortisone (P=0.08). The patient mean scores for itching were 1.2 for desoximetasone 0.25%, 2.5 for desoximetasone 0.05%, 1.9 for betamethasone, and 4.1 for hydrocortisone (P=0.014). There was no significant difference in patient mean scores for redness between the treatment groups (P=0.13). Secondary: Not reported
Delescluse et al.[53] (1996) Fluticasone 0.005% ointment applied BID vs betamethasone dipropionate 0.05% ointment applied BID	DB, MC, PG, RCT Patients with moderate to severe eczema	N=92 4 weeks	Primary: Physician assessment of clinical response, sign and symptom severity, patient assessment of treatment Secondary: Not reported	Primary: Improvement in signs and symptoms was seen in both treatment groups at two and four weeks. There was no significant difference in efficacy variables between fluticasone and betamethasone. Secondary: Not reported
Friedlander et al.[54] (2002) Fluticasone 0.05% cream applied BID	MC, OL Patients 3 months to 6 years of age with moderate to severe AD	N=51 4 weeks	Primary: Serum cortisol response, fluticasone levels Secondary: Not reported	Primary: Mean stimulated and unstimulated cortisol levels were similar before and after treatment (13.76 µg/dL pre-stimulation and 30.53 µg/dL post-stimulation vs 12.32 µg/dL pre-stimulation and 28.84 µg/dL post-stimulation). Two patients had endpoint post-stimulation results less than 18.0 µg/dL. Post-stimulation cortisol results were affected by the ratio of the amount of fluticasone used to total body surface area treated (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Eichenfield et al.[55] (2006) Fluticasone 0.05% lotion applied daily vs placebo	DB, PC, PG, RCT Patients ≥3 months of age with moderate to severe AD	N=438 4 weeks	Primary: Treatment success Secondary: Physician's global assessment, sign/symptom severity, and subject/parent assessment	Primary: In study A, 75% of fluticasone-treated patients were considered to have a treatment success compared to 31% of placebo-treated patients (P<0.001). In study B, 66% of fluticasone-treated patients were considered to have a treatment success compared to 26% of placebo-treated patients (P<0.001). For subjects aged three to 12 months, there were 13 (76%) treatment successes on fluticasone compared to 4 (36%) on placebo. Secondary: Physician's Global Assessment of lesional clearance was 75 and 66% in the fluticasone-treated patients compared to 31 and 26% in the placebo-treated patients (study A and study B, respectively; P<0.001 for both comparisons). Stable/improved in uncleared lesions was 85 and 62% in the fluticasone-treated patients compared to 47 and 47% of placebo-treated patients (study A and study B, respectively; P<0.001 and P=0.018, respectively). Subject assessment of excellent response to therapy was 51 and 50% in the fluticasone-treated patients compared to 15 and 7% of placebo-treated patients (study A and study B, respectively; P<0.001 for both comparisons).
Sears et al.[56] (1997) Hydrocortisone buteprate 0.1% cream applied daily vs placebo	DB, MC, PC, RCT Patients with AD	N=168 14 days	Primary: Severity of dermatitis signs based on the mean lesion score for: infiltration, scaling, erythema, lichenification, vesicles, papules, excoriation, pruritus	Primary: At day three evaluations, there was a decrease of 3.10 in the mean lesion score for the hydrocortisone group compared to a decrease of 1.71 for the placebo group (P=0.0027). The mean reductions in mean lesion score at day seven evaluations for the hydrocortisone group compared to placebo were 4.65 and 2.93, respectively (P=0.0061). At endpoint (day 14), the mean decrease was 6.38 for the hydrocortisone group and 3.39 for placebo (P=0.0001). Secondary: On day three, the investigators gave a rating of cleared, excellent, or good,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Overall improvement; overall treatment efficacy; cosmetic acceptability	in terms of overall improvement, to a total of 36 of 98 patients in the hydrocortisone group, compared to six of 58 patients in the placebo group (P=0.0004). The same ratings were given to 65 of 103 hydrocortisone patients and 17 of 60 in the placebo group on day seven (P=0.0001); and, at endpoint, there were 72 of 93 in the hydrocortisone group compared to 19 of 54 in the placebo group assessed as cleared, excellent, or good (P=0.0001). Investigator assessment of treatment efficacy at endpoint was noted as excellent or good for 69% (N=73) of the hydrocortisone patients compared to 26% (N=16) in the placebo group. Patient assessment had 69% (N=73) in the hydrocortisone group compared to 32% (N=20) of placebo patients (P<0.001). The only statistically significant difference in cosmetic acceptability was the response to "pleasant feeling on the skin", in which hydrocortisone was favored (P=0.02).
Fowler et al.[57] (2005) Hydrocortisone butyrate 0.1% cream vs fluticasone propionate 0.05% cream, prednicarbate 0.1% cream, or mometasone furoate 0.1% cream	DB, MC, PG, RCT Patients 18 to 65 years of age with moderate hand dermatitis or AD	N=89 2 weeks	Primary: Investigator and subject ratings of signs and symptoms: erythema, cracking/fissuring, scaling, papules/ vesicles Secondary: Not reported	Primary: Based on the investigators' observations, the rate of improvement of cracking/fissuring was greater in the hydrocortisone butyrate (43%) group compared to the prednicarbate (21%) group (P<0.05). There were no other values that reached statistical significance for the investigators' observations. Based on the subjects' observations, the rate of improvement of erythema was greater in the hydrocortisone butyrate (50%) group compared to the fluticasone propionate (35%) group (P<0.05). There were no other values that reached statistical significance for the investigators' observations. In terms of resolution from baseline, all treatment groups showed improvement (P<0.02). The differences between treatment groups were not statistically significant (P>0.06). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Abramovits et al.[58] (2010) Hydrocortisone butyrate 0.1% cream applied BID vs placebo	DB, MC, PC, RCT Patients ≥3 months to 18 years of age with mild to moderate AD	N=264 4 weeks	Primary: Treatment success (defined as a final physicians global assessment score of 0 or 1, with ≥2-point reduction) Secondary: Change in pruritus score, change in eczema area and severity index, total percent body surface area affected, safety	Primary: In the hydrocortisone group, 63% of patients were considered a "success," compared to 28% of patients in the placebo group (P<0.001). Secondary: In the intent-to-treat population, the change in pruritus ranged from –1 to 3 in the hydrocortisone group and –2 to 3 in the placebo group (P<0.001). In the hydrocortisone group, pruritus worsened by 1 grade in 2% of patients, showed no change in 18% of patients, showed a 1-grade improvement in 37% of patients, showed a 2-grade improvement in 36% of patients, and showed a 3-grade improvement in 7% of patients. In the placebo group, pruritus worsened by 2 grades in 2% of patients, worsened by 1 grade in 5% of patients, showed no change in 39% of patients, showed a 1-grade improvement in 34% of patients, showed a 2-grade improvement in 19% of patients, and showed a 3-grade improvement in 2% of patients. In the hydrocortisone group, the mean change in eczema area and severity index scores was 84.2% compared to 45.3% in the placebo group (P<0.001). In the hydrocortisone group, total percent body surface area affected decreased 82.1% compared to 43.6% in the placebo group. In the hydrocortisone group, 22% of patients reported at least 1 adverse events compared 21% of patients in the placebo group (P=0.319). The majority of adverse events were described as mild, and none of the adverse events related to study drug were reported as severe.
Mandelin et al.[59] (2010) Hydrocortisone acetate 1% ointment applied BID (head and neck) and	DB, RCT Adults with moderate to severe AD	N=80 1 year	Primary: Affected body surface area, and eczema area and severity index Secondary: Adverse events	Primary: At six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by affected body surface area: 5.4 and 15.5%, respectively (P<0.05). At six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by the eczema area and severity index score: 3.2 and 7.1, respectively (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydrocortisone butyrate 0.1% ointment applied BID (trunk and limbs) vs tacrolimus 0.1% ointment applied BID				Secondary: Adverse events occurred in 100% of patients in the tacrolimus group and in 85.0% of patients in the corticosteroid arm (P=0.03). This was primarily due to the higher incidence of application-site skin burning sensation with tacrolimus.
Roth et al.[60] (1978) Hydrocortisone valerate 0.2% cream applied TID vs hydrocortisone 0.1% cream applied TID vs betamethasone valerate 0.1% cream applied TID vs placebo	DB, RCT Patients 2 to 75 years of age with chronic AD	N=68 2 to 4 weeks	Primary: Overall response, pruritus, erythema, scaling, excoriation, lichenification, overall judgment of response Secondary: Not reported	Primary: Overall response was in favor of the hydrocortisone valerate group compared to the hydrocortisone group, with 11 patients showing a better response compared to three patients, respectively (P<0.05). A consistently greater improvement in signs and symptoms was seen in the hydrocortisone valerate group compared to the hydrocortisone group at days five to nine, 12 to 16 and 26 to 35 (there was insufficient data for days 17 to 25). The only instances that were not proven to be significant were erythema at days five to nine (P<0.10) and lichenification at days five to nine and days 12 to 16 (P>0.10 and P<0.10, respectively). Patients in the hydrocortisone valerate and betamethasone valerate groups had moderate improvement in clearing, which was not significantly different between the two groups. More patients in the hydrocortisone valerate treatment group demonstrated excellent improvement or better compared to placebo, a difference that was significant. Secondary: Not reported
Williamson[61] (1987) Hydrocortisone	RCT, SB Patients ≥12 years of age with eczema	N=32 3 weeks	Primary: Assessment of eczema severity; severity of	Primary: Overall severity scores showed a steady improvement in the patients' eczema over the three weeks of the study, this being the same for both preparations. The results of the six individual measures also showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1% and urea 10% cream applied BID to lesions on the left side of the body vs betamethasone valerate 0.1% applied BID to lesions on the right side of the body	of the limbs or trunk		erythema, dryness/scaling, papules, itching and excoriation Secondary: Patient self-assessment questionnaire	equivalent results. Secondary: Thirty-one of the thirty-two patients in the study completed the questionnaire. There was no statistically significant difference in the results obtained with either preparation. Overall, a total of 15 patients preferred the hydrocortisone and urea cream, and 16 preferred the betamethasone cream.
Pei et al.[62] (2001) Mometasone 0.1% ointment applied daily vs fluticasone 0.005% ointment applied daily One treatment group applied medication without wet wrap dressings (Group I [fluticasone] and II [mometasone]); the other had two weeks without wet wrap dressings followed by two	RCT, SB Patients with refractory AD	N=27 4 weeks	Primary: Disease extent and severity Secondary: Not reported	Primary: The difference in efficacy between the mometasone and fluticasone treatments was not statistically significant in terms of the extent of disease score (P=0.846) and the severity score (P=0.068). There was improvement in disease severity score for both study medications when all patients were not using any wet wrap dressing (P=0.043). Patients who used wet wrap dressings in weeks two to four of treatment had a greater improvement in disease severity compared to those who did not use wet wraps. Groups II, III, and IV had statistically significant improvements in disease severity score during week three with P values of 0.043, 0.008 and 0.011, respectively (P=0.116 for Group I). During week four, only the patients who received wet wraps continued to have statistically significant improvement in their disease severity score. The P value for groups III and IV were 0.018 and 0.050, respectively (P=0.091 for Group I and P=0.078 for group II). The extent of disease did not change significantly between group III and IV, with P values of 0.028 and 0.025, respectively (only patients who were using wet wrap dressings completed the study with less extensive disease).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks of medication application under a wet wrap (Group III [fluticasone] and IV [mometasone]).				Secondary: Not reported
Lebwohl[63] (1999) Mometasone 0.1% cream applied daily vs hydrocortisone valerate 0.2% cream applied BID	MC, RCT Patients 2 to 12 years of age with AD who had failed hydrocortisone	N=219 3 weeks	Primary: Total sign and symptom score, physician assessment of global clinical response Secondary: Not reported	Primary: The mean percentage improvement in total sign/symptom score was greater for the mometasone group (87.2%) compared to the hydrocortisone group (78.6%; P=0.011). Based on the physician's assessment of global clinical response, mometasone was found to be more efficacious than hydrocortisone (P=0.003). Secondary: Not reported
Moshang.[64] (2001) Prednicarbate 0.1% cream applied BID	MC, OL Patients 4 months to 12 years of age with AD	N=55 3 weeks	Primary: Global evaluations, sign/symptom scores, cosmetic acceptability Secondary: Not reported	Primary: The percentage of patients who had greater than or equal to 75% clearance of their atopic dermatitis was 33% of patients on day eight evaluations and 78% on day 22. The mean global score decreased over the course of the study, with a mean score value of 1.9 on day eight, 1.5 on day 15, and 1.1 on day 22. Total sign and symptom score improved by 85% at endpoint. Cosmetic acceptability was rated as excellent by 71% of the patients' parents or guardians. Secondary: Not reported
Korting et al.[65] (1992)	DB, RCT Patients with atopic	N=24 6 weeks	Primary: Skin thickness	Primary: Clobetasol and betamethasone were found to decrease skin thickness greater than either prednicarbate or its placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prednicarbate 0.25% cream vs betamethasone valerate 0.1% cream or clobetasol 0.05% cream	eczema		Secondary: Not reported	The decrease in skin thickness was greater with betamethasone compared to clobetasol, but this was statistically insignificant. The decrease in skin thickness was greater with prednicarbate compared to its placebo, but this was statistically insignificant. Secondary: Not reported
Berberian et al.[66] (1999) Doxepin 5% and hydrocortisone 2.5% cream applied QID vs doxepin 5% and triamcinolone 0.1% cream applied QID vs hydrocortisone 2.5% cream applied QID vs triamcinolone	DB, MC, PG, RCT Patients with pruritic AD who experienced moderate to severe pruritus associated with their eczematous lesions daily for at least 1 week, family history of atopy and/or a personal history of atopic dermatitis, ≤25% body surface area affected by atopic dermatitis, and good general health	N=349 8 days	Primary: Pruritus severity and pruritus relief Secondary: Not reported	Primary: Patients who received doxepin in addition to a steroid achieved significant reductions in pruritus than those treated with a steroid cream alone. The physician's global evaluations for pruritus relief demonstrated that the addition of doxepin to either hydrocortisone or triamcinolone treatment significantly improved itch relief over that of the topical corticosteroid alone. On day two, the doxepin 5% and hydrocortisone 2.5% combination was significantly better for pruritus relief than the hydrocortisone treatment alone (P=0.01) as was the doxepin 5% and triamcinolone 0.1% combination than the triamcinolone alone (P=0.027). By day eight, statistical significance was reached in favor of the doxepin 5% and hydrocortisone 2.5% combination over the steroid alone, but not for the doxepin 5% and triamcinolone 0.1% over triamcinolone alone. A faster improvement in the eczematous condition was noted by the physicians over the first couple of days of the study in those in the combination doxepin doxepin/steroid treatment groups vs steroid treatment alone. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.1% cream applied QID				
Doss et al.[67] (2010) Tacrolimus 0.03% ointment applied BID vs fluticasone 0.005% ointment applied BID	DB, MC, RCT Patients 2 to 15 years of age with moderate to severe AD who had responded inadequately to topical corticosteroids	N=239 6 weeks	Primary: Response rate at week three Secondary: Changes in the mEASI score, global assessment of clinical response by investigators and patients, pruritus, sleep quality	Primary: In the PP analysis, response rates were 86.3% with tacrolimus and 91.5% with fluticasone (95% CI, -11.8 to 1.2). Tacrolimus was found to be non-inferior to fluticasone. In the ITT analysis, response rates were 84.3% with tacrolimus and 89.5% with fluticasone (P=0.0012). Secondary: The overall mean percentage change in total mEASI score was -79.5% in the tacrolimus group and -82.3% in the fluticasone group. Moderate or better improvement on the physicians' global assessment occurred in 93.6 and 92.4% of patients in the tacrolimus and fluticasone groups, respectively (ITT; P=0.05). Patients/parents considered global condition to have improved or greatly improved in 86.9% of patients receiving tacrolimus and 88.6% of those receiving fluticasone (ITT; P=0.047, PP; P=NS). Patients' assessment of pruritus improved in those receiving tacrolimus, with median change at day 21 of -84.0% compared to -91.5% in those receiving fluticasone (P=0.008). There was no significant difference in quality of sleep between the treatment groups (median change: tacrolimus, -91.5%; fluticasone, 92.6%). The incidence of adverse events was similar among the treatment groups. Application site burning occurred more frequently with tacrolimus.
Doss et al.[68] (2009) Tacrolimus 0.1% ointment applied to facial lesions BID	DB, MC, RCT Patients ≥16 years of age with moderate to severe AD of the face	N=468 3 weeks	Primary: Change in the mLEASI score Secondary: Facial erythema and pruritus, global	Primary: After three weeks, the response rate was 93.3% with tacrolimus and 87.8% with fluticasone as assessed by mLEASI (ITT; P=0.026, PP; P=0.046). Secondary: After three weeks, median changes in facial pruritus scores were -89.3% with tacrolimus compared to -88.3% with fluticasone (P=NS). Facial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone 0.005% ointment applied to facial lesions BID			clinical response	erythema improved in both treatment groups (P=NS). The physicians' global assessment of clinical response for the facial region was significantly different between the two groups. A total of 88% of patients in the tacrolimus group and 79% of patients in the fluticasone group showed marked or excellent improvement, or clearance of lesions (P=0.043). The patients' global assessment of clinical response for the facial region was significantly different between the two treatment groups. A total of 64% of patients in the tacrolimus group and 55% of patients in the fluticasone group considering their condition to have 'greatly improved' (P=0.014).
Reitamo et al.[69] (2005) Tacrolimus 0.1% ointment applied BID until clear and then for seven additional days vs hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) and hydrocortisone acetate 1% ointment applied BID (head and neck)	DB, MC, RCT Patients ≥18 years of age with moderate to severe AD	N=972 6 months	Primary: Response rate at month three (improvement in mEASI) Secondary: Response rate at other time points, mEASI, EASI, physician's global evaluation of clinical response, patient's assessment of global response, physician's assessment of individual signs, affected BSA, patient's assessment of itch and quality of sleep, and the	Primary: At month three, 72.6% of patients in the tacrolimus group responded to treatment compared to 52.3% of patients in the corticosteroid group (P<0.001). Secondary: The tacrolimus group had a higher response rate at all other time points throughout the six months compared to the corticosteroid group (P<0.001). A significant improvement in mEASI was observed as early as day eight in both treatment groups and increased up to the six-month point. At month six, the median percentage change in mEASI was -87.7% in the tacrolimus group and -82.5% in the corticosteroid group (P<0.008). The improvement in EASI and affected BSA followed the same trend. For EASI, the median percentage change was -85.0% in the tacrolimus group and -81.5% in the corticosteroid group (P=0.01). For the BSA, the median percentage change was -88.2% for the tacrolimus group and -80.3% in the corticosteroid group (P=0.001). Physicians' global assessments of clinical response was higher in the tacrolimus group compared to the corticosteroid group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			number of days on treatment as a percentage of days in the study	There was a greater reduction in individual signs of AD in the tacrolimus group compared to the corticosteroid group and more patients in the tacrolimus group experienced clearance or excellent improvement (at month six, 61.3% of tacrolimus patients and 46.4% of corticosteroid patients had clearance or excellent improvement, P<0.001). Patients' assessments were significantly higher in the tacrolimus group compared to the corticosteroid group. At six months, 86.6% of patients in the tacrolimus group rated their AD as much better or better compared to 71.8% of patients in the corticosteroid group (P<0.001). Itch and quality of sleep improved significantly in both treatment groups. Patients in the tacrolimus group remained in the study longer compared to the corticosteroid group and had a lower number of treatment days as a percentage of days in the study.
Poole et al.[70] (2010) Tacrolimus 0.1% ointment applied BID until clear and then for seven additional days vs hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) and hydrocortisone acetate 1% ointment applied BID (head and neck)	DB, MC, RCT Patients ≥18 years of age with moderate to severe AD	N=972 6 months	Primary: Quality of life (SF-36) assessed using a physical component summary and a mental component summary Secondary: Not reported	Primary: For the physical component summary, patients receiving tacrolimus gained 3.3 points on average compared to 2.3 points in the corticosteroid group (P=0.033). For the mental component summary, patients receiving tacrolimus improved by an average 6.0 points compared to 3.4 points in the corticosteroid group (P<0.001). For the eight SF-36 domains, all except 'Physical Functioning' (P=0.106) showed significant differences in favor of tacrolimus. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ashcroft et al.[71] (2005) Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	MA Patients with AD	N=6,897 1 week to 12 months	Primary: For pimecrolimus: proportion of patients rated by the investigator as clear or almost clear For tacrolimus: proportion of patients achieving at least 90% improvement from baseline Secondary: Patients' global assessments of feeling better or much better, proportion of patients with flares of atopic dermatitis, improvements in quality of life, tolerability assessed by overall rates of withdrawal, withdrawal due to adverse effects, proportion of patients with burning of the skin and skin infections	Primary: <u>For pimecrolimus:</u> In five trials evaluating pimecrolimus vs placebo, pimecrolimus was significantly more effective than placebo at three weeks (P<0.0001), and three of these found that pimecrolimus retained this efficacy at six weeks (P<0.0001). Another trial found no significant difference at six months between pimecrolimus and placebo. In three placebo-controlled trials, there were significantly fewer flares at six months in the pimecrolimus group compared to the placebo group, and remained more effective at preventing flares at 12 months. One trial evaluated pimecrolimus and a potent corticosteroid and found that betamethasone valerate 0.1% was significantly more effective than pimecrolimus after three weeks treatment when evaluating the proportion of patients who were clear or almost clear (P=0.0008). One study evaluated pimecrolimus vs a potent corticosteroid on the trunk and a mild corticosteroid on the face and found that the combination of corticosteroids was significantly more effective than pimecrolimus (when evaluating the proportion of patients moderately clear or better) at one week, three weeks, and six months but found no difference at 12 months. One direct comparison of pimecrolimus 1% cream and tacrolimus 0.03% ointment found no difference in the proportion of patients (children) who were clear or almost clear at six weeks (P=0.15). One study evaluating pimecrolimus four times daily compared to pimecrolimus two times daily found no difference in the proportion of patients clear or almost clear at the end of three weeks. <u>For tacrolimus:</u> One trial compared tacrolimus 0.03%, tacrolimus 0.1%, and placebo and found that the 0.03% strength was significantly more effective compared to placebo when evaluating the proportion of patients clear or achieving excellent improvement (P=0.006), but that the 0.1% strength did not differ from placebo (P=0.13) at three weeks. When evaluating patients'

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				assessments of improvement as better or much better, both strengths proved significantly better than placebo. Three other trials reported the same outcomes as described above after 12 weeks and found both strengths to be significantly more effective than placebo (P<0.0001). Two trials compared tacrolimus 0.03% and 0.1% vs hydrocortisone 1% and found that tacrolimus was significantly more effective than hydrocortisone when evaluating the proportion of patients clear or achieving excellent improvement at three weeks (P<0.0001). One trial compared tacrolimus 0.1% and alclometasone 0.1% and found that tacrolimus was significantly more effective than alclometasone for treating facial dermatitis. One trial compared tacrolimus 0.03 and 0.1% and hydrocortisone butyrate 0.1% (a potent corticosteroid) and found that the 0.03% tacrolimus was significantly less effective than the hydrocortisone butyrate judged by the proportion of patients clear or achieving excellent improvement at three weeks (P=0.008); but no significant difference was seen between the 0.1% strength of tacrolimus and the hydrocortisone butyrate (P=0.65). Two trials compared tacrolimus 0.1% with betamethasone valerate 0.1% or hydrocortisone butyrate 0.1% and found that the tacrolimus was as effective as the corticosteroids in the proportion of patients achieving at least marked improvement. One trial compared tacrolimus 0.1% with a regimen of hydrocortisone butyrate 0.1% on the trunk and extremities and hydrocortisone acetate 1% on the head and neck. It found that tacrolimus was significantly more effective than the combined corticosteroid regimen when evaluating the proportion of patients clear or achieving excellent improvement at 12 weeks (P<0.0001). Six trials compared tacrolimus 0.1% and 0.03%. Three trials found no difference in proportion of patients clear or achieving excellent response at three weeks between the two strengths (P=0.44) and the remaining three found tacrolimus 0.1% to be significantly more effective than the 0.03% strength (P=0.04) at 12 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Significantly more patients withdrew from treatment in the placebo groups than with either pimecrolimus or tacrolimus (P<0.05). Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus group compared to the placebo group but was significantly higher in the tacrolimus group compared to the placebo group. Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus or tacrolimus groups compared to topical corticosteroids, nor did rates when comparing tacrolimus 0.03 to 0.1%. Skin irritation and skin burning did not differ significantly between pimecrolimus groups and placebo (P=0.257), but the rate was significantly higher with pimecrolimus compared to betamethasone valerate 0.1% or a combined regimen of triamcinolone acetonide 0.1% and hydrocortisone acetate 1%. Both strengths of tacrolimus were more likely to cause skin burning compared to placebo (P=0.010) and were more likely to cause skin burning compared to mild or potent corticosteroids. Quality of life was difficult to measure and different outcome measures were used in the studies. In two studies, parents judged quality of life to be improved in patients taking pimecrolimus compared to placebo, and three trials showed increases in quality of life in patients taking tacrolimus 0.03and 0.1% compared to placebo. Tacrolimus 0.1% was found to have a significantly greater improvement on quality of life in adults compared to the 0.03% strength, but no significant differences were found in infants and children. No quality of life assessments were found comparing pimecrolimus and tacrolimus to topical corticosteroids.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
El-Batawy et al.[72] (2009) Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	MA Patients with AD	N=7,378 (19 trials) Variable duration	Primary: Efficacy Secondary: Not reported	Primary: Pimecrolimus and tacrolimus were significantly more effective than placebo. Compared to topical corticosteroids, tacrolimus 0.1% and 0.03% ointment was as effective as moderate potency topical corticosteroids, and more effective than a combined steroid regimen. Tacrolimus was more effective than mild potency topical corticosteroids. Secondary: Not reported
Chen et al.[73] (2010) Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	MA Pediatric patients with AD	N=6,288 (20 trials) Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: More patients using tacrolimus had a good response than those in control groups including placebo, 1% hydrocortisone acetate and 1% pimecrolimus. The corresponding OR were 4.56 (95% CI, 2.80 to 7.44), 3.92 (95% CI, 2.96 to 5.20) and 1.58 (95% CI, 1.18 to 2.12). The effect difference between 0.03% and 0.1% tacrolimus ointments was not statistically significant (OR, 0.90; 95% CI, 0.55 to 1.48). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to the placebo. The major adverse events were burning and pruritus. Secondary: Not reported
Psoriasis				
Huntley et al.[74] (1985) Amcinonide 0.1% ointment applied BID vs betamethasone dipropionate	DB, PG, RCT Patients with moderate to severe psoriasis	N=31 2 weeks	Primary: Evaluation of papules/plaques, erythema, scales, itching, burning, and pain Secondary: Patient-evaluated cosmetic efficacy	Primary: At the week one evaluation point, an overall investigator rating of either "excellent" or "good" was made for 14 of 16 patients in the amcinonide group compared to eight of 15 patients in the betamethasone group (P<0.05). At the week one evaluation point, an overall patient rating of either "excellent" or "good" was made for 15 of 16 patients in the amcinonide group compared to 12 of 15 patients in the betamethasone group (P<0.05). There were no significant differences in the overall improvement between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.05% ointment applied BID				the two treatment groups during the second week of treatment. A greater improvement in the amcinonide group compared to betamethasone was seen for scaling at week one (P=0.05) and itching at week two (P=0.01). Secondary: There was no difference in the secondary end points between the two treatment groups.
Cornell et al.[75] (1983) Amcinonide 0.1% ointment applied BID vs fluocinonide 0.05% ointment applied TID	DB, PG, RCT Patients with psoriasis for a minimum of five years	N=39 2 weeks	Primary: Lesion severity (erythema, papules/plaques, scaling, itching, burning, and pain), overall improvement of lesions Secondary: Patient-evaluated cosmetic acceptability	Primary: There were no significant differences found in terms of efficacy between the two treatment groups. Both treatment groups saw an improvement in patient-reported itching. No significant difference in the amount of improvement was reported between the two groups. Erythema, papules/plaques, and scaling were completely resolved in 5, 20 and 35% of patients in the amcinonide group, compared to 5, 11 and 21% of patients in the fluocinonide group, respectively (P≤0.01). Secondary: No significant difference was reported between the two treatment groups.
Engel et al.[76] (1982) Amcinonide 0.1% ointment applied BID vs fluocinonide 0.05% ointment applied TID	DB, PG, RCT Patients with psoriasis	N=50 3 weeks	Primary: Total score based on severity of signs (crusting, erythema, papules/plaques, scales, pustules), severity of symptoms (itching, burning, pain) Secondary: Not reported	Primary: There were no significant differences found between the two treatment groups in improvements in signs and symptoms, and total score between the two treatment groups. Overall improvement of psoriasis at endpoint was noted as cleared, excellent, or good in 22 of 26 (85%) amcinonide patients and 18 of 24 (75%) fluocinonide patients, respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Millikan et al.[77] (1986) Amcinonide 0.1% ointment applied BID vs halcinonide 0.1% ointment applied BID	DB, PG Patients 18 to 75 years of age with psoriasis	N=32 2 weeks	Primary: Patient- and investigator-measured: itching, burning, pain, erythema, papules or plaques and scales Secondary: Not reported	Primary: Evaluation at day seven showed greater efficacy in the primary endpoints in the amcinonide treatment group compared to the halcinonide group (P<0.05). Patient ratings of either “excellent” or “good” improvement were achieved at day seven in 72.2% of the amcinonide treatment group compared to 42.9% of the halcinonide group, respectively. Investigators’ evaluations did not show any significant differences between treatment groups at either day seven or day 14. Investigators’ ratings of excellent improvement were achieved by day 14 evaluation in 37% of the amcinonide group compared to 8% of the halcinonide group, respectively. Secondary: Not reported
Katz et al.[78] (1995) Betamethasone dipropionate 0.05% lotion applied BID vs clobetasol 0.05% solution applied BID	MC, PG, RCT, SB Patients ≥18 years of age with moderate to severe scalp psoriasis	N=193 2 weeks	Primary: Scaling, induration, erythema, pruritus, complied into a total sign and symptom score Secondary: Not reported	Primary: At day four, the mean percent improvement for the betamethasone group was 39.1% compared to 31.8% in the clobetasol group, respectively (P=0.010). The percent improvement was greater in the betamethasone group at day eight, with a 66.0% improvement compared to a 57% improvement for the clobetasol group, respectively (P≤0.005). Evaluations at day 15 showed an 82.8% improvement in the sign/symptom score for the betamethasone group compared to 74.9% improvement in the clobetasol group, respectively (P≤0.015). Erythema was the only individual sign that was significantly different between the two treatment groups at 14 days (P=0.023). The mean sign/symptom score was 1.5 in the betamethasone group, compared to 2.3 in the clobetasol group, respectively (P≤0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Jacobson et al.[79] (1986) Betamethasone dipropionate 0.05% ointment applied BID vs clobetasol 0.05% ointment applied BID	DB, MC Patients with moderate-to-severe psoriasis	N=130 2 weeks	Primary: Treatment preference, assessment of efficacy of one side compared to the other (erythema, scaling, skin thickening), overall magnitude of response Secondary: Not reported	Primary: At the end of the two-week treatment period, 41% of investigators preferred the response obtained from clobetasol compared to the 8% of investigators who favored the response from betamethasone (P≤0.001). Overall magnitude of response (or at least a 75% reduction in erythema, scaling, and skin thickening) was greater on the clobetasol side (27 patients [22%]) compared to betamethasone (three patients [2 %]; P<0.001). Both treatment sides had an improvement in lesion severity in 59 patients (48%), and neither treatment side showed improvement in 35 patients (28%; P<0.001). Secondary: Not reported
Shupack et al.[80] (1993) Betamethasone dipropionate 0.05% ointment vs diflorasone 0.05% ointment	DB, PG, RCT Patients ≥18 years of age with moderate to severe plaque-type psoriasis for at least 6 months	N=44 2 weeks	Primary: Erythema, scaling, induration, investigator's evaluation Secondary: Patient satisfaction	Primary: No statistically significant differences were found between the treatment groups in erythema, scaling, and induration. At the week one physician evaluation, 18 of 21 patients in both the betamethasone and diflorasone treatment groups were rated as either cleared or improved, with these results remaining virtually unchanged for week two. Secondary: Patient satisfaction was considered high within both treatment groups.
Barsky et al.[81] (1976) Betamethasone 0.025% gel applied TID vs	DB, MC, RCT Patients ≥2 years of age with psoriasis	N=263 3 weeks	Primary: Physician evaluation of therapeutic response Secondary: Physician and	Primary: A greater number of patients in the fluocinonide group had complete clearing or an excellent response compared to the betamethasone group. Fifty-five patients in the fluocinonide group demonstrated moderate improvement compared to 86 in the betamethasone group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluocinonide 0.05% gel applied TID			patient preference	The mean physician preference score was 0.912, and the mean patient preference score was 0.908 (P<0.0001).
Pacifico et al.[82] (2006) Betamethasone valerate 0.12% cream applied daily vs betamethasone valerate 0.1% tape applied daily	PRO, RCT, SB Patients with mild to moderate psoriasis	N=42 30 days	Primary: PASI scores; hydration based on cutaneous trophism evaluation Secondary: Patient quality-of-life questionnaire	Primary Lesions treated with betamethasone tape had a greater reduction in the PASI score compared to the betamethasone cream with a mean percentage reduction of 59.3 and 38.4%, respectively (P<0.001). The self-administered PASI score had a greater percentage reduction on the tape side (61.8%) compared to the cream side (34.0%), respectively (P<0.001). The mean percentage of skin hydration was increased with the betamethasone tape treatment area (38.8%) compared to the cream treatment area (11.1%, P<0.001). Secondary: Patients had a higher cosmetic acceptability and tolerability for the tape compared to the cream, citing that tape application was easier and that the cream was too greasy.
Reygagne et al.[83] (2005) Calcipotriol 0.005% solution applied BID vs clobetasol 0.05% shampoo applied QD	MC, PG, RCT, SB Patients ≥12 years of age with moderate to severe scalp psoriasis	N=151 4 weeks	Primary: GSS and theTSS Secondary: Pruritus, surface area of scalp affected by psoriasis	Primary: Clobetasol propionate was shown to be significantly more efficacious compared to calcipotriol in TSS measures (P<0.001 at week two and P=0.028 at week four) and GSS measures (P<0.001 at week two and P=0.016 at week four). Secondary: Erythema, plaque thickening, adherent desquamation, and pruritus improved in both treatments groups but a greater improvement was observed in the clobetasol group. The percentage of scalp surface area affected showed significant difference in favor of clobetasol (P=0.02).
Menter et al.[84] (2013)	DB, MC, RCT Patients ≥18 years	N=1,152 8 weeks	Primary: Proportion of patients achieving	Primary: At week four, there was a significantly greater proportion of patients achieving controlled disease in the calcipotriene and betamethasone group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calcipotriene 50 µg/g and betamethasone dipropionate 0.5 mg/g suspension vs betamethasone dipropionate 0.5 mg/g suspension vs calcipotriene 50 µg/g suspension vs vehicle suspension	of age with mild to moderate psoriasis for ≥6 months involving ≥10% of the arms, legs or trunk and amenable to treatment with ≤100 g of medication per week		controlled disease (IGA score of clear or almost clear and ≥2 point change from baseline) at weeks four and eight Secondary: Change from baseline in PASI at weeks four and eight	(13.3%) compared to calcipotriene groups (5.2%; P=0.019) and vehicle (2.1%; P=0.001). There was no significant difference in achievement of controlled disease between the calcipotriene and betamethasone and betamethasone groups (12.5%; P=0.82). At week eight, the calcipotriene and betamethasone group had a significantly greater proportion of patients achieving controlled disease (29%) compared to the betamethasone (21.5%), calcipotriene (14.6%) and vehicle groups (6.3%; P≤0.008 for all comparisons). Secondary: At week four, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (46.4%) compared to the betamethasone (42.7%), calcipotriene (32.2%) and vehicle groups (17.4%; P≤0.038 for all comparisons). At week eight, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (55.8%) compared to the betamethasone (48.6%), calcipotriene (43.6%) and vehicle groups (20.9%; P<0.001) for all comparisons).
Douglas et al.[85] (2002) Calcipotriene and betamethasone ointment applied BID (CB) vs betamethasone ointment applied BID (B) vs calcipotriene	DB, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,106 4 weeks of treatment and an additional 4 weeks of OL treatment with calcipotriene	Primary: Mean percent change in PASI from baseline after four weeks Secondary: Speed of response as assessed from percent change in PASI after one week, mean percentage decrease in the thickness of psoriatic lesion from baseline after	Primary: There was a significant reduction in mean percent change in PASI from baseline to week four in the CB group compared to the B group and the C group (74.4, 61.3, and 55.3% respectively; P<0.001). Secondary: There was a significant reduction in mean percent change in PASI after week one in the CB group compared to the B group and the C group (47.4, 39.8, and 31% respectively; P<0.001). There was a significant reduction in the mean percent change in thickness of the psoriatic lesion from baseline to week four in the CB group compared to the B group and the C group (79.4, 61.7, and 63% respectively; P<0.001). There was no significant difference in the percent of patients reporting adverse effects in any of the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied BID (C)			four weeks	
Kaufman et al.[86] (2002) Calcipotriene and betamethasone ointment applied QD (CB) vs betamethasone ointment applied QD (B) vs calcipotriene ointment applied QD (C) vs vehicle ointment QD (V)	DB, PC, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body regions	N=1,603 4 weeks	Primary: PASI score, IGA score, PGA score assessing patients with treatment success (defined as marked improvement or clearance of disease) Secondary: Not reported	Primary: There was a significant decrease in PASI score in the CB group compared to the B, C, and V groups (-71.3, -57.2, -46.1, and -22.7% respectively; P<0.001). There was a significantly larger number of patients assessed as having controlled disease according to the IGA score in the CB group compared to the B, C, and V groups (276, 176, 107, and 16 respectively; P<0.001). There was a significantly larger number of patients assessed as having treatment success according to the PGA scores after four weeks in the CB group compared to the B, C, and V groups (316, 216, 137, and 15 respectively; P<0.001). Secondary: Not reported
Papp et al.[87] (2003) Calcipotriene and betamethasone ointment applied BID (CB) vs betamethasone	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body areas	N=1,028 4 weeks	Primary: Mean percent reduction in PASI from baseline to the end of treatment Secondary: Speed of response assessed as the mean percent	Primary: There was a significant percent reduction in PASI at the end of treatment in the CB group compared to the B, C, V groups (73.2, 48.8, 63.1, and 28.8% respectively; P<0.001). Secondary: There was a significant reduction in the mean percent change in PASI from baseline to after one week of treatment in the CB group compared to the B, C, and V groups (48.1, 28.4, 41.4, and 21.5% respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied BID (B) vs calcipotriene ointment applied BID (C) vs vehicle ointment BID (V)			change in PASI from baseline after one week of treatment	
Luger et al.[88] (2008) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g	DB, MC, RCT Patients with moderate to severe scalp psoriasis	N=869 52 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: Disease was satisfactorily controlled in 92.3% of visits in the calcipotriol-betamethasone group vs 80.0% in the calcipotriol group (P<0.001). Adverse drug reactions were less frequent in the calcipotriol-betamethasone group compared to the calcipotriol group (17.2 vs 29.5%; P<0.001). Incidences of adverse events possibly associated with long-term corticosteroid use were low in both the calcipotriol-betamethasone (2.6%) and the calcipotriol (3.0%) groups. Secondary: Not reported
van de Kerkhof et al.[89] (2009) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g	DB, MC, PG, RCT Patients with scalp psoriasis involving >10% of the scalp	N=1417 8 weeks	Primary: Proportion of patients with 'absence of disease' or 'very mild disease' according to investigators' assessments Secondary:	Primary: The proportion of patients with 'absence of disease' or 'very mild disease' at week eight was significantly higher in the calcipotriol and betamethasone group (68.4%) than the betamethasone dipropionate (61.0%; P=0.0079) or calcipotriol (43.4%; P<0.0001) groups. Secondary: The proportion of patients rating their scalp psoriasis as 'clear' or 'almost clear' was significantly higher in the calcipotriol and betamethasone group (69.6%) than for betamethasone dipropionate (59.9%; P=0.0006) or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g			Patient ratings of scalp psoriasis and adverse events	calcipotriol (44.7%; P<0.0001). The incidence of lesional/perilesional adverse events was lower in the calcipotriol and betamethasone and betamethasone dipropionate groups than the calcipotriol group.
Jemec et al.[90] (2008) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g applied QD vs betamethasone dipropionate 0.5 mg/g applied QD vs calcipotriol 50 µg/g applied QD vs placebo	DB, MC, RCT Patients with scalp psoriasis	N=1505 8 weeks	Primary: Patients with ‘‘absence of disease’’ or ‘‘very mild disease’’ according to IGA of disease severity at week eight Secondary: Total Sign Score at week eight, proportion of patients who were ‘‘almost clear’’ or ‘cleared’’ by patients’ assessment	Primary: The proportion of patients who achieved ‘‘absent’’ or ‘‘very mild’’ disease at week eight was significantly greater in the calcipotriol and betamethasone group (71.2%) compared to the betamethasone dipropionate group (64.0%; P=0.011), the calcipotriene group (36.8%; P<0.0001), and the placebo group (22.8%; P<0.0001). Secondary: At week eight, the percentage change in Total Sign Score was significantly larger for the calcipotriol and betamethasone group (-70.8%) than for calcipotriene (-49.0%; P<0.0001) and for placebo (-35.6%; P<0.001). The difference vs betamethasone dipropionate, (-67.7%) was not statistically significant (P=0.12). The proportion of patients who rated their scalp psoriasis as ‘‘cleared’’ or ‘‘almost clear’’ at week eight was 68.6% for the calcipotriol and betamethasone group, 62.5% for betamethasone dipropionate, 38.3% for calcipotriene, and 20.7% for the placebo alone. The calcipotriol-betamethasone group was significantly more effective than calcipotriene (P<0.0001) and the placebo alone (P<0.0001). The difference vs betamethasone dipropionate was not statistically significant (P=0.2).
Camarasa et al.[91] (2003) Calcitriol 3 µg/g	DB, MC, RCT Adults with chronic plaque-type	N=258 Treatment: 6 weeks	Primary: Global improvement of treated psoriatic	Primary: After six weeks, both calcitriol and betamethasone were found to be efficacious. Similar proportions of patients (79% in the calcitriol group and 82% in the betamethasone group) showed definite or considerable

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied BID vs betamethasone dipropionate 0.05% ointment applied BID	psoriasis of at least moderate severity	Follow-up: 8 weeks	lesions; PASI; relapse Secondary: Not reported	improvement in their psoriasis, or total clearance of lesions by treatment endpoint. The mean of the global improvement scores at endpoint were similar (2.31 for calcitriol and 2.55 betamethasone; P<0.05). Both treatment groups showed a clinically relevant decrease in the mean GSS which, at endpoint, was 1.58 for the calcitriol group and 1.36 for the betamethasone group (P<0.05). Each treatment also resulted in a marked improvement in the PASI from baseline to endpoint, with the absolute reduction in the mean PASI at endpoint being comparable between the groups (P>0.05). Relapse warranting new treatment within eight weeks of the study endpoint was required in 52% of patients who had been receiving calcitriol, at a mean of 25.3 days post-treatment. In the betamethasone group, relapse was required for 75% of patients at a mean of 23.4 days post-treatment. The proportion of responders remaining in remission at eight weeks post-treatment (48 and 25% for the calcitriol and betamethasone groups, respectively; P<0.01). The two study ointments were similar in terms of cosmetic acceptability. The overall opinion of the ointments by the majority of patients was generally 'good' or 'acceptable' (91 and 92%, for the calcitriol and betamethasone groups, respectively). Secondary: Not reported
Bergstrom et al.[92] (2003) Clobetasol 0.05% foam applied to the skin and scalp	RCT, SB Patients with psoriasis	N=32 14 days	Primary: Patient quality of life; effectiveness, user satisfaction; severity based on the PASI and self-	Primary: Improvement in psoriasis severity was greater in the clobetasol foam group compared to the clobetasol cream and solution combination group (P=0.05). There was a greater improvement in scalp psoriasis for the foam group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clobetasol cream 0.05% applied to the skin and clobetasol 0.05% solution applied to the scalp			administered PASI Secondary: Not reported	compared to the solution group (P=0.03). Global QOL was greater for the foam group compared to cream (P=0.05) and solution (P=0.02). Secondary: Not reported
Jegasothy et al.[93] (1990) Clobetasol 0.05% ointment applied BID vs diflorasone 0.05% ointment applied BID	DB, RCT Patients with mild to severe psoriasis	N=60 2 weeks	Primary: Physician and patient preferences Secondary: Assessment of sign and symptom severity	Primary: At two weeks post treatment 75% of physicians and 68% of patients favored clobetasol treatment compared to 9% of physicians and 11% of patients who favored diflorasone, respectively (P<0.05). Secondary: At day 15, lesion clearing was greater with clobetasol in 21% of the patients compared to 9% of patients who had greater clearing with diflorasone (P<0.05). Clobetasol was more efficacious in terms of relieving erythema, scaling, and skin thickening on day eight, day 15 and at follow-up when compared to diflorasone (P<0.05).
Decroix et al.[94] (2004) Clobetasol lotion applied BID vs clobetasol cream applied BID vs placebo	MC, PC, PG, RCT, SB Patients ≥18 years of age with moderate to severe plaque type psoriasis	N=213 4 weeks	Primary: Dermatologic sum score, global severity score Secondary: Patient cosmetic acceptability survey	Primary: Both the dermatologic sum score and the global severity score had a greater improvement in the lotion and cream groups when compared to the placebo group (P<0.001). Overall improvement was seen in 74% in the lotion group and 78% in the cream group compared to 15% in the placebo group (P<0.001). Secondary: Patients favored the lotion over the cream in terms of satisfactory penetration time (P=0.043), drying quickly (P=0.002), feeling greasy (P<0.001), possessing a pleasing aspect and perfume (P=0.001), and leaving a film on the skin (P<0.017).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lowe et al.[95] (2005) Clobetasol lotion applied BID vs clobetasol cream applied BID vs placebo	MC, PC, RCT, SB Patients with moderate to severe plaque-type psoriasis	N=192 4 weeks	Primary: Erythema, plaque elevation, scaling, dermatological sum score, pruritus, global improvement global severity Secondary: Not reported	Primary: The difference in dermatologic sum score between clobetasol lotion and its placebo was statistically significant, with values of 2.21 and 5.93, respectively (P<0.001). When compared to the cream, the lotion resulted in no significant difference in dermatologic sum score improvement. The number of patients that had mild or no signs and symptoms was greater in the lotion group compared to its placebo (P<0.001). The difference in sign and symptom severity was not statistically significant between the lotion and the emollient cream group (0.168≤P≤0.868). Secondary: Not reported
Sofen et al.[96] (2011) Clobetasol 0.05% spray applied BID for up to four weeks vs placebo	DB, MC, RCT, VC Patients with moderate-to-severe (global severity score=3 or 4) plaque psoriasis of the scalp	N=81 4 weeks	Primary: Global severity score of psoriasis of the scalp after four weeks Secondary: Safety	Primary: At week four, 85% of patients in the clobetasol group achieve treatment success (global severity score clear or almost clear) compared to 13% of patients in the placebo group (P<0.001). The proportion of patients in the clobetasol group who achieved a global severity score of 0 after two weeks and at the end of treatment was 12 and 51%, respectively. Secondary: Globetasol spray was well-tolerated and there were no serious adverse events or reports of folliculitis or Cushing's syndrome.
Menter et al.[97] (2009) Clobetasol 0.05% spray applied BID for four weeks vs	MC, RCT Patients 18 to 80 years of age with stable plaque psoriasis involving 3 to 20% of the body surface area	N=122 8 weeks	Primary: Efficacy as assessed by overall disease severity, investigator global assessment, PQOL-12 Secondary:	Primary: After two weeks, 41% of patients receiving clobetasol had treatment success (clear or almost clear) compared to 27% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, 75% of patients receiving clobetasol were clear or almost clear compared to 45% of patients receiving calcipotriene and betamethasone dipropionate (P=0.003). After eight weeks, 14% of patients receiving clobetasol were clear or almost clear compared to 8% of calcipotriene and betamethasone dipropionate patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment applied daily for four weeks			Not reported	After four weeks, there was no significant difference in treatment success (clear or mild as assessed using the investigator global assessment scale) among the treatment groups (73% for clobetasol vs 65% for calcipotriene and betamethasone dipropionate). After two weeks, 52% of patients receiving clobetasol were clear or mild compared to 33% of patients receiving calcipotriene and betamethasone dipropionate (P=0.054). After eight weeks, 41% of patients receiving clobetasol were clear or mild compared to 24% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, PQOL-12 scores decreased by 36.1 points with clobetasol and by 30.8 points with calcipotriene and betamethasone dipropionate. After two weeks, PQOL-12 scores decreased by 24.4 points with clobetasol and by 21.4 points with calcipotriene and betamethasone dipropionate. After eight weeks, PQOL-12 scores decreased by 15.9 points with clobetasol and by 10.1 points with calcipotriene and betamethasone dipropionate. Patient satisfaction surveys indicate that more patients were satisfied with clobetasol than with calcipotriene and betamethasone dipropionate. Compliance was similar in both treatment groups (100% for clobetasol and 97% for calcipotriene and betamethasone dipropionate). Erythema, scaling and dryness were similar in both treatment groups. More patients experienced stinging/burning with clobetasol. Secondary: Not reported
Tan et al.[98] (2009) Clobetasol 0.05% shampoo applied daily	MC, OL Patients ≥18 years of age with moderate or severe scalp psoriasis (global severity	N=288 4 weeks	Primary: Patient-administered questionnaires assessing effect of treatment on skin-related quality of	Primary: For skin-related quality of life, the mean dermatology life quality index score decreased significantly from 7.0 at baseline to 3.2 at week four (P<0.001). After four weeks of treatment, 81.7% of patients indicated that scalp psoriasis had a small effect or no effect on their quality of life compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	score of 3 or 4 on a 0 to 5 scale)		life (using dermatology life quality index); patient satisfaction and treatment preference; efficacy (global severity scale); adverse events Secondary: Not reported	45.6% of patients at baseline (P<0.001). The percentage of patients who considered the disease to have a very large effect or extremely large effect on their life decreased from 19.4 to 3.4% (P<0.001). At week four, most patients reported that the disorder had no effect on their daily activities or symptoms/feelings (85.8 and 61.2%, respectively) compared to 54.8 and 14.5% at baseline, respectively. The percentage of patients considering the disease as having no effect on their leisure, work/school, personal relationships, and treatment increased from 83.0%, 91.5, 86.2 and 87.6%, respectively, to 95.1, 98.1, 93.7 and 93.7%, respectively. The percentage of patients who had none or mild pruritus increased from 24.6% at baseline to 83.0% at week four. The percentage of patients who experienced none or mild scaling increased from 0.7% at baseline to 64.9% at week four. The percentage of patients with moderate or severe pruritus decreased from 75.4% at baseline to 17.0% at week four. The percentage of patients with severe or very severe scaling decreased from 57.3% at baseline to 4.5% at week four. Most patients (>90%) were highly satisfied with the cosmetic acceptability of clobetasol: 92.8% of patients considered it pleasant to use, and 91.7% agreed that they could easily incorporate it into their daily routine. According to 95.1% of patients, clobetasol lathered and cleansed hair as well as regular shampoo. Overall, 90.2% of patients were satisfied with the efficacy of the treatment, while 86.4% were unaffected by adverse events. At week four, 78.1% of patients achieved the score of mild, very mild, or clear on the Global Severity Scale. The percentage of patients having severe psoriasis decreased from 41.7% to 3.5%. Only 2.1% of patients reported treatment-related adverse events, which were considered mild or moderate in severity. A total of 80.7% of patients considered clobetasol to be better than prior treatments, with 57.3% indicating it was much better. Overall, 86.5% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients indicated that they would use clobetasol again. Secondary: Not reported
Poulin et al.[99] (2010) Clobetasol 0.05% shampoo applied twice weekly for up to 6 months vs placebo All patients were enrolled in an initial four-week OL trial. Patients with a global severity scale ≤2 (clear, very mild or mild) were then randomized into the maintenance phase of the study.	DB, PC, RCT Patients with moderate scalp psoriasis (global severity scale of 3 on a 0 to 5 scale)	N=136 6 months	Primary: Relapse rate, safety; patient satisfaction Secondary: Not reported	Primary: The percentage of patients who had no relapse was significantly greater with clobetasol than with placebo (P<0.01) at all time points. After one month, 44% of patients in the placebo group had no relapse; whereas this rate was observed approximately four months later in the clobetasol group. After six months of maintenance treatment, the percentage of patients who had no relapse was 40.3% with clobetasol compared to 11.6% with placebo. The median time to first relapse was 30.5 days with placebo and 141.0 days with clobetasol (P<0.0001). Among the patients who had relapse and entered the alternate treatment regimen, a significantly greater percentage of those in the clobetasol group (73.2%) experienced only one relapse over six months compared to those in the placebo group (34.1%; P<0.001). More patients in the placebo group had two or three relapses (38.3 and 27.6%, respectively) during the maintenance phase than in the clobetasol group (16.8 and 10.0%, respectively; P<0.001). More adverse events occurred in the placebo group (50 events) than in the clobetasol shampoo group (34 events). At the end of treatment, 72.7% of patients in the clobetasol group preferred the twice-weekly treatment for a long period, compared to a daily treatment in case of relapse. There were 86.0% of patients in the clobetasol group willing to continue the treatment in the same way, and 57.1% reported that they could adopt such a regimen for as long as one year. Significantly more patients in the clobetasol group than the placebo group agreed that the treatment was enough to control their disease (73.7 vs 39.7%; P<0.001), considered themselves not bothered at all by side effects (93 vs 79.7%; P<0.05), and were satisfied or very satisfied with the overall treatment (84.2 vs 59.7%; P<0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Bovenschen et al.[100] (2010) Clobetasol 0.05% shampoo applied daily for 15 minutes .	PRO Patients ≥18 years of age with scalp psoriasis	N=56 4 weeks	Primary: Questionnaire assessing treatment satisfaction, user convenience, safety and effectiveness Secondary: Not reported	Primary: A total of 66% of patients judged the treatment as satisfactory after four weeks. A total of 79% of patients reported a positive user convenience with clobetasol. The severity of symptoms decreased as follows after four weeks of treatment (all, P<0.05): pruritus, -46%; pain, -44%; desquamation, -43%; social impairment (-39%). Treatment was generally well-tolerated and there were no major adverse events other than a mild skin irritation in two patients (5%). One patient had mild hair loss (3%). Secondary: Not reported
Mraz et al.[101] (2008) Clobetasol 0.05% spray applied BID for up to four weeks vs clobetasol 0.05% foam applied BID for two weeks	RCT Patients with moderate to severe plaque psoriasis	N=77 4 weeks	Primary: Efficacy Secondary: Quality of life (as determined by the dermatology life quality index) and adverse events	Primary: Patients treated with clobetasol spray had a median 64% reduction in affected body surface area compared to a median 25% reduction in patients treated with the clobetasol foam (P=0.004). At the end of the treatment period, 22% of clobetasol spray-treated patients were completely clear compared to 5% of clobetasol foam-treated patients (P=0.04). Secondary: Improvements in quality of life as determined by the dermatology life quality index were statistically significantly greater at all time points for patients treated with clobetasol spray compared to patients treated with clobetasol foam (P<0.04). The majority of adverse events for both products were mild in severity.
Willis et al.[102] (1986)	DB, MC, PG, RCT Patients with scalp	N=123 2 weeks	Primary: Mean sign and symptom score	Primary: There was an insignificant difference in the mean overall evaluation scores between the desoximetasone group and the fluocinonide group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desoximetasone 0.05% gel applied BID vs fluocinonide 0.05% gel applied BID	psoriasis		based on severity of erythema, scaling, thickening, and pruritus Secondary: Patient cosmetic acceptability	Eighty-nine percent (54 of 61) of patients in the desoximetasone group and 82% (49 of 60) in the fluocinonide group achieved either good or excellent improvement. Secondary: No significant difference was found between the treatment groups in terms of cosmetic acceptability.
Zachariae et al.[103] (1976) Desoximetasone 0.25% applied BID vs hydrocortisone butyrate 0.1% applied BID	DB, RCT Patients with psoriasis	N=27 2 weeks	Primary: Erythema, induration, scaling, pruritus, pustulation Secondary: Patient preference	Primary: After two weeks of treatment, there was a greater improvement of symptoms in the desoximetasone treatment group compared to the hydrocortisone group. Desoximetasone was more efficacious when compared to hydrocortisone in improving erythema, scaling, and induration (P<0.05). Secondary: Thirteen patients preferred desoximetasone and three patients preferred hydrocortisone (P<0.05).
Anonymous[104] (1985) Desoximetasone 0.25% ointment applied BID vs fluocinonide 0.05% ointment applied BID	MC, PG, RCT, SB Patients ≥3 years of age with stable or exacerbating psoriasis	N=121 14 days	Primary: Assessment of sign and symptom severity scores (based on pruritus, erythema, scaling, and thickening), clinical improvement Secondary: Patients' evaluation of cosmetic attributes	Primary: There was a greater improvement in the overall sign and symptom severity score in the desoximetasone group compared to the fluocinonide group. The mean sign and symptom scores for desoximetasone and fluocinonide were 2.47 and 2.66, respectively, at day four (P=0.065); 2.00 and 2.28, respectively at day seven (P=0.080); and, 1.75 and 2.07, respectively at day 14 (P=0.014). These results were statistically significant at day 14. Patient response to treatment was greater in the desoximetasone group compared to the fluocinonide group at day 14 (P≤0.029). Secondary: The percentage of patients with an excellent improvement was greater in the desoximetasone group compared to the fluocinonide group at day four and 14 (day four, 32 vs 18%, respectively; P=0.046, day 14, 42 vs 25%, respectively; P=0.028).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lee et al.[105] (2009) Fluocinonide 0.1% cream vs clobetasol 0.05% cream vs halobetasol 0.05% cream vs placebo	PC, SB, SC Patients ≥18 years of age with clinically diagnosed plaque-type psoriasis	N=5 12 days	Primary: Reduction of erythema, scaling and induration Secondary: Not reported	Primary: After three days, a reduction of erythema, scaling and induration (mild to moderate improvement) was seen in all of the treatment sites. Moderate improvement was seen in 40% of test sites treated with fluocinonide and 20% of sites treated with halobetasol and clobetasol. After five days, moderate improvement or clear or almost clear was seen in 80% of test sites treated with fluocinonide and 60% of sites treated with halobetasol or clobetasol. After seven days, 80% of all active-treated sites were assessed as moderate or clear or almost clear. There was no significant difference among the active treatment groups. The best response was reached by day seven in 10 of 15 (67%) of active-treated sites. The other five sites reached their best response in the second week of treatment. The best response was maintained at each site until the end of the 12-day test period. The active treatments were well tolerated. Secondary: Not reported
Krueger et al.[106] (1987) Flurandrenolide tape 4 mg/cm^2 applied daily for up to 16 hours vs diflorasone 0.05% ointment applied BID	RCT, SB Patients ≥18 years of age with stable psoriasis	N=30 4 weeks	Primary: Erythema, scaling, and induration individually and in aggregate erythema, scaling, and infiltration scores Secondary: Not reported	Primary: At baseline, the erythema, scaling, and infiltration scores values for both groups were 5.8 (P=0.68). At the week two evaluations, the erythema, scaling, and infiltration scores score was less in the flurandrenolide group compared to the diflorasone group at values of 1.9 and 3.3, respectively; also, these scores were decreased from the values obtained at baseline by 67 and 43%, respectively (P<0.01). At the week four evaluation, the erythema, scaling, and infiltration scores was also less for the flurandrenolide tape group vs the diflorasone group, with values of 1.6 and 2.7, respectively. Compared to baseline, the erythema, scaling, and infiltration scores score for the flurandrenolide tape group decreased by 72%, and the diflorasone ointment group decreased by 53% (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Flurandrenolide-tape-treated psoriatic plaques showed more positive results in overall treatment success with a rate of 60% at week two and 64% at week four. The overall treatment success rates for diflorasone ointment at week two and week four were 22 and 33%, respectively (P<0.01). Secondary: Not reported
Swinehart et al.[107] (1989) Mometasone 0.1% lotion applied daily vs triamcinolone 0.1% lotion applied BID	MC, PG, RCT Patients with scalp psoriasis	N=202 21 days	Primary: Changes in disease sign and symptom scores for erythema, scaling, induration, pruritus Secondary: Patient evaluation of efficacy and cosmetic acceptability of treatment	Primary: There was a greater improvement in the sign and symptom scores in the mometasone group compared to the triamcinolone group. Seventy-seven percent of patients in the mometasone group and 62% in the triamcinolone group showed improvement or clearing of disease (P≤0.05). Secondary: Patients considered mometasone the better treatment in terms of efficacy and cosmetic acceptability. Eight-eight percent of patients in the mometasone group and 80% in the triamcinolone group rated their response as either good or excellent (P<0.01).
Medansky et al.[108] (1988) Mometasone 0.1% ointment or cream applied daily vs fluocinolone 0.025% ointment or cream applied TID and	MC, PG, RCT, SB Patients with chronic moderate to severe psoriasis vulgaris	N=764 21days	Primary: Evaluation of individual disease signs in the target areas and change in disease sign score; change in overall disease status Secondary: Not reported	Primary: The mean disease sign score showed a greater percentage improvement in the mometasone ointment patients compared to the fluocinolone ointment group (58 vs 41%; P<0.01). There was a greater percentage improvement in the mometasone ointment group compared to the triamcinolone ointment group with disease sign score improvements of 60 and 37%, respectively (P<0.01). There was a greater percentage improvement in the mean disease sign score in the mometasone cream group compared to the fluocinolone cream group (51 vs 29%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mometasone 0.1% ointment or cream applied daily vs triamcinolone 0.1% ointment or cream applied BID				The mometasone cream group had a slight increase in percentage improvement compared to the triamcinolone cream group, but the results were not statistically significant (54 vs 51%). A moderate improvement was found in the mometasone group compared to a slight improvement in the fluocinolone and triamcinolone group (P<0.01). Patients in the mometasone cream group were determined to have moderate improvements in overall disease status, as compared to the fluocinolone cream group with slight improvements (P<0.001). Secondary: Not reported
Rigopoulos et al.[109] (2007) Tazarotene 0.1 % cream applied QHS for 12 weeks vs clobetasol 0.05% cream applied QHS for 12 weeks	DB, RCT Patients with psoriasis including nail involvement	N=23 24 weeks	Primary: Assessment of pitting, onycholysis, subungual hyperkeratosis and salmon patches using the NAPSI Secondary: Not reported	Primary: There was no significant difference in pitting, onycholysis, subungual hyperkeratosis, or salmon patches between tazarotene and clobetasol after 12 weeks of treatment. Post hoc analysis at the end of the follow-up period (24 weeks) demonstrated clinical improvement for hyperkeratosis with tazarotene compared to clobetasol (P<0.001). All adverse events reported were mild, with the symptoms ameliorating after a few days. All patients in both groups declared satisfaction with the results at the end of the treatment period. Secondary: Not reported
Angelo et al.[110] (2007) Tazarotene 0.1% cream applied on one side of the body for 12 weeks	RCT, SB Patients with psoriasis and bilateral symmetrical lesions	N=36 16 weeks	Primary: Assessment of erythema, scaling and induration on a 4-point scale; investigators' overall assessment of psoriasis	Primary: During the 12-week treatment period, both tazarotene cream and clobetasol cream were associated with reduction in erythema scores from the baseline except at week two where tazarotene showed no improvement. Clobetasol cream was better than tazarotene cream in reducing the erythema throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene at weeks two, four, six and eight.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clobetasol 0.05% cream applied on the other side of the body for 12 weeks			including extent and severity; treatment success Secondary: Not reported	During the 12-week treatment period, both tazarotene and clobetasol creams were associated with reduction in induration scores from baseline. Tazarotene was better than clobetasol in reducing the induration at weeks two, four, 10 and 12. The difference was statistically significant at week two. Both were equally effective at weeks six and eight. During the 12-week treatment period both tazarotene and clobetasol creams were associated with reduction in desquamation scores from baseline except at week two where tazarotene showed no reduction. Clobetasol cream was better than tazarotene cream in reducing the scaling throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene over the entire 12-week treatment period. The overall improvement at weeks two, four six, eight, 10 and 12 for tazarotene was ~20, ~33, ~43, ~53, ~55 and ~58% respectively and for clobetasol was ~33, ~55, ~73, ~78,~95 and ~95% respectively. Statistically significant differences favored clobetasol cream over tazarotene cream over the entire 12-week treatment period. Clobetasol produced higher success rates than tazarotene over the 12-week treatment period. Statistically significant differences favored clobetasol over tazarotene at weeks two and four. Treatment success rate was 100% at week six with clobetasol and was 73% with tazarotene. At week 12, it was 100% with clobetasol and 88% with tazarotene. Secondary: Not reported
Choonhakarn et al.[111] (2010) Triamcinolone 0.1% cream applied BID	DB, RCT Patients ≥18 years of age with a clinical diagnosis of psoriasis	N=80 8 weeks	Primary: Change in PASI score Secondary: Quality of life assessed using the dermatology life	Primary: After eight weeks, no patients experienced complete clearance of psoriasis in either group. Six patients (16.2%) in the aloe vera group and four patients (10.5%) in the triamcinolone group achieved a PASI 75 ('marked' response) by week eight. Twenty patients (54.1%) in the aloe vera group achieved a PASI 50 ('moderate' response) compared to 25 patients (65.8%) in the triamcinolone group. Ten patients (27%) in the aloe vera group and nine patients (23.7%) in the triamcinolone group experienced a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aloe vera cream applied BID			quality index	'slight' improvement in their lesions (PASI scores decreased <50% from baseline) by week eight. There was no change observed in the lesion in one patient (2.7%) receiving aloe vera. After eight weeks, the mean PASI score was 3.9 in the aloe vera group and 4.3 in the triamcinolone group (95% CI –0.37 to 1.28; P=0.2783). The between-group difference in the adjusted means was 1.1 in favor of aloe vera (95% CI, -2.13 to -0.16; P=0.0237). Secondary: The mean dermatology life quality index scores decreased in both treatment groups; however, there was no significant difference between the groups after eight weeks of therapy. Patients in the aloe vera group had a mean dermatology life quality index score of 8.6 at baseline, decreasing to 2.5 after eight weeks of treatment. The triamcinolone group showed a dermatology life quality index score decrease from 8.1 at baseline to 2.3 at week eight. The between-group difference in adjusted means was 0.3 (95% CI, -1.18 to -0.64; P=0.5497). There were no serious adverse events reported in either group. Six patients receiving aloe vera cream experienced stinging and itching at the lesions.
Multiple Dermatoses				
Rocha et al.[112] (1976) Amcinonide 0.1% cream applied BID vs betamethasone valerate 0.1% cream applied BID	DB Patients with atopic dermatitis, contact dermatitis, and eczema	N=60 3 weeks	Primary: Investigator assessment of clinical response, patient assessment of clinical response Secondary: Cosmetic acceptability	Primary: Amcinonide and betamethasone treatment groups demonstrated improvement in objective and subjective parameters over the course of three weeks. Investigator's overall ratings of efficacy was comparable for the two treatment groups (P=0.38). All 30 amcinonide patients rated its efficacy as excellent compared to 27 of 30 betamethasone patients (the remaining three gave a rating of good; P=0.24). Secondary: No significant difference was found between treatment groups (P≤1.00).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenberg et al.[113] (1979) Amcinonide 0.1% cream applied BID vs betamethasone valerate 0.1% cream applied BID	DB, PG, RCT Patients with eczematous dermatitis, including contact dermatitis, atopic dermatitis, nummular eczema, seborrheic dermatitis, and eczema	N=35 2 weeks	Primary: Mean overall improvement rating of disease status and symptoms Secondary: Not reported	Primary: Both treatment groups demonstrated a decrease in pruritus, lichenification, erythema, crust, scaling, papules and excoriation. The amcinonide treatment group had a greater improvement compared to the betamethasone group in pruritus, lichenification, erythema, crust, scaling and excoriation. The betamethasone treatment group had a greater improvement compared to the amcinonide group in papules. None of these differences were found to be statistically significant. Mean percent improvement was greater for the amcinonide group compared to the betamethasone group (P<0.5). Secondary: Not reported
Rhodes et al.[114] (1983) Betamethasone dipropionate 0.05% cream applied BID vs betamethasone valerate 0.1% cream applied BID	DB, MC Patients with dermatoses, predominantly eczema	N=75 3 weeks	Primary: Signs and symptoms of erythema, scaling, induration, crusting, pruritus, excoriation, pain; patient and investigator overall response to therapy Secondary: Not reported	Primary: An “excellent” response to treatment was reported in 42.9% patients in the Diprosone® group and 10.3% of patients in the betamethasone valerate (P<0.01). Greater than 50% clearing was observed in 78.6% of patients in the Diprosone® group, and 41.4% of patients in the betamethasone valerate group (P<0.01). Secondary: Not reported
Levy et al.[115] (1977) Betamethasone dipropionate 0.05% cream applied BID vs	RCT Patients with acute and chronic dermatoses, including psoriasis, lichen chronicus simplex, eczema, contact dermatitis,	N=53 4 weeks	Primary: Psoriasis: removal of scales with a decrease in number of plaques; lichen chronicus simplex: decrease in excoriation, pruritus, and	Primary: Psoriasis: There was a greater improvement in the four patients with psoriasis treated with betamethasone compared to those treated with halcinonide. There was no significant difference between either treatment groups in the treatment of psoriasis. Lichen chronicus simplex: There was no significant difference between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
halcinonide 0.1% applied daily	neurodermatitis, and atopic dermatitis		infiltration and remission of chronic inflammation; acute dermatoses at the exacerbation stage (eczema, contact dermatitis, neurodermatitis): relief of acute inflammation, pruritus Secondary: Not reported	Eczema: Six of eight patients had a greater improvement when using halcinonide treatment compared to treatment with betamethasone. Contact dermatitis: Halcinonide was shown to be more effective when compared to betamethasone in the 10 patients with contact dermatitis. Atopic dermatitis: There was no significant difference found between the two treatment groups. Neurodermatitis: There was no significant difference between the two treatment groups. Secondary: Not reported
Bluefarb et al.[116] (1972) Betamethasone valerate 0.1% cream vs desonide 0.05% cream	DB, RCT Patients with dermatological conditions, including atopic eczema, contact dermatitis, lichen simplex, nummular eczema, psoriasis, seborrheic dermatitis	N=117 4 weeks	Primary: Pruritus, erythema, induration, scaling; global response Secondary: Not reported	Primary: Dermatitides: Desonide cleared a greater percent of dermatitides (70.4%) compared to betamethasone (56.5%). Eczematous conditions: There was a greater rate of clearance for the betamethasone group (62.5%) compared to the desonide group (45.5%). Psoriasis: A greater percentage of patients had their psoriasis rated as either clear or excellent in the desonide group (48%) compared to the betamethasone group (35%). Secondary: Not reported
Vollum et al.[117] (1979)	DB, RCT Patients with lesions	N=38	Primary: Improvement in lesions on one side	Primary: There were ten clinicians who chose betamethasone valerate, zero that preferred halcinonide and five that found no difference (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Betamethasone valerate 0.1% ointment applied to one side of the face vs halcinonide 0.1% applied to the other side of the face	of bilateral eczema or psoriasis		of the patient's face compared to the other Secondary: Not reported	Among patients with eczema, there was no statistical difference between the two medications. Secondary: Not reported
Wishart et al.[118] (1993) Betamethasone valerate 0.1% cream applied BID vs mometasone 0.1% cream applied daily	MC, PG, RCT Patients with a variety of dermatoses, including atopic dermatitis, eczema, seborrheic dermatitis, psoriasis, and allergic dermatitis	N=58 4 weeks	Primary: Scoring of target lesion Secondary: Not reported	Primary: At four weeks, disease improvement was seen in 93% of patients in the mometasone group and in 90% of patients in the betamethasone group. The difference in the number of patients with improvement in their disease in the mometasone group compared to the betamethasone group was not statistically significant at any endpoint. Secondary: Not reported
Jegasothy et al.[119] (1985) Clobetasol 0.05% cream applied TID vs fluocinonide 0.05% cream applied TID	DB, MC, PG Patients 13 to 75 years of age with psoriasis or chronic eczema	N=227 2 weeks	Primary: Physician global assessment, sign and symptom severity, patient evaluation of improvement Secondary: Not reported	Primary: After two weeks, 82% of the psoriasis patients treated with clobetasol had clearance of their lesions compared to 46% of the fluocinonide group (P<0.001). Mild or absent signs and symptoms among the psoriasis patients was found in 91% of patients in the clobetasol group and 55% of patients in the fluocinonide group (P<0.001). Eight-six percent of patients in the clobetasol group had either excellent or good improvement in their psoriasis compared to 61% in the fluocinonide group, respectively (P<0.01). After two weeks, 89% of eczema patients treated with clobetasol had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				clearance of their lesions compared to 70% of the patients in the fluocinonide group (P<0.05). There was a significant difference in the signs and symptoms among eczema patients in the two treatment groups. Secondary: Not reported
Bleeker et al.[120] (1975) Clobetasol 0.05% cream applied BID vs halcinonide 0.1% applied BID	DB Patients with psoriasis, atopic dermatitis or eczema	N=100 14 days	Primary: Decrease in erythema, edema, transudation, lichenification, scaling, pruritus and pain, overall therapeutic response Secondary: Not reported	Primary: Psoriasis: Among the 53 patients with psoriasis, 15 had either marked or slight improvement with halcinonide, compared to 13 with clobetasol. The remaining 25 patients had an equal response to both treatments. Atopic dermatitis: Of the 27 patients with atopic dermatitis, seven had either marked or slight improvement with halcinonide, compared to six with clobetasol. The remaining 14 patients had an equal response to both treatments. Eczema: Among the 20 patients with atopic dermatitis, one had either marked or slight improvement with halcinonide, compared to five with clobetasol. The remaining 14 patients had an equal response to both treatments. Secondary: Not reported
Barsky et al.[121] (1976) Desonide 0.05% cream applied BID vs fluocinonide 0.05% cream applied BID	DB, RCT Patients with dermatologic disorders, including eczema, seborrheic dermatitis, contact dermatitis, and lichen simplex	N=78 2 weeks	Primary: Erythema, scaling, pruritus, palpable induration Secondary: Physician's scoring of improvement	Primary: The desonide group had a greater improvement in erythema and scaling compared to the fluocinonide group in week one (P<0.05); however, the difference was not statistically significant in week two. There was no significant difference between the treatment groups in all other signs and symptoms (all P values >0.25 or more). Secondary: There was no significant difference in the overall physician evaluation between treatment groups at week one or endpoint (P>0.20 and P>0.60,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively).
Kelly et al.[122] (1991) Mometasone furoate 0.1% cream applied daily vs betamethasone dipropionate 0.05% cream applied BID	MC, PG, RCT, SB Patients ≥15 years of age with a variety of dermatoses, including psoriasis, atopic dermatitis, and eczema	N=67 12 weeks	Primary: Erythema, induration, scaling, crusting, pruritus, excoriation, pain Secondary: Mean plasma cortisol levels	Primary: There were 15 of 33 patients in the mometasone furoate group who left the study prior to day 85 due to the fact that their lesions were cleared. This corresponds to 18 of 32 patients in the betamethasone dipropionate patients. The difference in mean sign and symptom scores at end point was not statistically significant between the two treatment groups (mometasone furoate mean=3.0; betamethasone dipropionate mean=2.5; P=0.68). The mean percent improvement was not statistically significant; there was a 74.4% improvement for the mometasone furoate group and an 80.1% improvement in the betamethasone dipropionate side (P=0.51). Secondary: The only instance in which the mean plasma cortisol levels between the two groups reached statistical significance was at day eight. The change in mean plasma cortisol level for the mometasone furoate group at day eight was 6.1, and for the betamethasone dipropionate group the change was -86.0 (P=0.02).
Miscellaneous				
Barikbin et al.[123] (2009) Betamethasone valerate 0.1% cream applied BID vs pimecrolimus 1% cream applied BID	DB, RCT Patients 20 to 53 years of age with moderate to severe discoid lupus erythematosus of the face	N=10 8 weeks	Primary: Clinical severity score Secondary: Not reported	Primary: Before treatment, mean disease severity was 4.2 in the pimecrolimus group and 4.4 in the betamethasone group. Following eight weeks of therapy, the mean disease severity was 0.67 and 1.2 in the pimecrolimus and betamethasone groups, respectively. The mean clinical severity scores decreased 86% and 73% in the pimecrolimus and betamethasone groups, respectively (both, P=0.043). There was no significant difference between the groups in terms of therapeutic efficacy (P=0.1). There were no recurrences at the eight-week follow-up. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rigopoulos et al.[124] (2009) Betamethasone valerate 0.1% ointment applied BID vs tacrolimus 0.1% ointment applied BID vs placebo	OL, RCT Patients with chronic paronychia	N=45 Treatment: 3 weeks Follow-up: 6 weeks	Primary: Treatment response Secondary: Not reported	Primary: Eight patients in the betamethasone group were considered as cured, two as improved and four as nonresponders at the end of the treatment period. Thirteen patients in the tacrolimus group were considered as cured and one as improved at the end of the treatment period. Nine patients in the placebo group were considered as stable and six failed to respond. Patients in the betamethasone and tacrolimus groups had greater cure or improvement rates compared to patients in the placebo group (P<0.001). Secondary: Not reported
Goldstein et al.[125] (2011) Clobetasol 0.05% cream daily vs pimecrolimus 1% cream applied BID	DB, RCT Female patients ≥18 years of age with biopsy-proven active vulvar lichen sclerosus	N=38 12 weeks	Primary: Change in inflammation as assessed by biopsy Secondary: Change in pruritus and burning/pain as assessed by patients using a visual analog scale, clinical evaluation of an investigator global assessment of the severity of the disease, clinical evaluation of lichenification,	Primary: The improvement in inflammation was significant both for the clobetasol and pimecrolimus groups (P=0.001 and P=0.008, respectively). Clobetasol was found to be more effective in improving inflammation compared to pimecrolimus (P=0.015). There were nine nonresponders (i.e., no improvement in inflammation), one in the clobetasol group and eight in the pimecrolimus group. Secondary: The mean change in the visual analog scale-pruritus score in the clobetasol and pimecrolimus groups were 4.5 and 3.5, respectively (P=0.319). The mean change in visual analog scale-burning/pain score in the clobetasol and pimecrolimus groups was 3.7 and 3.8, respectively (P=0.932). Clobetasol and pimecrolimus were found to be effective in decreasing both the total score on the investigator global assessment (P=0.001) and all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and clinical evaluation of ulceration/fissuring	three subscales (severity of disease, P=0.001; lichenification, P=0.001; and ulceration, P=0.025). No adverse events were reported and no herpetic events occurred.
Greer et al.[126] (1984) Hydrocortisone 1% and pramoxine 1% applied QID vs placebo	DB, PC, RCT Female patients entering the postnatal ward complaining of episiotomy pain	N=40 5 days	Primary: Edema, erythema, pain, impairment of mobility and analgesic requirements graded by the treating physicians on a scale of 1 to 4 Secondary: Healing and overall subjective response to treatment at day five	Primary: No significant difference was found between mean total daily scores on days one or three, but a significant difference in favor of placebo was seen on day five. Secondary: Subjective response to treatment showed no difference between groups (P>0.1) although healing was better with placebo (P<0.05). Mean individual criterion scores were also compared, but showed no difference except in edema on day five, mobility on day three, and analgesic requirements on days three and five, when placebo was more effective.
Köse et al.[127] (2010) Mometasone 0.1% cream applied daily vs pimecrolimus 1% cream applied BID	OL, SC Patients with stable vitiligo	N=50 12 weeks	Primary: Response to treatment Secondary: Not reported	Primary: Patients receiving mometasone had a better response to treatment than patients in the pimecrolimus group (P=0.008 in the per protocol population). Lesion size decreased from 19.20 to 16.85 cm^2 in the pimecrolimus group (P=0.002) and from 18.65 to 10.45 cm^2 in the mometasone group (P<0.001). There was no significant difference between the treatment groups (P=0.154). Complete remission occurred in three patients (15%) receiving mometasone. There were no patients who achieved complete remission in the pimecrolimus group (P=0.018 in the per protocol population). Moderate and marked responses were recorded in 11 patients (55%) in the mometasone group and in seven patients (35%) in the pimecrolimus group. No change and minimal responses were observed in six patients (30%) in the mometasone group, and in 13 patients (65%) in the pimecrolimus group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				After six months, three patients (15%) in the pimecrolimus group and four patients (20%) in the mometasone group showed some areas of depigmentation over re-pigmented vitiliginous lesions. Initial repigmentation started after 9.25 weeks in the mometasone group and after 11.25 weeks in the pimecrolimus group (P=0.064 in the per protocol population). The mean repigmentation rate was 65% in the mometasone group and 42% in the pimecrolimus group at the end of therapy. Both agents were well tolerated. The reported adverse events with mometasone were atrophy, telangiectasia, and erythema. Patients receiving pimecrolimus reported a burning sensation and pruritus. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QD=daily, QHS=at bedtime, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ITT=intent to treat, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SC=single center, VC=vehicle controlled
Miscellaneous abbreviations: AD=atopic dermatitis, BSA=body surface area, GSS=Global Severity Score, IGA=Investigator Global Assessment, mEASI=Modified Eczema Area and Severity Index, mLEASI=Modified Local Eczema Area and Severity Index, PASI=Psoriasis Area and Severity Index, PGA=Physician Global Assessment, PQOL-12=Psoriasis Quality of Life Questionnaire, SF-36=short form 36, TSS=Total Severity Score

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Skin and Mucous Membrane Anti-Inflammatory Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Alclometasone	cream, ointment	N/A	N/A	$$$
Amcinonide	cream, lotion, ointment	N/A	N/A	$$$$$
Betamethasone dipropionate	cream, gel, lotion, ointment	N/A	N/A	$$$$
Betamethasone valerate	cream, foam, lotion, ointment	Luxiq®*	$$$$$	$$$
Clobetasol	cream, foam, gel, lotion, ointment, shampoo, solution, spray	Clobex®*, Cormax®*, Olux®*, Olux-E®*, Temovate®*, Temovate Emollient®*	$$$$$	$$
Clocortolone	cream	Cloderm®	$$$$$	N/A
Desonide	cream, foam, gel, lotion, ointment	Desonate®, Verdeso®, Lokara®*	$$$$$	$$$$$
Desoximetasone	cream, gel, ointment, spray	Topicort®*	$$$$$	$$$$
Diflorasone	cream, ointment	ApexiCon E®	$$$$-$$$$$	$$$$
Dimethyl	solution^	Rimso-50®	$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
sulfoxide				
Fluocinolone	cream, oil, ointment, shampoo, solution	Capex Shampoo®, Derma-Smoothe/FS®*, Synalar®*	$$$$$	$$$$
Fluocinonide	cream, gel, ointment, solution	Vanos®	$$$$-$$$$$	$$
Flurandrenolide	tape	Cordran®	$$$$$	N/A
Fluticasone	cream, lotion, ointment	Cutivate®*	$$-$$$$$	$$
Halcinonide	cream, ointment	Halog®	$$$-$$$$	N/A
Halobetasol	cream, ointment	Ultravate®*	$$$$-$$$$$	$$$$
Hydrocortisone	cream, lotion, ointment, rectal cream, rectal enema, solution	Anusol-HC®*, Cortenema®*, Proctocort®*, ProctoCream-HC®*, Texacort®	$-$$$$	$
Hydrocortisone acetate	rectal foam	Cortifoam®	$-$$$$$	$
Hydrocortisone butyrate	cream, ointment, solution	N/A	N/A	$$$
Hydrocortisone probutate	cream	Pandel®	$$$-$$$$$	N/A
Hydrocortisone valerate	cream, ointment	N/A	N/A	$$$
Mometasone	cream, ointment, solution	Elocon®*	$-$$$	$$
Prednicarbate	cream, ointment	Dermatop®*	$$$	$$
Triamcinolone	aerosol, cream, dental paste, lotion, ointment	Kenalog®, Oralone®*, Trianex®	$$$	$
Combination Products				
Betamethasone dipropionate and propylene glycol	cream, lotion, ointment	Diprolene®*, Diprolene AF®*	$$$-$$$$	$-$$$
Halobetasol and ammonium lactate	combination package	Halonate®, Halonate PAC®, Ultravate PAC®	$$$$-$$$$$	$$$$
Halobetasol and lactic acid	combination package	Ultravate X®	$$$$-$$$$$	N/A
Hydrocortisone, mineral oil, and white petrolatum	ointment	N/A	N/A	$
Hydrocortisone acetate and aloe vera	gel	N/A	N/A	$
Hydrocortisone acetate and lidocaine	cream	N/A	N/A	$
Hydrocortisone acetate and pramoxine	rectal cream, rectal foam	PramCort®, ProCort®, ProctoFoam-HC®	$$$	N/A
Hydrocortisone acetate and urea	cream	N/A	N/A	$$
Mometasone and ammonium lactate	combination package	Momexin®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
N/A=Not available

X. Conclusions

The skin and mucous membrane anti-inflammatory agents are approved for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The topical corticosteroids are classified based on their relative potency: super high potency (Class I), high potency (Classes II to III), medium potency (Classes IV to V) and low potency (Classes VI to VII).[30] They are available in a variety of vehicles, including cream, foam, gel, lotion, ointment, paste, shampoo, solution, spray and tape. There is at least one topical corticosteroid available in a generic formulation in each potency category. Hydrocortisone is also available over-the-counter.

For the treatment of atopic dermatitis, emollients are considered the standard of care.[31-36] They are steroid-sparing and are useful for both prevention and maintenance therapy. Topical corticosteroids provide symptomatic relief and are safe to use in the short term. The selection of therapy should take into consideration the disease severity, location of the lesions, patient's age and anticipated duration of therapy.[32,31,34] Guidelines do not give preference to one topical corticosteroid over another.[31-36]Clinical trials have demonstrated similar efficacy among the various topical corticosteroids for the treatment of atopic dermatitis.[44-46,49,51,53,57,60-62,65,106,112,113,115,117,118,120-122] While some studies have demonstrated greater efficacy with one agent over another, they were often comparing corticosteroids with different potencies.[50,52,60,63,65,114,116,119]

There are numerous topical and systemic therapies available for the treatment of psoriasis. The selection of therapy should take into consideration the disease severity, location of the lesions, and patient preference. Patients with mild to moderate disease can often be treated with a topical agent, while those with moderate to severe disease may need systemic therapy.[38-39] Topical preparations that are effective include corticosteroids, tar-based products, dithranol preparations, vitamin A analogs and vitamin D analogs. Emollients should also be used to soften scaling and reduce irritation. Guidelines do not give preference to one topical agent over another.[38-39] Clinical trials have demonstrated similar efficacy among the various topical corticosteroids for the treatment of psoriasis.[74-77,70,102,103,115,118,120,122] Some studies have demonstrated greater efficacy with one agent over another; however, these studies were often comparing corticosteroids with different potencies.[43,78,93,103,107,108,116,119]

For the treatment of seborrheic dermatitis, the Finnish Medical Society Duodecim guidelines recommend the use of salicylic acid to soften scales.[40] Topical corticosteroids, antifungal agents and moisturizing emollients are also frequently prescribed to decrease fungal growth and control symptoms. Clinical trials in patients with multiple dermatoses, including seborrheic dermatitis, have demonstrated similar efficacy among the various topical corticosteroids.[113,118,121]

For the treatment of hemorrhoids, adequate fiber intake and water is the cornerstone of therapy.[41,42] Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge or fecal seepage. Although topical corticosteroids may relieve local perianal inflammation, there is no data to suggest that they actually reduce hemorrhoidal swelling, bleeding or protrusion.[42] Over-the-counter preparations are often used in the empirical treatment of hemorrhoids; however, data supporting their use is lacking.[42] A literature search did not reveal any published studies evaluating the use of the various hydrocortisone rectal preparations for the treatment of hemorrhoids.

There is insufficient evidence to support that one brand skin and mucous membrane anti-inflammatory agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane anti-inflammatory agents within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane anti-inflammatory agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2013. Available from Wolters Kluwer Health, Inc. Accessed December 2013.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2013; December 2013.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed December 2013.
4. Aclovate® [package insert]. Melville, NY: PharmaDerm; May 2012.
5. Diprolene® and Diprolene AF® [package insert]. Kenilworth, NJ: Schering Corporation; October 2005.
6. Luxiq® [package insert]. Research Triangle Park, NC: Stiefel Laboratories, Inc.; 2011.
7. Temovate® and Temovate E® [package insert]. Pittsburg, PA: GlaxoSmithKline; December 2012.
8. Clobex® spray [package insert]. Fort Worth, TX: Galderma Laboratories; September 2012.
9. Clobex® shampoo [package insert]. Fort Worth, TX: Galderma Laboratories; January 2013.
10. Clobex® lotion [package insert]. Fort Worth, TX: Galderma Laboratories; February 2011.
11. Olux-E® [package insert]. Research Triangle Park, NC: Stiefel Laboratories, Inc.; December 2010.
12. Cloderm® [package insert]. Fort Worth, TX: Coria Laboratories. April 2010.
13. Verdeso® [package insert]. Coral Gables, FL: Stiefel Laboratories, Inc.; April 2013.
14. Desonate® [package insert]. Morristown, NJ: Intendis; November 2010.
15. Topicort® [package insert]. Hawthorne, NY: Taro Pharmaceuticals USA, Inc.; October 2009.
16. ApexiCon® [package insert]. Melville, NY: PharmaDerm; September 2009.
17. ApexiCon E® [package insert]. Melville, NY: PharmaDerm; September 2009.
18. Vanos® [package insert]. Scottsdale, AZ: Medicis, the Dermatology Company; April 2012.
19. Cordran® [package insert]. Corona, CA: Watson Pharmaceuticals, Inc.; November 2011.
20. Cutivate® [package insert]. Melville, NY: PharmaDerm; October 2013.
21. Proctocort® [package insert]. Morrisville, NC: Salix Pharmaceuticals, Inc. January 2011.
22. Anusol-HC® [package insert]. Morrisville, NC: Salix Pharmaceuticals, Inc.; November 2009.
23. Cortenema® [package insert]. Baltimore, MD: ANI Pharmaceuticals, Inc.; August 2012.
24. Cortifoam® [package insert]. Marietta, GA: Alaven Pharmaceutical LLC; November 2009.
25. ProctoFoam-HC® [package insert]. Marietta, GA: Alaven Pharmaceutical LLC; September 2008.
26. Carmol-HC® [package insert]. Fairfield, NJ: Doak Dermatologics; July 2012.
27. Pandel® [package insert]. Melville, NY: PharmaDerm; September 2009.
28. Dermatop® [package insert]. Bridgewater, NJ: Dermik Laboratories; October 2011.
29. West DP, West LE, Scuderi L, Micali G. Psoriasis. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 6th ed. New York, NY: McGraw-Hill Companies, Inc.; 2005:1769-1783.
30. Goldstein BG, Goldstein AO. General principles of dermatologic therapy and topical corticosteroid use. In: Corona, R (Ed), UpToDate, Waltham, MA, 2013.
31. Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care. Edinburgh: SIGN; 2011. (SIGN publication no. 125). Available at: http://www.sign.ac.uk/pdf/sign125.pdf. Accessed December 2013.
32. Primary Care Dermatology Society & British Association of Dermatologists. Guidelines for the management of atopic eczema. Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PCDS-BAD%20Eczema%20reviewed%202010.pdf. Accessed December 2013.
33. Darsow U, Wollenberg A, Simon D, et al. Position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol. 2009;24:317-28.
34. National Collaborating Centre for Women's and Children's Health. Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Dec. 39 p. Available at: http://www.nice.org.uk/nicemedia/live/11901/38597/38597.pdf. Accessed December 2013.
35. Schneider L, Tiles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: A practice parameter update 2012. J Allergy Clin Immunol. 2013;131:295-9.
36. Hanifin JM, Cooper KD, Ho VC et al. Guidelines of care for atopic dermatitis. J Am Acad Dermatol. 2004;50:391-404.
37. Bourke J, Coulson I, English J. British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of contact dermatitis: an update. Br J Dermatol. 2009;160:946-54.

38. Menter A, Korman NJ, Elmets CA, et al.; American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60:643-59.
39. British Association of Dermatologists & Primary Care Dermatology Society. Recommendations for the initial management of psoriasis. Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/BAD-PCDS%20Psoriasis%20reviewed%202010.pdf. Accessed December 2013.
40. Finnish Medical Society Duodecim. Seborrhoeic dermatitis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007 Apr 19. Available at: http://www.guideline.gov/content.aspx?id=11044&search=finnish. Accessed December 2013.
41. American Gastroenterological Association medical position statement: Diagnosis and treatment of hemorrhoids. Clinical Practice Committee. Gastroenterology. 2004;126:1461-2.
42. American Gastroenterological Association. Technical review on the diagnosis and treatment of hemorrhoids. Gastroenterology. 2004;126:1463-73.
43. Kuokkanen K, Sillantaka I. Alclometasone dipropionate 0.05% vs hydrocortisone 1.0%: potential to induce cutaneous atrophy in children. Clin Ther. 1987;9:223-31.
44. Lassus A. Alclometasone dipropionate cream 0.05% vs clobetasone butyrate cream 0.05%. A controlled clinical comparison in the treatment of atopic dermatitis in children. Int J Dermatol. 1984 Oct;23(8):565-6.
45. Bickers DR. A comparative study of amcinonide and halcinonide in the treatment of eczematous dermatitis. Cutis. 1984 Aug;34(2):190-4.
46. Guenther L, Solomon AR, Voorhees JJ. A controlled comparison of amcinonide cream 0.1 percent and halcinonide cream 0.1 percent in the treatment of eczematous dermatitis. Cutis. 1981;28:461-2, 4, 7.
47. Breneman D, Fleischer A, Kaplan D, et al. Clobetasol propionate 0.05% lotion in the treatment of moderate to severe atopic dermatitis: a randomized evaluation vs clobetasol propionate emollient cream. J Drugs Dermatol. 2005;4:330-6.
48. Kircik LH, Eastman WJ, Gwazdauskas J. A randomized, double-blind phase 4 study of the efficacy and safety of ethanol-free clobetasol propionate foam, 0.05%, vs vehicle foam in the treatment of chronic hand dermatitis. J Drugs Dermatol. 2013;12(3):328-34.
49. Wolkerstorfer A, Strobos MA, Glazenburg EJ, Mulder PG, Oranje AP. Fluticasone propionate 0.05% cream once daily vs clobetasone butyrate 0.05% cream twice daily in children with atopic dermatitis. J Am Acad Dermatol. 1998 Aug;39(2 Pt 1):226-231.
50. Jorizzo J, Levy M, Lucky A, Shavin J, Goldberg G, Dunlap F, Hinds A, Strelka L, Baker M, Tuley M, et al. Multicenter trial for long-term safety and efficacy comparison of 0.05% desonide and 1% hydrocortisone ointments in the treatment of atopic dermatitis in pediatric patients. J Am Acad Dermatol. 1995;33:74-7.
51. Lucky AW, Grote GD, Williams JL, et al. Effect of desonide ointment, 0.05%, on the hypothalamic-pituitary-adrenal axis of children with atopic dermatitis. Cutis. 1997;59:151-3.
52. Ashton RE, Catterall M, Morley N, Fairris G, Joseph DN. A double-blind comparison of 0.25% and 0.05% desoximetasone, 0.1% betamethasone valerate and 1% hydrocortisone creams in the treatment of eczema. J Int Med Res. 1987 May-Jun;15(3):160-6.
53. Delescluse J, van der Endt JD. A comparison of the safety, tolerability, and efficacy of fluticasone propionate ointment, 0.005%, and betamethasone-17,21-dipropionate ointment, 0.05%, in the treatment of eczema. Cutis. 1996;57(2 Suppl):32-8.
54. Friedlander SF, Herbert AA, Allen DB. Safety of fluticasone propionate cream 0.05% for the treatment of severe and extensive atopic dermatitis in children as young as three months. J Am Acad Dermatol. 2002;46:387-93.
55. Eichenfield LF, Miller BH. Two randomized, double-blind, placebo-controlled studies of fluticasone propionate lotion 0.05% for the treatment of atopic dermatitis in subjects from three months of age. J Am Acad Dermatol. 2006;54:715-7.
56. Sears HW, Bailer JW, Yeadon A. Efficacy and safety of hydrocortisone buteprate 0.1% cream in patients with atopic dermatitis. Clin Ther. 1997;19:710-9.
57. Fowler JF, Fransway AF, Jackson M, et al. Hydrocortisone butyrate 0.1% cream in the treatment of chronic dermatitis. Cutis. 2005;75:125-31.
58. Abramovits W, Oquendo M. Hydrocortisone butyrate 0.1% lipocream in pediatric patients with atopic dermatitis. Skinmed. 2010;8:72-9.
59. Mandelin J, Remitz A, Virtanen H, et al. One-year treatment with 0.1% tacrolimus ointment vs a corticosteroid regimen in adults with moderate to severe atopic dermatitis: A randomized, double-blind, comparative trial. Acta Derm Venereol. 2010;90:170-4.

60. Roth HL, Brown EP. Hydrocortisone valerate. Double-blind comparison with two other topical steroids. Cutis. 1978 May;21(5):695-8.
61. Williamson DM. Comparison of a modified hydrocortisone/urea cream and betamethasone valerate cream in the treatment of dry eczema. J Int Med Res. 1987;15(2):99-105.
62. Pei AY, Chan HH, Ho KM. The effectiveness of wet wrap dressings using 0.1% mometasone furoate and 0.005% fluticasone propionate ointments in the treatment of moderate to severe atopic dermatitis in children. Pediatr Dermatol. 2001 Jul-Aug;18(4):343-8.
63. Lebwohl M. A comparison of once-daily application of mometasone furoate 0.1% cream compared to twice-daily hydrocortisone valerate 0.2% cream in pediatric atopic dermatitis patients who failed to respond to hydrocortisone: mometasone furoate study group. Int J Dermatol. 1999 Aug;38(8):604-6.
64. Moshang T. Prednicarbate emollient cream 0.1% in pediatric patients with atopic dermatitis. Cutis. 2001;68:63-9.
65. Korting HC, Vieluf D, Kerscher M. 0.25% Prednicarbate cream and the corresponding vehicle induce less skin atrophy than 0.1% betamethasone-17-valerate cream and 0.05% clobetasol-17-propionate cream. Eur J Pharmacol. 1992;42:159-61.
66. Berberian BJ, Breneman DL, Drake LA, et al. The addition of topical doxepin to corticosteroid therapy: an improved treatment regimen for atopic dermatitis. Int J Dermatol. 1999;38:145-8.
67. Huntley AC, Isseroff R. Amcinonide vs betamethasone dipropionate ointments in the treatment of psoriasis. Cutis. 1985 May;35(5):489-92.
68. Cornell RC. Comparison of amcinonide ointment 0.1 percent twice daily and fluocinonide ointment 0.05 percent three times daily in the treatment of psoriasis. Cutis. 1983 May;31(5):566-9.
69. Engel MF. Treatment of psoriasis with amcinonide 0.1 percent and fluocinonide 0.05 percent ointments. A comparative double-blind study. Cutis 1982;29:646-50.
70. Millikan LE, Mroczkowski TF. A comparative study of amcinonide and halcinonide 0.1% ointments in the treatment of psoriasis. Int J Dermatol 1986;25:542.
71. Katz HI, Lindholm JS, Weiss JS, Shavin JS, Morman M, Bressinck R, Cornell R, Pariser DM, Pariser RJ, Weng W, et al. Efficacy and safety of twice-daily augmented betamethasone dipropionate lotion vs clobetasol propionate solution in patients with moderate-to-severe scalp psoriasis. Clin Ther. 1995 May-Jun;17(3):390-401.
72. Jacobson C, Cornell RC, Savin RC. A comparison of clobetasol propionate 0.05 percent ointment and an optimized betamethasone dipropionate 0.05 percent ointment in the treatment of psoriasis. Cutis. 1986 Mar;37(3):213-4, 6, 8-20.
73. Shupack JL, Jondreau L, Kenny C, Stiller MJ. Diflorasone diacetate ointment 0.05% vs betamethasone dipropionate ointment 0.05% in moderate-severe plaque-type psoriasis. Dermatology. 1993;186(2):129-32.
74. Barsky S. Multicenter trial analysis. Fluocinonide and betamethasone gel in psoriasis. Arch Dermatol. 1976 Dec;112(12):1729-33.
75. Pacifico A, Daidone R, Peris K. A new formulation of an occlusive dressing containing betamethasone valerate 0.1% in the treatment of mild to moderate psoriasis. J Eur Acad Dermatol Venereol. 2006 Feb;20(2):153-7.
76. Bergstrom KG, Arambula K, Kimball AB. Medication formulation affects quality of life: a randomized single-blind study of clobetasol propionate foam 0.05% compared to a combined program of clobetasol cream 0.05% and solution 0.05% for the treatment of psoriasis. Cutis. 2003;72:407-11.
77. Jegasothy BV. Clobetasol propionate ointment 0.05% vs diflorasone diacetate ointment 0.05% in moderate to severe psoriasis. Int J Dermatol. 1990 Dec;29(10):729-30.
78. Decroix J, Pres H, Tsankov N, Poncet M, Arsonnaud S. Clobetasol propionate lotion in the treatment of moderate to severe plaque-type psoriasis. Cutis. 2004 Sep;74(3):201-6.
79. Lowe N, Feldman SR, Sherer D, Weiss J, Shavin JS, Lin YL, Foley V, Soto P. Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. J Dermatolog Treat. 2005 Aug;16(3):158-64.
80. Sofen H, Hudson CP, Cook-Bolden FE, Preston N, Colon LE, Caveney SW, et al. Clobetasol propionate 0.05% spray for the management of moderate-to-severe plaque psoriasis of the scalp: results from a randomized controlled trial. J Drugs Dermatol. 2011 Aug;10(8):885-92.
81. Menter A, Abramovits W, Colón LE, et al. Comparing clobetasol propionate 0.05% spray to calcipotriene 0.005% betamethasone dipropionate 0.064% ointment for the treatment of moderate to severe plaque psoriasis. J Drugs Dermatol. 2009;8:52-7.
82. Tan J, Thomas R, Wang B, et al. Short-contact clobetasol propionate shampoo 0.05% improves quality of life in patients with scalp psoriasis. Cutis. 2009;83:157-64.

83. Poulin Y, Papp K, Bissonnette R, et al. Clobetasol propionate shampoo 0.05% is efficacious and safe for long-term control of moderate scalp psoriasis. J Dermatolog Treat. 2010;21:185-92.
84. Bovenschen HJ, Van de Kerkhof PC. Treatment of scalp psoriasis with clobetasol-17 propionate 0.05% shampoo: a study on daily clinical practice. J Eur Acad Dermatol Venereol. 2010;24:439-44.
85. Mraz S, Leonardi C, Colón LE, et al. Different treatment outcomes with different formulations of clobetasol propionate 0.05% for the treatment of plaque psoriasis. J Dermatolog Treat. 2008;19:354-9.
86. Willis I, Cornell RC, Penneys NS, Zaias N. Multicenter study comparing 0.05% gel formulations of desoximetasone and fluocinonide in patients with scalp psoriasis. Clin Ther. 1986;8(3):275-82.
87. Zachariae H. Comparison of desoximetasone and hydrocortisone butyrate in psoriasis. Acta Derm Venereol. 1976;56(4):309-10.
88. Anonymous. Comparative study of desoximetasone ointment 0.25% vs fluocinonide ointment 0.05% in patients with psoriasis. Clin Ther. 1985;8(1):118-25.
89. Lee CS, Koo J. The efficacy of three class I topical synthetic corticosteroids, fluocinonide 0.1% cream, clobetasol 0.05% cream and halobetasol 0.05% cream: a Scholtz-Dumas bioassay comparison. J Drugs Dermatol. 2009;8:751-5.
90. Krueger GG, O'Reilly MA, Weidner M, et al. Comparative efficacy of once-daily flurandrenolide tape vs twice-daily diflorasone diacetate ointment in the treatment of psoriasis. J Am Acad Dermatol. 1998;38:186-90.
91. Swinehart JM, Barkoff JR, Dvorkin D, Fisher G, Peets E. Mometasone furoate lotion once daily vs triamcinolone acetonide lotion twice daily in psoriasis. Int J Dermatol. 1989 Dec;28(10):680-1.
92. Medansky RS, Bressinck R, Cole GW, Deeken JH, Ellis CN, Guin JD, Herndon JH, Lasser AE, Leibsohn E, Menter MA, et al. Mometasone furoate ointment and cream 0.1 percent in treatment of psoriasis: comparison with ointment and cream formulations of fluocinolone acetonide 0.025 percent and triamcinolone acetonide 0.1 percent. Cutis. 1988 Nov;42(5):480-5.
93. Choonhakarn C, Busaracome P, Sripanidkulchai B, et al. A prospective, randomized clinical trial comparing topical aloe vera with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. J Eur Acad Dermatol Venereol. 2010;24:168-72.
94. Rocha GL, Quinete SS, Dantas FE, Faria T. A double-blind comparative study between amcinonide and betamethasone valerate in the treatment of eczematoid conditions. Curr Ther Res Clin Exp. 1976 May;19(5):538-49.
95. Rosenberg EW. Management of eczematous dermatitis with amcinonide or betamethasone valerate. A double-blind comparative study. Cutis. 1979 Dec;24(6):642-5.
96. Rhodes EL, Scott LV. Diprosone (betamethasone dipropionate) cream 0.05%. A review and interim report of a comparative multi-center study vs betamethasone valerate 0.1%. Br J Clin Pract. 1983;37:130-2.
97. Levy A. Comparison of 0.1% halcinonide with 0.05% betamethasone dipropionate in the treatment of acute and chronic dermatoses. Curr Med Res Opin. 1977-1978;5(4):328-32.
98. Bluefarb SM. Clinical comparison of desonide cream with betamethasone valerate cream. A double-blind randomized study. Int J Dermatol. 1972 Apr-Jun;11(2):73-6.
99. Vollum DI, Sparkes CG. Influence of the base on the results of clinical trials with topical corticosteroids. Dermatologica. 1979;158(4):293-8.
100. Wishart JM, Lee IS. Mometasone vs betamethasone creams: a trial in dermatoses. N Z Med J. 1993 May 26;106(956):203-5.
101. Jegasothy B, Jacobson C, Levine N, Millikan L, Olsen E, Pinnell S, Cole G, Weinstein G, Porter M. Clobetasol propionate vs fluocinonide creams in psoriasis and eczema. Int J Dermatol. 1985;24:461-5.
102. Bleeker J. Double-blind comparison between two new topical corticosteroids, halcinonide 0.1% and clobetasol propionate cream 0.05%. Curr Med Res Opin. 1975;3:225-8.
103. Barsky S. Clinical comparison of desonide cream with fluocinonide cream in steroid-responsive dermatologic disorders. Cutis. 1976;18:826-30.
104. Kelly JW, Cains GD, Rallings M, Gilmore SJ. Safety and efficacy of mometasone furoate cream in the treatment of steroid responsive dermatoses. Australas J Dermatol. 1991;32:85-91.
105. Barikbin B, Givrad S, Yousefi M, et al. Pimecrolimus 1% cream vs betamethasone 17-valerate 0.1% cream in the treatment of facial discoid lupus erythematosus: a double-blind, randomized pilot study. Clin Exp Dermatol. 2009;34:776-80.
106. Rigopoulos D, Gregoriou S, Belyayeva E, et al. Efficacy and safety of tacrolimus ointment 0.1% vs betamethasone 17-valerate 0.1% in the treatment of chronic paronychia: an unblinded randomized study. Br J Dermatol. 2009;160:858-60.

107. Goldstein AT, Creasey A, Pfau R, et al. A double-blind, randomized controlled trial of clobetasol vs pimecrolimus in patients with vulvar lichen sclerosus. J Am Acad Dermatol. 2011;64:e99-104.
108. Greer IA, Cameron AD. Topical pramoxine and hydrocortisone foam vs placebo in relief of post-partum episiotomy symptoms and wound healing. Scott Med J. 1984;29(2):104-6.
109. Köse O, Arca E, Kurumlu Z. Mometasone cream vs pimecrolimus cream for the treatment of childhood localized vitiligo. J Dermatolog Treat. 2010;21:133-9.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antipruritics and Local Anesthetics
AHFS Class 840800
February 12, 2014

I. Overview

The skin and mucous membrane antipruritics and local anesthetics have a variety of uses, including relief of itching and pain caused by insect bites, minor burns and sunburns, atopic dermatitis, lichen simplex chronicus and hemorrhoids.[1-8] They are also used to prevent and treat pain due to postherpetic neuralgia, venipuncture, intravenous cannulation, minor operative/dermatological procedures, endoscopic/diagnostic procedures, as well as other procedures.

The local anesthetics (lidocaine, prilocaine and tetracaine) inhibit the conduction of nerve impulses from sensory nerves.[1-3] The topical anesthetics are poorly absorbed through intact skin and are readily absorbed through mucous membranes. When skin permeability increases (such as with abrasions and ulcers), there is an increase in absorption. Systemic absorption may also occur if topical anesthetics are applied over a large area of the skin, if a large amount is applied, or if the skin temperature increases. Increased absorption may lead to serious adverse events.

Ethyl chloride is a vapocoolant (skin refrigerant) intended for topical application to control pain.[1-3] Doxepin is a tricyclic antidepressant which blocks histamine receptors; however, the exact mechanism by which it exerts its antipruritic effect is unknown.[4-5] Hydrocortisone is a glucocorticosteroid which has been combined with several local anesthetics to reduce inflammation and alleviate itching.[1-3]

The skin and mucous membrane antipruritics and local anesthetics that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Several of the products are available in a generic formulation. The most noteworthy generic to recently become available is lidocaine transdermal patch. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Antipruritics and Local Anesthetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Doxepin	cream	Prudoxin®, Zonalon®	none
Ethyl chloride	spray	N/A	ethyl chloride
Lidocaine	cream, lotion, ointment, solution, transdermal patch	Lidoderm®*, Pre-attached LTA	lidocaine
Combination Products			
Hydrocortisone and lidocaine	rectal cream, rectal gel, rectal kit	N/A	hydrocortisone and lidocaine
Hydrocortisone, lidocaine, and aloe vera	rectal gel, rectal kit	N/A	hydrocortisone, lidocaine, and aloe vera
Lidocaine and prilocaine	cream, kit	N/A	lidocaine and prilocaine
Lidocaine and tetracaine	transdermal patch	Synera®	none

*Generic is available in at least one dosage form or strength.
N/A=Not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antipruritics and local anesthetics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antipruritics and Local Anesthetics

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network: **Management of Atopic Eczema in Primary Care[9] (2011)**	Emollient therapy • Patients with atopic eczema should receive ongoing treatment with emollients. Topical corticosteroid therapy • Patients should continue with emollient therapy during treatment with topical corticosteroids. • Patients with atopic eczema should be advised to apply topical corticosteroids once daily. • Twice weekly maintenance therapy with a topical corticosteroid should be considered in patients with moderate to severe atopic eczema experiencing frequent relapses. • There is no good quality evidence to assist in the choice of topical corticosteroid potency in the treatment of atopic eczema. • The choice of topical corticosteroid potency should be tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed. For delicate areas of skin, such as the face and flexures, only mild or moderately potent preparations should be used. On the face, especially in children, it is reasonable to start with a mildly potent topical corticosteroid. • Topical corticosteroids should be used with caution in the periocular region. Topical calcineurin inhibitors • Tacrolimus should be considered for short-term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids, or if there is a serious risk of important adverse effects from further topical corticosteroid use (e.g., skin atrophy). • Topical calcineurin inhibitors should not be applied to skin which appears actively infected. • Due to long-term safety issues, topical calcineurin inhibitors should not be used as first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Antihistamines • Short-term bedtime use of sedating antihistamines should be considered in patients with atopic eczema when there is sleep disturbance.
Primary Care Dermatology Society/British Association of Dermatologists: **Guidelines for the Management of Atopic Eczema[10] (2009)**	Emollients • Most patients have dry skin and require the general use of emollients. • Emollients should be applied as liberally and frequently as possible. They are best applied when the skin is moist but they can and should be applied at other times as well. Emollients should be applied every four hours or at least three to four times per day. • Continual treatment with complete emollient therapy (combinations of cream, ointment, bath oil and emollient soap substitute) will help provide maximal effect. • Intensive use of emollients will reduce the need for topical steroids. Topical Steroids • Topical steroids provide symptomatic relief and are safe in the short term. • The potency should be matched to the disease severity and the affected site.

Clinical Guideline	Recommendation(s)
	Weaker corticosteroids should be used on the face and flexures. • The weakest steroid that controls the disease effectively should be chosen. • Steroid use should be limited to a few days to a week for acute eczema and up to four to six weeks to gain initial remission for chronic eczema. • Very potent corticosteroids may rarely be indicated in resistant severe eczema on the hands and feet of adults. • Patients using moderate and potent steroids must be kept under review for both local and systemic side-effects, including the use of growth charts for children. • Topical steroids should not be used to provide an emollient effect. Emollients should not be applied shortly after application of a topical steroid. <u>Immunomodulatory treatments</u> • Immunomodulatory agents (e.g., tacrolimus or pimecrolimus) are an alternative to topical steroids. • They should only be considered if the patient is intolerant to or has failed with conventional corticosteroid therapy. • They do not cause skin atrophy. • The long-term adverse effects of tacrolimus and pimecrolimus are unknown. • Treatment with tacrolimus or pimecrolimus should be initiated only by physicians with experience in dermatology, after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options. <u>Other treatments</u> • Sedating antihistamines may be used to reduce pruritus. Non-sedating antihistamines have very limited benefit. • Third-line treatments include phototherapy and various immunosuppressive agents.
European Academy of Dermatology and Venereology: **Position Paper on Diagnosis and Treatment of Atopic Dermatitis[11] (2009)**	• Topical corticosteroids are a first-line anti-inflammatory therapy. Application two to three times monthly with emollients should suffice in mild disease. • Topical calcineurin inhibitors have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Tacrolimus 0.1% ointment is similar to an intermediately potent topical corticosteroid and an intermediately potent topical corticosteroid is more active than pimecrolimus 1% cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and pre-clinical data do not indicate an increased risk for photo carcinogenicity, though ultraviolet protection is advised. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma over a period of six years or photo carcinogenicity for topical calcineurin inhibitors. But since the continuous oral administration of the cyclosporine is associated with an increased photo carcinogenicity risk in solid organ transplant patients, ultraviolet protection e.g. with sunscreens has been advised.
National Institute for Health and Clinical Excellence: **Management of Atopic Eczema in Children From Birth Up to the Age of 12 Years[12]**	<u>General considerations</u> • A stepped approach should be used for managing atopic eczema in children. Treatment should be tailored based on the severity of the atopic eczema. • Emollients should always be used, even when the atopic eczema is clear. Treatment can be stepped up or down, according to the severity of symptoms, with the addition of the other treatments as necessary as follows: ○ Mild atopic eczema: emollients and mild potency topical

Clinical Guideline	Recommendation(s)
(2007)	corticosteroids. o Moderate atopic eczema: emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages. o Severe atopic eczema: emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy. <u>Emollients</u> • Emollients should be used on the whole body when the atopic eczema is clear and while using all other treatments. <u>Topical corticosteroids</u> • Use mild potency topical corticosteroids on the face and neck, except for short-term (three to five days) use of moderate potency agents for severe flares. • Use moderate or potent topical corticosteroids for short periods only (seven to 14 days) for flares in sites such as axillae and groin. • Do not use very potent preparations in children without specialist dermatological advice. • Topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily. • In children ≥12 months of age, potent topical corticosteroids should be used for the shortest amount of time as possible; no longer than 14 days. They should not be used on the face or neck. Potent topical corticosteroids should not be used in children <12 months of age without specialist dermatological supervision. • Consider treating problem areas with topical corticosteroids for two consecutive days per week to prevent flares, rather than treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled. • A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected. <u>Topical calcineurin inhibitors</u> • Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity. • Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Pimecrolimus is recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged two to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Treatment with tacrolimus or pimecrolimus should only be initiated by physicians (including general practitioners) with a special interest and experience in dermatology. • For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors.

Clinical Guideline	Recommendation(s)
	Antihistamines • Oral antihistamines should not be used routinely in the management of atopic eczema in children. • A one-month trial of a nonsedating antihistamine should be offered to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every three months. • A seven to 14 day trial of an age-appropriate sedating antihistamine should be offered to children aged six months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful. Phototherapy and systemic treatments • Phototherapy or systemic treatments should be considered for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life.
American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma and Immunology/Joint Council on Allergy, Asthma and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter[13] (2012)**	General considerations • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. Skin hydration • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. Topical corticosteroids • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. Topical calcineurin inhibitors • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids.

Clinical Guideline	Recommendation(s)
	• Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. Tar preparations • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. Antihistamines • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. Vitamin D • Patients with atomic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. Dilute bleach baths • The addition of dilute bleach baths twice weekly may reduce the severity of atomic dermatitis, especially in patients with recurrent skin infections. Microbes • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atomic dermatitis, and patients with moderate-to-severe atomic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atomic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atomic dermatitis and might contribute to exacerbations. Systemic Immunomodulating Agents • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. Phototherapy • Ultraviolet therapy can be a useful treatment for recalcitrant atomic

Clinical Guideline	Recommendation(s)
	dermatitis. Allergen immunotherapy • Select patients with atomic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for Atopic Dermatitis[14] (2004)**	Topical agents • Topical corticosteroids are the standard of care for the treatment of atopic dermatitis. • Cutaneous complications such as striae, atrophy, and telangiectasia limit the long-term use of these agents. • Despite the extensive use of topical corticosteroids, there are limited data regarding optimal corticosteroid concentrations, duration and frequency of therapy, and quantity of application; similarly, data supporting the perception that long-term corticosteroid use is not associated with extracutaneous adverse effects are lacking. • Altering the local environment by hydration and/or occlusion as well as varying the vehicle can impact the absorption and effect of the topical corticosteroid administered. • The use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies. • Emollients are a standard of care, steroid-sparing, and useful for prevention and maintenance therapy. • Pimecrolimus and tacrolimus have been shown to reduce the extent, severity, and symptoms of atopic dermatitis in adults and children. • Tar may be associated with therapeutic benefits, but is limited by compliance. • Short-term adjunctive use of topical doxepin may reduce pruritus, but adverse events may limit its usefulness. Antibiotics and antiseptics • Patients with atopic dermatitis are commonly colonized with *Staphylococcus aureus*. Systemic and topical antibiotics temporarily reduce *Staphylococcus aureus* colonization on the skin. • Topical antibiotics can be effective when infection is present; however, development of resistance is a concern. Oral antihistamines • For patients with significant sleep disruption due to itch, allergic dermatographism, or allergic rhinoconjunctivitis, sedating antihistamines may be useful. • Many patients with atopic dermatitis may also have allergic rhinoconjunctivitis, urticaria, and dermatographism and may benefit from the use of antihistamines.
British Association of Dermatologists: **Guidelines for the Management of Contact Dermatitis[15] (2009)**	• Most irritant contact dermatitis involves the hands. Gloves are therefore the mainstay of protection. • Barrier creams by themselves are of questionable value in protecting against contact with irritants. After-work creams confer some degree of protection against developing irritant contact dermatitis. • Topical corticosteroids, soap substitutes and emollients are widely accepted as the treatment of established contact dermatitis. • Second-line treatments such as psoralen plus ultraviolet A, azathioprine and cyclosporine are used for steroid-resistant chronic hand dermatitis.
American Gastroenterological Association: **Medical Position**	• Treatment of hemorrhoids depends on their severity. • The cornerstone of medical therapy is fiber and water. • Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge, or fecal seepage.

Clinical Guideline	Recommendation(s)
Statement: Diagnosis and Treatment of Hemorrhoids[16] (2004)	• Prolonged use of potent corticosteroid preparations may be harmful and should be avoided.
American Gastroenterological Association: **Technical Review on the Diagnosis and Treatment of Hemorrhoids[17] (2004)**	• Add dietary fiber and avoid straining at stool. • Over-the-counter topical agents and suppositories have become equally ubiquitous in the empirical treatment of hemorrhoidal symptoms, but data supporting their use are lacking. • Topical analgesics may bring relief of local pain and itching. • Corticosteroid creams may ameliorate local perianal inflammation, but no data suggest that they actually reduce hemorrhoidal swelling, bleeding, or protrusion. • Long-term use of high-potency corticosteroid creams is deleterious and should be avoided.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain[18] (2010)**	<u>Postherpetic neuralgia</u> • Tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line therapy of postherpetic neuralgia. • Topical lidocaine may be considered as first-line therapy in the elderly, especially if there are concerns regarding the central nervous system side effects of oral medications. A two to four week trial is recommended before starting other therapy. • Strong opioids and capsaicin cream are recommended as second-line therapy. • Capsaicin patches are promising, but the long-term effects of repeated applications particularly on sensation are not clarified.

National Institute for Health and Clinical Excellence: **Pharmacological Management of Neuropathic Pain in Adults in Non-Specialist Settings[19] (2010)**	• When selecting pharmacological treatments, take into account:
	  ○ Adverse effects.
	  ○ Safety considerations and contraindications.
	  ○ Patient preference.
	  ○ Lifestyle factors (such as occupation).
	  ○ Mental health problems (such as depression and/or anxiety).
	  ○ Concomitant medications.
	• Amitriptyline or pregabalin are recommended as first-line therapy.
	• For patients with painful diabetic neuropathy, duloxetine is recommended as first-line therapy. If duloxetine is contraindicated, oral amitriptyline is an alternative agent.
	• If pain reduction is not achieved with first-line treatment, switching to another agent or use of combination therapy should be considered.
	  ○ If first-line treatment was with amitriptyline (or imipramine or nortriptyline), switch to or combine with oral pregabalin.
	  ○ If first-line treatment was with pregabalin, switch to or combine with oral amitriptyline (or imipramine or nortriptyline).
	• For patients with painful diabetic neuropathy:
	  ○ If first-line treatment was with duloxetine, switch to amitriptyline or pregabalin, or combine with pregabalin.
	  ○ If first-line treatment was with amitriptyline, switch to or combine with pregabalin.
	• If satisfactory pain reduction is not achieved with second-line treatment:
	  ○ Consider tramadol as third-line treatment instead of or in combination with the second-line treatment.
	  ○ Consider topical lidocaine for treatment of localized pain for people who are unable to take oral medication because of medical conditions and/or disability.
	  ○ Do not start treatment with opioids other than tramadol without an assessment by a specialist pain service.

International Association	<u>General treatment considerations</u>

Clinical Guideline	Recommendation(s)

for the Study of Pain: **Pharmacologic Management of Neuropathic Pain: Evidence-Based Recommendations[20] (2010)**	• Medication selection should be individualized, considering side effects, comorbidities, and onset of pain relief.
	• Recommended first-line treatments include tricyclic antidepressants (nortriptyline, desipramine) and selective serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine), calcium channel α2-δ ligand (gabapentin and pregabalin), and topical lidocaine.
	• Opioid analgesics and tramadol are recommended as second-line treatments that can be considered for first-line use in select clinical circumstances.
	• Other medications that would be used as third-line treatments include certain antiepileptic (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine, N-methyl-D-aspartate receptor antagonists, and topical capsaicin.
	
	<u>Stepwise pharmacologic management of neuropathic pain</u>
	Step 1:
	• Assess pain and establish the diagnosis of neuropathic pain.
	• Establish and treat the cause of neuropathic pain.
	• Identify comorbidities that might be relieved or exacerbated by neuropathic pain treatment, or that might require dosage adjustment or additional monitoring of therapy.
	Step 2:
	• Initiate therapy of the disease causing neuropathic pain, if applicable.
	• Initiate symptom treatment with one or more of the following:
	  ○ Tricyclic antidepressant (nortriptyline, desipramine) or a selective serotonin and norepinephrine reuptake inhibitor (duloxetine, venlafaxine).
	  ○ Calcium channel α2-δ ligand (gabapentin or pregabalin).
	  ○ Topical lidocaine used alone or in combination with one of the other first-line therapies for patients with localized peripheral neuropathic pain.
	  ○ Opioid analgesics or tramadol alone or in combination with one of the first-line therapies for patients with acute neuropathic pain, neuropathic cancer pain, or exacerbations of severe pain.
	Step 3:
	• Reassess pain and quality of life frequently.
	• If substantial pain relief (average pain reduced to ≤3/10) and tolerable side effects, continue treatment.
	• If partial pain relief (average pain remains ≥4/10) after an adequate trial, add one of the other first-line medications.
	• If no or inadequate pain relief (<30% reduction) at target dosage after an adequate trial, switch to an alternative first-line medication.
	Step 4:
	• If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center.

Infectious Diseases Society of America: **Recommendations for the Management of Herpes Zoster[21] (2007)**	• Antiviral therapy does not prevent postherpetic neuralgia in all patients. • The combination of antiviral therapy with effective relief of acute pain may lessen the risk of postherpetic neuralgia beyond that achieved with antiviral therapy alone. • Effective relief of acute pain is a desirable treatment goal. The choice of therapy depends on pain severity, comorbidities, and prior response to therapy. • Patients with mild to moderate pain may be managed with acetaminophen or non-steroidal antiinflammatory drugs, alone or in combination with a weak

Clinical Guideline	Recommendation(s)
	opioid analgesic or tramadol. • For pain that is moderate to severe in intensity, treatment with a strong opioid analgesic is recommended. • If moderate to severe pain has not responded to treatment with an opioid analgesic, the addition of one of the following three classes of oral medications in combination with the opioid analgesic should be considered: (1) gabapentin or pregabalin; (2) tri-cyclic antidepressants, especially nortriptyline; or (3) corticosteroids (e.g., prednisone), if there are no contraindications. • For patients with moderate or severe pain who are unable to tolerate an opioid analgesic, treatment with these three classes of medications, alone and in combination, can be considered. • Although topical capsaicin may have benefit in some patients with postherpetic neuralgia, there is no basis for its use in patients with herpes zoster, in whom it can be expected to exacerbate pain.
American Academy of Neurology: **Treatment of Postherpetic Neuralgia[22] (2004)**	• Tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of postherpetic neuralgia. • Aspirin in cream is possibly effective in the relief of pain in patients with postherpetic neuralgia but the magnitude of benefit is low, as is seen with capsaicin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antipruritics and local anesthetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-8]

Indications	Single Entity Agents			Combination Products			
	Doxepin	Ethyl Chloride	Lidocaine	Hydrocortisone and Lidocaine	Hydrocortisone and Lidocaine and Aloe Vera	Lidocaine and Prilocaine	Lidocaine and Tetracaine
Anesthetic lubricant for intubation			✔ †				
For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatologic procedures such as excision, electrodesiccation, and shave biopsy of skin lesions							✔
Management of myofascial pain, restricted motion, and muscle tension		✔					
Production of anesthesia of the mucous membranes of the oropharynx			✔ †				
Production of anesthesia of the mucous membranes of the respiratory tract			✔ §				
Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes			✔ ‖				
Relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area				✔	✔		
Relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation			✔ †	✔			
Relief of pain associated with post-herpetic neuralgia			✔ ‡				
Short-term (up to eight days) management of moderate pruritus in adults with atopic dermatitis or	✔						

Indications	Single Entity Agents			Combination Products			
	Doxepin	Ethyl Chloride	Lidocaine	Hydrocortisone and Lidocaine	Hydrocortisone and Lidocaine and Aloe Vera	Lidocaine and Prilocaine	Lidocaine and Tetracaine
lichen simplex chronicus							
Topical application to control pain associated with injections, starting IV's and venipuncture, minor surgical procedures (such as lancing boils or incision and drainage of small abscesses), and the temporary relief of minor sports injuries		✔					
Topical anesthetic for use on normal intact skin for local analgesia or genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.						✔	

‖Cream and lotion formulations.
†Ointment formulation.
§Solution formulation.
‡Transdermal patch formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antipruritics and local anesthetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Doxepin	Not reported	80	Hepatic	Renal	Not reported
Ethyl chloride	Not reported	Not reported	Not reported	Not reported	Not reported
Lidocaine	Patch: 3	33 to 80	Hepatic	Renal	Not reported
Combination Products					
Hydrocortisone and lidocaine	Variable	H: 90 L: 33 to 80	Hepatic	Renal	Not reported
Hydrocortisone, lidocaine, and aloe vera	Variable	H:90 L: 30 to 80 A: Not reported	Hepatic	Renal	Not reported
Lidocaine and prilocaine	Variable	L: 70 P: 40 to 55	L: Hepatic P: Hepatic, Renal	L: Renal (98)	L: 1 to 2.5 P: 10 to 150 minutes
Lidocaine and tetracaine	Variable	75	L: Hepatic T: Plasma	L: Renal (98)	Not reported

A=aloe vera, H=hydrocortisone, L=lidocaine, P=prilocaine, T=tetracaine

V. Drug Interactions

Significant drug interactions with the skin and mucous membrane antipruritics and local anesthetics are listed in Table 5.

Table 5. Significant Drug Interactions with the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Doxepin	1	Monoamine oxidase inhibitors	Altered catecholamine uptake and metabolism may occur when doxepin and monoamine oxidase inhibitors are taken concurrently. This may result in hyperpyrexia, convulsions, and death.
Doxepin	2	Anticoagulants	The hypoprothrombinemic effect of anticoagulants may be increased by doxepin.
Doxepin	2	Carbamazepine	Carbamazepine may alter the parent drug-hydroxylated metabolite ratio resulting in increase of toxicity or loss of efficacy of doxepin.
Doxepin	2	Cimetidine	Concurrent administration of doxepin and cimetidine may cause fluctuations, specifically elevations, in serum doxepin concentrations. Elevated serum doxepin concentrations may result in anticholinergic side effects.
Doxepin	2	Clonidine	The antihypertensive effects of clonidine may be decreased by doxepin.

Generic Name(s)	Significance Level	Interaction	Mechanism
Doxepin	2	Fluconazole	Plasma concentrations and toxic effects of doxepin may be increased by fluconazole.
Doxepin	2	Fluoxetine	Plasma concentrations and toxic effects of doxepin may be increased by fluoxetine.
Doxepin	2	Fluvoxamine	Plasma concentrations and pharmacologic effects of doxepin may be increased by fluvoxamine.
Doxepin	2	Guanethidine	Antihypertensive effects of guanethidine may be decreased by doxepin.
Doxepin	2	Guanfacine	The antihypertensive effect of guanfacine may be decreased by doxepin.
Doxepin	2	Paroxetine	Paroxetine may increase pharmacologic effects and plasma concentrations of doxepin.
Doxepin	2	Sympathomimetics	The alpha-adrenergic effects of sympathomimetics may be increased or decreased by doxepin.
Doxepin	2	Tramadol	Increased risk of seizures is a possibility when tramadol and doxepin are coadministered.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antipruritics and local anesthetics are listed in Table 6. The Food and Drug Administration (FDA) issued a public health advisory about potentially serious hazards of using topical anesthetics for relieving pain from medical tests and conditions. The FDA remains concerned about the potential for topical anesthetics to cause serious and life-threatening adverse effects when applied to a large area of skin or when the area of application is covered. Skin temperature can increase during exercise, by covering the skin with a wrap, or with use of a heating pad. Under these circumstances, the amount of topical anesthetic that reaches the systemic circulation is unpredictable and may be high enough to cause life-threatening adverse effects such as arrhythmias, seizures, respiratory difficulties, coma and death.[23]

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-8]

Adverse Events	Single Entity Agents			Combination Products			
	Doxepin	Ethyl Chloride	Lidocaine	Hydrocortisone and Lidocaine*	Hydrocortisone, Lidocaine and Aloe Vera	Lidocaine and Prilocaine	Lidocaine and Tetracaine
Cardiovascular							
Cardiac arrest	-	-	-	-	-	-	-
Cyanosis	-	-	✔	-	-	-	-
Hypotension	-	-	-	-	-	✔	<1
Shock	-	-	-	-	-	✔	-
Tachycardia	-	-	✔	-	-	-	-
Central Nervous System							
Anxiety	<1	-	✔	-	-	-	-
Confusion	-	-	✔	-	-	-	-
Convulsions	-	-	-	-	-	-	-
Dizziness	2	-	✔	-	-	-	-
Drowsiness	22	-	-	-	-	-	-
Emotional changes	2	-	-	-	-	-	-
Lethargy	-	-	✔	-	-	-	-
Lightheadedness	-	-	✔	-	-	-	-
Nervousness	-	-	-	-	-	-	-
Paresthesia	-	-	✔	-	-	-	-
Somnolence	-	-	✔	-	-	-	-
Stupor	-	-	-	-	-	-	<1
Syncope	-	-	-	-	-	-	<1
Dermatological							
Blanching	-	-	-	✔	✔	-	12
Bruising	-	-	✔ †	-	-	-	-
Burning sensation	23	-	-	✔	✔	✔	-
Contact dermatitis	<1	-	✔	-	-	-	✔

Adverse Events	Single Entity Agents			Combination Products			
	Doxepin	Ethyl Chloride	Lidocaine	Hydrocortisone and Lidocaine*	Hydrocortisone, Lidocaine and Aloe Vera	Lidocaine and Prilocaine	Lidocaine and Tetracaine
Edema	1	-	✔	-	-	✔	12 to 14
Erythema	-	-	-	✔	✔	✔	47 to 71
Irritation	-	1 to 10	✔ †	-	-	-	-
Petechia	-	-	✔ †	-	-	-	-
Pruritus	-	-	✔	-	-	✔	-
Rash	-	-	✔	-	-	✔	✔
Skin pigment alteration	-	1 to 10	✔ †	-	-	✔	<4 to 16
Stinging	23	-	-	✔	✔	✔	-
Tenderness	-	-	-	-	-	-	-
Urticaria	-	-	✔	-	-	✔	-
Gastrointestinal							
Nausea	-	-	-	-	-	-	-
Taste alteration	2	-	-	-	-	-	-
Vomiting	-	-	-	-	-	-	-
Xerostomia	10	-	-	-	-	-	-
Respiratory							
Bronchospasm	-	-	-	-	-	✔	<1
Hypoxia	-	-	✔	-	-	-	-
Respiratory arrest	-	-	-	-	-	-	-
Other							
Allergic reaction/anaphylaxis	-	-	-	-	-	-	<1
Alteration in temperature sensation	-	-	-	-	-	✔	-
Angioedema	-	-	✔	-	-	✔	<1
Hypersensitivity	-	-	-	-	-	✔	-
Infection	-	-	-	-	-	-	<1
Methemoglobinemia	-	-	✔	-	-	-	-
Pain	-	-	✔ †	-	-	-	-
Pupil constriction	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	-	-	-
Tongue numbness	<1	-	-	-	-	-	-
Weakness	-	-	✔	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
*With or without aloe vera.
†Transdermal patch.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antipruritics and local anesthetics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Doxepin	Short-term (up to eight days) management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus: Cream: apply a thin film to affected area four times per day with at least three to four hours between applications; do not use for more than eight days	Safety and efficacy in children have not been established.	Cream: 5%
Ethyl chloride	Management of myofascial pain, restricted motion, and muscle tension; topical application to control pain associated with injections, starting intravenous injections and venipuncture, minor surgical procedures (such as lancing boils or incision and drainage of small abscesses), and the temporary relief of minor sports injuries: Spray: spray the target area continuously for three to seven seconds until the skin just turns white; do not frost the skin	Safety and efficacy in children have not been established.	Spray: 100%
Lidocaine	Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes: Cream, lotion: apply to the affected area two to three times per day Anesthetic lubricant for intubation, production of anesthesia of the mucous membranes of the oropharynx, relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation: Ointment: apply ≤5 g (300 mg lidocaine) to the affected area Relief of pain associated with post-herpetic neuralgia: Patch: apply up to three patches to the most painful area, for up to 12 hours within a 24-hour period	Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes: Cream, lotion: apply to the affected area two to three times per day; dosages in children should be reduced, commensurate with age and body weight Anesthetic lubricant for intubation, production of anesthesia of the mucous membranes of the oropharynx, relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation: Ointment: apply ≤5 g (300	Cream: 3% Lotion: 3% Ointment: 5% Patch: 5% (700 mg) Solution: 4%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Production of anesthesia of the mucous membranes of the respiratory tract : Solution: spray 1 to 5 mL (40 to 200 mg lidocaine) to the affected area; maximum, 300 mg or 4.5 mg/kg	mg lidocaine) to the affected area; maximum, 4.5 mg/kg Production of anesthesia of the mucous membranes of the respiratory tract: Solution: spray 1 to 5 mL (40 to 200 mg lidocaine) to the affected area; maximum, 300 mg or 4.5 mg/kg; dosages in children should be reduced, commensurate with age and body weight	
Combination Products			
Hydrocortisone and lidocaine	Relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area; relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation: Topical: Apply to affected area two to three times per day	Safety and efficacy in children have not been established.	Rectal cream: 0.5%-3% 1%-3% Rectal cream kit: 0.5%-3% 1%-3% Rectal gel: 2.5%-3%
Hydrocortisone, lidocaine, and aloe vera	Relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area: Topical: Apply to affected area two to three times per day	Safety and efficacy in children have not been established.	Rectal gel: 0.55%-2.8% Rectal kit: 2%-2% 2.5%-3%
Lidocaine and prilocaine	Topical anesthetic for use on normal intact skin for local analgesia or genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia: Cream: for minor dermal procedures*, apply 2.5 g (1/2 of the 5 g tube) over 20 to 25 cm^2 of skin surface for at least one hour and cover with an occlusive dressing; for major dermal procedures†, apply 2 g per 10 cm^2 of skin and leave on for at least two hours and cover with an occlusive dressing; for adult male genital skin, apply a thick layer (1 g /10 cm^2) to skin for 15 minutes and cover with an occlusive dressing, perform procedure immediately following removal of the cream; for adult female genital mucous membranes, apply a thick layer (5 to 10 g) to mucous membranes for 5 to 10 minutes and perform procedure immediately following removal of the cream	Topical anesthetic for use on normal intact skin for local analgesia or genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia: Cream: for intact skin, 0 to three months of age (<5 kg), 1 g/dose applied to a maximum area of 10 cm^2 for up to one hour; for three to 12 months of age (>5 kg), 2 g/dose applied to a maximum area of 20 cm^2 for up to four hours; for one to six years of age (10 kg), 10 g/dose applied to a maximum area of 100 cm^2 for up to four hours; for seven to 12 years of age (>20 kg), 20 g/dose applied to a maximum area of 200 cm^2 for up to four hours; do not use in neonates <37 weeks gestational age or in	Cream: 2.5%-2.5% Kit: 2.5%-2.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	(occlusion is not necessary)	infants less than 12 months who are being treated with other agents associated with methemoglobinemia	
Lidocaine and tetracaine	For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatologic procedures such as excision, electrodesiccation, and shave biopsy of skin lesions: Transdermal patch: apply to intact skin for 20 to 30 minutes	For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatologic procedures such as excision, electrodesiccation, and shave biopsy of skin lesions >3 years of age: Transdermal patch: apply to intact skin for 20 to 30 minutes	Transdermal patch: 70 mg-70 mg

*Venipuncture or intravenous cannulation.
†Split thickness skin graft harvesting.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antipruritics and local anesthetics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Skin and Mucous Membrane Antipruritics and Local Anesthetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Drake et al.[24] (1994) Doxepin 5% cream applied QID vs placebo	DB, MC, PC, RCT Patients with atopic dermatitis who had daily moderate to severe pruritus for at least 1 week	N=270 7 days	Primary: Relief of pruritus, pruritus severity, and adverse events Secondary: Not reported	Primary: Relief of pruritus was achieved in 85% of patients receiving doxepin and 57% of patients receiving placebo. Pruritus severity scores demonstrated significantly greater improvement with doxepin at each study visit (P<0.01). Using visual analog scales, pruritus severity and pruritus relief showed similar improvement in patients receiving doxepin. The physician's global evaluation for relief of pruritus showed significant improvement in the doxepin treatment group (P<0.01). The physician's global evaluations of eczema significantly favored topical doxepin (P<0.01). The most commonly reported adverse events were localized stinging or burning and drowsiness, which decreased in frequency and severity over time. Secondary: Not reported
Drake et al.[25] (1995) Doxepin 5% cream applied QID vs placebo	DB, PC, RCT Patients 12 to 65 years of age diagnosed with lichen simplex chronicus, nummular eczema, or contact dermatitis experiencing	N=309 7 days	Primary: Pruritus severity rating scale, physician's global evaluation for pruritus relief, patient's assessment of pruritus relief on a visual analog scale	Primary: Significantly more patients in the doxepin group experienced pruritus relief in the first 24 hours compared to placebo patients in all forms of eczema included in the study (P<0.04). After seven days, the response to doxepin ranged from 76 to 89%, and there were significant differences favoring doxepin cream in patients with contact dermatitis and lichen simplex chronicus (P<0.05). In the first 24 hours of treatment, patients in the doxepin group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	moderate to severe pruritus on a daily basis for ≥1 week		Secondary: Not reported	experienced at least a 50% reduction in pruritus for all forms of eczema studied. Significant differences were only observed in the lichen simplex chronicus group compared to placebo (visual analog scale; P=0.001). At day seven, patients in the doxepin group experienced at least a 70% reduction in pruritus for all forms of eczema studied. Significant differences were only observed in the lichen simplex chronicus group compared to placebo (visual analog scale; P=0.001). In the first 24 hours, a greater percentage of patients in the doxepin group experienced pruritus relief compared to the placebo group. Significant differences were only observed in lichen simplex chronicus and nummular eczema (physician's global evaluation; P<0.02). At day seven, a greater percentage of patients in the doxepin group experienced pruritus relief compared to the placebo group. Significant differences were only observed in lichen simplex chronicus and nummular eczema (physician's global evaluation; P<0.02). Secondary: Not reported
Breneman et al.[26] (1997) <u>SB Phase</u> Doxepin 5% cream applied QID for 7 days <u>DB Phase</u> Doxepin 5% cream applied QID for 7 days vs	DB, RCT, SB Patients with atopic dermatitis or lichen simplex chronicus with moderate to severe pruritus	N=120 14 days	Primary: Pruritus severity, pruritus relief, eczema severity Secondary: Not reported	Primary: Fifteen minutes following application of doxepin cream, there was a significant improvement in antipruritic activity as measured by visual analog scales of pruritus severity (P<0.001) and pruritus relief (P<0.001). A total of 75% of patients reported reductions in pruritus severity in just 15 minutes and 84% reported reductions by 120 minutes following doxepin cream application. Decreasing pruritus severity and increasing pruritus relief continued significantly through day seven. A significant improvement in pruritus severity rating and physician's global evaluation of pruritus relief was present on day seven and continued to day 14 compared to baseline in both treatment groups (P<0.001). Eczema severity was significantly improved on both days seven and 14 in all treatment groups compared to baseline (P<0.001), with significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo for 7 days				continued improvement in the doxepin group on day 14 compared to day seven (P=0.011). Adverse events were mild to moderate in severity and decreased throughout the study. Secondary: Not reported
Berberian et al.[27] (1999) Doxepin 5% and hydrocortisone 2.5% cream applied QID vs doxepin 5% and triamcinolone 0.1% cream applied QID vs hydrocortisone 2.5% cream applied QID vs triamcinolone 0.1% cream applied QID	DB, MC, PG, RCT Patients with pruritic atopic dermatitis who experienced moderate to severe pruritus associated with their eczematous lesions daily for at least 1 week, family history of atopy and/or a personal history of atopic dermatitis, ≤25% body surface area affected by atopic dermatitis, and good general health	N=349 8 days	Primary: Pruritus severity and pruritus relief Secondary: Not reported	Primary: Patients who received doxepin in addition to a steroid achieved significant reductions in pruritus than those treated with a steroid cream alone. The physician's global evaluations for pruritus relief demonstrated that the addition of doxepin to either hydrocortisone or triamcinolone treatment significantly improved itch relief over that of the topical corticosteroid alone. On day two, the doxepin 5% and hydrocortisone 2.5% combination was significantly better for pruritus relief than the hydrocortisone treatment alone (P=0.01) as was the doxepin 5% and triamcinolone 0.1% combination than the triamcinolone alone (P=0.027). By day eight, statistical significance was reached in favor of the doxepin 5% and hydrocortisone 2.5% combination over the steroid alone, but not for the doxepin 5% and triamcinolone 0.1% over triamcinolone alone. A faster improvement in the eczematous condition was noted by the physicians over the first couple of days of the study in those in the combination doxepin and steroid treatment groups vs steroid treatment alone. Secondary: Not reported
Ramsook et al.[28] (2001)	DB, PC, RCT Patients 3 to 18	N=222 1 day	Primary: Results of the Faces Pain Scale	Primary: Pain scores reported by the patients did not differ between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ethyl chloride spray vs isopropyl alcohol spray	years of age who presented to the emergency department requiring intravenous cannulation for fluids or medication administration, or venipuncture for diagnostic tests		(used for patients three to 10 years of age) and the Numeric Pain Score (used for patients 10 to 18 years of age) Secondary: Not reported	There was no significant difference in pain scores between groups when stratified for age (<6 years, six to 12 years, and >12 years). Significantly more procedures in the ethyl chloride group were rated as difficult compared to the isopropyl alcohol group (P<0.05). Secondary: Not reported
Davies et al.[29] (2006) Ethyl chloride spray applied to the site of the venipuncture no more than 45 seconds prior to procedure vs tetracaine cream applied to site of the venipuncture, covered with an occlusive dressing, and left in place for 30 to 45 minutes	XO Patients admitted for measurement of glomerular filtration rate which involved a series of 3 venipunctures in a 4 hour period. The first 2 venipunctures constituted the XO and children could choose their own treatment for the third venipuncture	N=77 1 day	Primary: Children's self-reported pain measured by the Wong-Baker faces scale Secondary: Not reported	Primary: The pain scores were higher on the second venipuncture compared to the first for both groups. Ethyl chloride was associated with lower pain scores compared to tetracaine cream on the first and second venipuncture. Both ethyl chloride and tetracaine cream were associated with lower pain scores for the third venipuncture compared to the first two, with ethyl chloride being lower. Secondary: Not reported
Robinson et al.[30] (2007) Ethyl chloride sprayed for 5 to 10	RCT Patient ≥15 years of age requiring intravenous	N=300 1 day	Primary: Pain from intravenous cannulation using a visual analog scale	Primary: Lidocaine, ethyl chloride and nitrous oxide reduced the pain of intravenous cannulation. Lidocaine was significantly more effective than all other groups (P≤0.001). Patients cannulated without analgesia reported the most pain.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
seconds 15 to 20 cm from intended site of cannulation vs nitrous oxide inhaled for 1 minute prior to and during cannulation vs lidocaine 1% injected with a 26-gauge needle vs immediate cannulation with no anesthesia	cannulation		Secondary: Not reported	Lidocaine provided the greatest reduction in the pain of cannulation (median visual analog scale 1 mm vs control visual analog scale 20 mm, P≤0.0001). The ethyl chloride and nitrous oxide groups were not significantly different (P=0.3). Ethyl chloride reduced the pain of cannulation compared to control (median visual analog scale 11 mm, vs control visual analog scale 20 mm; P≤0.003), but this did not reach clinical significance. Nitrous oxide reduced the pain of cannulation compared to control (median visual analog scale 13 mm vs control visual analog scale 20 mm, P=0.047), but this did not reach clinical significance. Neither pain from presenting symptoms (P=0.3), nor size of cannula (P=0.8) affected pain scores. Cannulation success was not affected by either the choice of analgesia or cannulation site. Secondary: Not reported
Celik et al.[31] (2011) Ethyl chloride sprayed for 2 seconds 10 cm from intended site vs lidocaine-prilocaine cream 2 mL applied to	PC, RCT, XO Patients ≥18 years of age undergoing conventional hemodialysis three times a week	N=41 3 dialysis sessions	Primary: Pain caused by venipuncture of arteriovenous fissula Secondary: Not reported	Primary: Lidocaine-prilocaine application resulted in significantly lower total pain scores compared to control and all other interventions (P<0.05). Patients reported less moderate and severe pain with lidocaine-prilocaine, and ethyl chloride spray compared placebo. Moderate and severe pain scores were similar between lidocaine-prilocaine and ethyl chloride spray (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
puncture site under occlusive dressing for 45 to 60 minutes vs placebo cream				
Kokinsky et al.[32] (1999) Lidocaine 10% aerosol vs placebo vs control group	DB, PC, RCT Patients 9 months to 11 years of age undergoing unilateral inguinal hernia repair	N=44 12 hours	Primary: Pain scores assessed by nurse or patient (depending on age) upon arrival to the recovery room, one, four, and 12 hours postoperatively, and reaction scores after gentle palpation of the wound by the nurse Secondary: Plasma concentrations of lidocaine	Primary: At one hour after arrival in the recovery room, pain scores were significantly lower in the lidocaine group compared to the placebo group for nurse and patient assessments (P<0.05). There were no significant differences between the lidocaine group and the placebo group or the lidocaine and the control groups one, four, or 12 hours postoperatively. At one hour postoperatively, reaction scores to palpation were lower in the lidocaine group compared to the placebo and control groups (P<0.05). The number of patients not reacting to wound palpation was significantly higher in the lidocaine group compared to the placebo and control groups (P<0.01 and P<0.05 respectively). There were no significant differences between groups in this endpoint at 0, four, or 12 hours. Secondary: The mean peak lidocaine plasma concentration was 0.40 µg/mL.
Corkill et al.[33] (2001) Lidocaine 2% gel applied up to every 4 hours vs	DB, PC, RCT Female patients who had a normal delivery of a healthy baby and sustained a first or second degree perineal tear	N=149 2 days	Primary: Perineal pain at 24 hours post-delivery Secondary: Perineal pain 48 hours post-delivery, the consumption of	Primary: There were no significant differences between the lidocaine and placebo groups at 24 hours according to the 101-point Numerical Rating Scale (P=0.5). Secondary: At 48 hours, the lidocaine group reported significantly less pain compared to the placebo group according to the 101-point Numerical Rating Scale (P=0.023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			additional analgesia, maternal satisfaction	There was no significant difference observed in the amount of additional analgesia used between the two groups (P<0.227). Women in the placebo group applied significantly more study gel compared to women in the lidocaine group (P=0.015). There were no significant differences between groups in the satisfaction with analgesia received.
Minassian et al.[34] (2002) Lidocaine 5% ointment applied up to every 4 hours vs placebo	DB, PC, RCT Female patients 21 to 23 years of age with an episiotomy or a first, second, third, or fourth degree perineal laceration during their peripartum period	N=200 2 days	Primary: Pain relief Secondary: Results of a pain questionnaire administered on the first and second day postpartum	Primary: There was no significant difference in the amount of lidocaine or placebo used on postpartum day one or two (P=0.13 and P=0.08, respectively). There was no significant difference in the amount of pain pills taken in the lidocaine group and the placebo group (P=0.53). There was no significant difference in the satisfaction from the ointment in the lidocaine group compared to the placebo group (P=0.99). Patients who received an episiotomy used more pain medications compared to those with lacerations (P=0.003). Patients with minor lacerations used fewer pain pills and less ointment on the first postpartum day (P<0.001 and P=0.02, respectively). Secondary: There was no significant difference in subjective pain parameters from the pain questionnaire between the lidocaine group and the placebo group (P=0.36).
Habib et al.[35] (2009) Lidocaine 5% patch applied on each side of the wound	DB, RCT Patients undergoing radical retropubic prostatectomy under general anesthesia	N=71 24 hours	Primary: Verbal rating score for pain at rest and after coughing Secondary: Postoperative morphine	Primary: Observed mean pain scores were reduced by 17 to 32% at rest up to 12 hours and by 19 to 33% on coughing up to 24 hours after surgery in the lidocaine group. The pain scores were significantly lower on coughing at all times (P<0.0001) and at rest up to six hours (P=0.0003) compared to placebo, after accounting for morphine consumption. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			consumption, sedation scores, pruritus, and nausea scores	There was no significant difference in the amount of cumulative morphine consumed at any of the time points. There was no difference in the incidence or severity of postoperative nausea/vomiting, pruritus, or duration of post-anesthesia care unit and hospital stays among the treatment groups. Patients in the lidocaine group rated the quality of postoperative pain control significantly better than patients in the placebo group (P=0.037). Patients who received the lidocaine patch reported that pain interfered with their walking, deep breathing, and mood significantly less than patients in the placebo group (P=0.05).
Ingalls et al.[36] (2010) Lidocaine 5% patch applied for 12 hours daily directly over the rib fractures vs placebo	DB, PC, RCT Adult patients with rib fractures admitted to the trauma service	N=48 Up to 72 hours	Primary: Total narcotic use Secondary: Non-narcotic pain medication, average pain score, pulmonary complications, and length of stay	Primary: There was no difference between the lidocaine and placebo groups in the amount of total intravenous narcotics used (0.23 vs 0.26 units; P=0.56) or total oral narcotics used (4 vs 7 units; P=0.11). Secondary: There was no difference in pain scores (5.6 vs 6.0; P=0.39), pulmonary complications (72.7 vs 72%; P=0.95), or length of stay (7.8 vs 6.2 days; P=0.28) with lidocaine compared to placebo.
Cheville et al.[37] (2009) Lidocaine 5% patch applied for 18 hours daily for 4 weeks (up to 3 patches could be applied at once) vs placebo	DB, MC, RCT, XO Patients ≥18 years of age with persistent pain (with neuropathic features) associated with a surgical procedure as part of cancer treatment	N=28 8 weeks	Primary: Pain intensity rating Secondary: Brief pain inventory interference scores	Primary: Average weekly pain intensity ratings were not significantly reduced with the lidocaine patch compared to placebo (4.1 vs 3.8; P=0.36). There was no significant difference during period one between the lidocaine and placebo groups in the proportion of patients experiencing 10% relief (64 vs 71%, respectively; P=0.69) or in week four minus baseline change (mean −0.9 vs −0.6, respectively; P=0.91). Secondary: All period one brief pain inventory interference scores improved to a greater degree in the lidocaine group compared to placebo. Significant improvements in both physical (general activity; P=0.02, and work; P=0.04) and psycho-emotional (mood; P=0.06; and relations with others;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.02) domains were demonstrated. Few other endpoints were significantly different when patients used the lidocaine patch compared to placebo.
Galer et al.[38] (1999) Lidocaine 5% patch applied for 12 hours daily (up to 4 patches could be applied at once) vs placebo	PC, RCT, XO Patients 62 to 96 years of age with postherpetic neuralgia already enrolled in the OL protocol and using lidocaine patches on a regular basis for at least 1 month	N=33 28 days	Primary: Time to exit the study Secondary: Not reported	Primary: The median time to exit was >14 days in the lidocaine group compared to 3.8 days in the placebo group (P<0.001). Significantly more patients (78.1%) preferred treatment with lidocaine compared to 9.4% who preferred treatment with placebo (P<0.001). The number of patients reporting moderate or greater pain relief was 29 in the lidocaine group compared to 13 in the placebo group. A total of seven patients used rescue pain relief medications throughout the study (three in the lidocaine group and four in the placebo group). Secondary: Not reported
Meier et al.[39] (2003) Lidocaine 5% patch applied for 12 hours daily (up to 4 patches could be applied at once) vs placebo	DB, PC, PRO, RCT, XO Patients ≥21 years of age suffering from chronic painful peripheral focal neuropathic syndromes that were superficial and localized to a limited skin zone	N=58 28 days	Primary: Ongoing pain intensity, allodynia, quality of neuropathic symptoms, and quality of sleep Secondary: Not reported	Primary: Ongoing pain intensity decreased in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at two hours (P=0.003), four hours (P=0.004), day four (P=0.03), day five (P=0.02), and day seven (P=0.002). Lidocaine was more effective during the first eight hours and over the course of the treatment week compared to placebo (P=0.017 and P=0.018, respectively). At all time points, allodynia decreased compared to pretreatment values in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at two hours (P=0.005), four hours (P=0.009), six hours (P=0.017) after the first patch application and at day five (P=0.035). Treatment with lidocaine led to better allodynia relief compared to placebo during the first 8 hours (P=0.023) and for the remainder of the treatment period (P=0.03). There was a significant reduction in neuropathic symptoms in the lidocaine group compared to baseline (P=0.032), but no significant differences were observed between the lidocaine and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant differences were observed between the lidocaine and placebo groups in quality of sleep. Secondary: Not reported
Galer et al.[40] (2002) Lidocaine 5% patch applied for 12 hours daily vs placebo	DB, PC, PG, RCT Adults diagnosed with postherpetic neuralgia involving the torso area for at least 1 month and in whom allodynia was observed on physical examination	N=150 3 weeks	Primary: Change from baseline to week three in neuropathic pain scale Secondary: Not reported	Primary: The reduction in pain scores for all four composite endpoints was consistently greater in the lidocaine patch group compared to the placebo group (P=0.043, P=0.042, P=0.022, and P=0.013 respectively). Secondary: Not reported
Lin et al.[41] (2008) Lidocaine 5% patch applied at 12-hour intervals vs placebo	DB, PC, PG, RCT Patients suffering from moderate to severe pain caused by acute herpes zoster infection	N=46 48 hours	Primary: Analgesic efficacy and adverse events Secondary: Not reported	Primary: Both groups of patients experienced significant pain relief during rest and movement. The difference in the mean reduction of pain intensity during rest was 14 mm for patients wearing the lidocaine patch compared to the vehicle patch (P=0.005). The difference in the mean reduction of pain intensity during movement was 11 mm for patients wearing the lidocaine patch compared to the vehicle patch (P=0.007). The lidocaine patch produced a greater percentage change in a patient's global impression than the vehicle patch. The incidence and severity of adverse events were low with both treatments. Secondary: Not reported
Katz et al.[42] (2002) Lidocaine 5%	OL Patients 20 to 99 years of age	N=332 28 days	Primary: Changes in pain intensity, pain interference in	Primary: Mean scores for all measures of pain intensity were significantly lower than baseline scores at all evaluations (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patch applied for 12 hours daily (up to 3 patches could be applied at once)	diagnosed with postherpetic neuralgia		quality of life, pain relief, and patient and physician global assessments Secondary: Not reported	At the end of the study 40% of patients experienced a ≥50% reduction in average daily pain intensity. Mean pain interference with quality of life scores were significantly lower compared to baseline at all evaluations (P=0.0001). The majority of patients responded to lidocaine treatment within the first week. There was a significant improvement from baseline in pain relief at all evaluations (P=0.0001). Overall, 58% of patients reported moderate to complete pain relief at day 28. The results of the physician global assessments and patient global assessments were similar. Approximately 60% of patients were judged to have complete improvement or moderate ("a lot of") improvement at day 28, slight improvement was reported in approximately 15% of patients, and no change was reported in 20% of patients. Secondary: Not reported
Devers et al.[43] (2000) Lidocaine 5% patch applied for 12 hours daily (up to 3 patches could be applied at once)	OL Patients 23 to 85 years of age diagnosed with peripheral neuropathic pain	N=16 12 weeks	Primary: Degree of pain relief Secondary: Not reported	Primary: Thirteen patients (81%) reported either "moderate relief", "a lot of relief", or "complete relief" from the lidocaine patch. Of these 13 patients, all noted a reduction in brush-evoked mechanical allodynia. All patients who responded to medication continued to experience relief throughout the duration of the study. Secondary: Not reported
Fleming et al.[44] (2009) Lidocaine 5% patch	RETRO Inpatients and outpatients prescribed lidocaine 5% patch	N=97 Up to 1 year	Primary: Analgesic efficacy Secondary: Not reported	Primary: For the treatment of neuropathic pain syndromes, lidocaine had a 'potent analgesic effect' in 25% of patients and a 'partial analgesic effect' in 24% of patients. There was no analgesic effect in 47% of patients. The lidocaine patch made pain worse in 3.2% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A 'potent analgesic effect was seen in patients treated for postherpetic neuralgia (38%), persistent postsurgical pain (35%), pain due to other or multiple treatments for cancer (27%), mixed neuropathic pain syndromes (13%) and neuropathic pain directly attributed to cancer (12%). Secondary: Not reported
Affaitati et al.[45] (2009) Lidocaine 5% patch applied at 12-hour intervals for 4 days vs bupivacaine 0.5%, 2 injections given 2 days apart vs placebo patch applied at 12-hour intervals for 4 days	DB, RCT (patch), SB (injection) Patients 18 to 80 years of age with a history of recurrent or chronic regional musculoskeletal pain caused by trigger points and a diagnosis of myofascial pain syndrome	N=60 9 days	Primary: Number of pain attacks, pain intensity at rest, pain intensity on movement, pressure and electrical pain thresholds of the skin, subcutis, and muscle in the trigger point Secondary: Not reported	Primary: In the placebo group, there were no significant changes in any of the subjective symptoms at days five or nine compared to baseline. In the lidocaine and infiltration groups, all subjective symptoms decreased significantly (P<0.001) at days five and nine compared to baseline. There were no significant differences in pain symptoms among the active treatment groups at any time point. The difference between the placebo group and the active treatment groups was significant at days five and nine (both, P<0.001). The visual analog scale score for the discomfort caused by therapy (day five) was significantly higher for patients who underwent infiltration than for those who received a lidocaine or placebo patch (both, P<0.001). Mean scores were 0.91 mm for the placebo patch, 0.87 mm for the lidocaine patch, and 51.45 mm for infiltration. At day nine, 90% of the patients in the placebo group asked for bupivacaine infiltration because of the persistence of pain symptoms. None of the patients in the other two groups requested infiltration (both, P<0.001). Pain thresholds did not vary with the placebo patch from baseline to end, but increased significantly with the lidocaine patch and injection (all, P<0.001). The comparison of thresholds between the placebo group and each of the active-treatment groups showed significant differences at day five and day nine (both, P<0.001). The comparison of the two groups that received active treatments showed no significant differences except for electrical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				pain thresholds in muscles (greater increase in the infiltration group), at the level of the trigger point (day five and day nine; both, P<0.001) and target area (day five, P<0.03; day nine, P<0.007). No systemic or local adverse events were reported by the patients in any treatment group. Secondary: Not reported
Luhmann et al.[46] (2004) Lidocaine 5% cream applied 30 minutes before intravenous insertion vs lidocaine injected subcutaneously 5 minutes before intravenous insertion	RCT, SB Patients 4 to 17 years of age requiring peripheral intravenous insertion	N=69 1 day	Primary: Pain ratings, anxiety, technical difficulty, and treatment satisfaction Secondary: Not reported	Primary: No significant differences were observed in mean pain ratings between treatment groups reported by children (P=0.19), parents (P=0.17), and blinded observer (P=0.2). No significant differences were observed in anxiety between treatment groups reported by children (P=0.18), parents (P=0.50), and blinded observer (P=0.96). No significant differences were observed between the treatment groups in technical difficulty (P=1.0) or overall satisfaction (P=0.19) according to nurses self-report. Secondary: Not reported
Gursoy et al.[47] (2007) Lidocaine-prilocaine cream applied 60 minutes before biopsy vs placebo	DB, PC Patients with nodular thyroid disease undergoing fine-needle aspiration biopsy	N=99 1 day	Primary: Patient-rated pain using a 100-mm visual analog scale, an 11-point numeric rating scale, and a four-category verbal rating scale; adverse events Secondary:	Primary: For patients receiving lidocaine-prilocaine, the mean visual analog scale score was 25.0 vs 40.0 mm in the placebo group (P=0.006). For patients receiving lidocaine-prilocaine, the mean numeric rating scale score was 2.9 vs 4.0 points in the placebo group (P=0.02). The absolute numbers according to verbal rating scale score in each group was also significantly different (P=0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	
Shaikh et al.[48] (2009) Lidocaine-prilocaine cream applied for 30 to 60 minutes before surgery vs placebo	DB, PC, PG, RCT Patients scheduled for elective minor surgical procedures under local anesthesia	N=72 1 day	Primary: Patient's perception of pain on needle insertion for local anesthetic infiltration and pain during the minor surgical procedure Secondary: Not reported	Primary: The mean needle-stick pain score in the lidocaine-prilocaine group was significantly lower than in the placebo group (2.7 vs 5.7; P<0.001). There was significantly less procedure pain in the lidocaine-prilocaine group than in the placebo group (0.83 vs 1.86; P=0.009). There were no complications associated with the use of lidocaine-prilocaine. There was less pain when lidocaine-prilocaine cream was applied for 60 minutes than for 30 minutes. The site of application of lidocaine-prilocaine cream and procedure resulted in a difference in pain. Secondary: Not reported
McCluskey et al.[49] (2003) Lidocaine-prilocaine cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol vs placebo cream applied 60 minutes prior to cannulation and induction of anesthesia with	DB, PC, RCT Patients 18 to 70 years of age presenting for gynecological day surgery	N=90 1 day	Primary: Pain severity scores for insertion of cannula, pain severity scores during injection of propofol Secondary: Not reported	Primary: There was a significant reduction in the incidence of pain associated with insertion of the cannula in the lidocaine-prilocaine group compared to the other two groups (P=0.015). There was no significant difference in the frequency of pain associated with injection of propofol between the lidocaine-prilocaine group and the placebo group. Significantly greater pain frequency was seen in the lidocaine-prilocaine group compared to the lidocaine and propofol mixed injection group (P=0.002). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propofol mixed with saline vs placebo cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol mixed with lidocaine				
Koh et al.[50] (2004) Lidocaine-prilocaine cream applied to the skin for 60 minutes vs lidocaine 4% cream applied to the skin for 30 minutes	DB, RCT Patients 8 to 17 years of age having an intravenous inserted prior to surgery	N=60 1 day	Primary: Pain scores according to the visual analog scale and difficulty of placing the intravenous according to the investigator Secondary: Not reported	Primary: There was no significant difference in pain ratings according to the visual analog scale scores between the groups (P=0.87). There was no significant difference in the investigator ratings of difficulty of the procedure between the groups (P=0.73). There was significantly more blanching in the lidocaine-prilocaine group compared to the lidocaine group (P=0.04). Secondary: Not reported
Kuvaki et al.[51] (2003) Lidocaine-prilocaine cream applied to the outer half of the inferior orbital margin at least 45 minutes prior to retrobulbar	DB, RCT Patients presenting for cataract surgery under local anesthesia	N=103 1 day	Primary: Subjective pain intensity on a 10-point scale Secondary: Not reported	Primary: There were no significant differences in pain scores reported between the lidocaine-prilocaine treatment group and the lidocaine treatment group (P=0.67). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
injection vs lidocaine 5% ointment applied to the outer half of the inferior orbital margin at least 45 minutes prior to retrobulbar injection				
Usmani et al.[52] (2009) Lidocaine-prilocaine cream applied to the incision site 2 hours before surgery vs lidocaine 1% injected into the incision site 3 minutes before surgery vs placebo Fentanyl was a rescue analgesic in the immediate	DB, PC, RCT Children 4 to 12 years of age undergoing elective inguinal hernia repair under general anesthesia	N=90 1 day	Primary: Time to the first dose of rescue analgesic, number of patients requiring fentanyl in the recovery room Secondary: Not reported	Primary: The time to the first dose of rescue analgesic was significantly shorter in the placebo group (71 minutes) compared to the study groups (lidocaine-prilocaine, 143 minutes; lidocaine, 148 minutes; P<0.05). The number of patients requiring fentanyl in the recovery room was significantly less in the study groups (five in the lidocaine-prilocaine group and six in the lidocaine group) as compared to the placebo group (20 patients; P<0.05). In the placebo group, 17 patients required both fentanyl and acetaminophen compared to four patients each in the lidocaine-prilocaine and lidocaine groups (P<0.05). Sixty-seven percent of patients in the placebo group required more than one dose of acetaminophen in the first six hours compared to 23% of patients receiving lidocaine-prilocaine and 20% of patients receiving lidocaine. Two patients in the lidocaine group and one patient each of the lidocaine-prilocaine and placebo groups had a subcutaneous infection at the site of incision between the 10th and 15th postoperative day. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
postoperative period and acetaminophen was a rescue analgesic in the surgical ward.				
Berman et al.[53] (2005) Lidocaine-tetracaine patch applied 30 minutes prior to procedure vs placebo	DB, PC, PRO, RCT Patients 20 to 80 years of age presenting for minor dermatological procedures not requiring sutures	N=49 1 day	Primary: Pain intensity according to the visual analog scale, patients' overall assessment of the effectiveness of the patch, the need for rescue medication, investigator ratings of patients' pain intensity and anesthetic efficacy Secondary: Not reported	Primary: Median visual analog scale scores were significantly lower in the lidocaine and tetracaine group compared to the placebo group (P<0.001). Median visual analog scale scores were significantly lower in the lidocaine and tetracaine group compared to the placebo group in patients undergoing excision, electrodessication, keloid injection, cryotherapy, and skin tag removal (P<0.05). Injected lidocaine as rescue medication was administered to 22% of patients in the lidocaine and tetracaine group compared to 49% of patients in the placebo group (P=0.008). Adequate anesthetic effect was reported in 73% of patients in the lidocaine and tetracaine group compared to 37% in the placebo group (P<0.001). Adequate anesthetic effect was reported by the investigator in 71% of patients in the lidocaine and tetracaine group compared to 39% in the placebo group (P=0.004). A significantly higher number of patients in the lidocaine and tetracaine group were assessed by the investigators and independent witnesses as being pain-free during the procedure compared to the placebo group (P<0.004 and P<0.001 respectively). Secondary: Not reported
Schecter et al.[54] (2005) Lidocaine-	DB, PC, RCT Patients ≥65 years of age presenting	N=79 1 day	Primary: Pain rating according to the visual analog scale	Primary: The visual analog scale scores were significantly lower in the lidocaine-tetracaine group compared to the placebo group in patients undergoing excisions (P=0.020) and procedures on the head and neck (P=0.043).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tetracaine patch applied 30 minutes prior to minor dermatological procedures vs placebo	for minor dermatological procedures		Secondary: Patient's assessment of anesthesia, investigator's assessment of the degree of anesthesia	Scores for shave biopsies and procedures on the arm/shoulder, chest/abdomen, back, hip/leg, or penis did not show any statistically significant differences (P≥0.092). Secondary: There were no significant differences between groups in patients reporting adequate pain relief (P=0.767) or in the percentage of patients saying they would use the patch again (P=0.726). There were no significant differences between groups in the investigator's assessments of patient pain or impression of whether or not the local anesthetic provided adequate anesthesia (P=0.461 and P=0.838, respectively).
Sethna et al.[55] (2005) Lidocaine-tetracaine patch applied for 20 minutes prior to the procedure vs placebo	DB, PC, PRO, RCT Patients 3 to 17 years of age requiring intravenous access or blood sampling	N=64 1 day	Primary: Pain intensity according to the Oucher Pain Scale, investigator and independent observer assessments of the degree of analgesia provided on a four4-point scale Secondary: Not reported	Primary: Significantly lower pain scores were reported in patients in the lidocaine-tetracaine group compared to the placebo group (P<0.001). No pain was reported in 59% of patients in the lidocaine-tetracaine group compared to 20% in the placebo group (P<0.001). Investigator and independent observer evaluations show significant pain relief in the lidocaine-tetracaine group compared to the placebo group (P<0.001). Secondary: Not reported
Singer et al.[56] (2008) Lidocaine-tetracaine patch applied for 20 minutes prior to intravenous cannulation	DB, PC, RCT Patients 3 to 17 years of age who required non-emergency IV cannulation	N=40 1 day	Primary: Pain of cannulation measured using a validated 100-mm visual analog scale or Wong Baker scale Secondary: Not reported	Primary: The median pain of intravenous cannulation in the lidocaine-tetracaine treatment group (18 mm) was significantly lower than in the placebo group (35 mm; P=0.04). Adequate pain relief was more common in the lidocaine-tetracaine group (75%; 95% CI, 53 to 89) vs the placebo group (35%; 95% CI, 18 to 57). The number of successful intravenous cannulations after the first attempt was similar in the lidocaine-tetracaine group (90%; 95% CI, 70 to 97) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				the placebo group (85%; 95% CI, 64 to 95). Secondary: Not reported
Curry et al.[57] (2007) Lidocaine-tetracaine patch applied for 20 minutes prior to vascular access procedure vs placebo	DB, PC, RCT Adults undergoing a vascular access procedure	N=40 1 day	Primary: Pain intensity using a 100 mm visual analog scale, patient perception of pain relief, investigator and independent observer rating of patients' pain, investigator's perception of pain relief Secondary: Not reported	Primary: The median patient visual analog scale score was lower for lidocaine-tetracaine compared to placebo (5 vs 28 mm). Forty-nine percent of patients had lower visual analog scale scores with lidocaine-tetracaine than placebo, and 17% had lower visual analog scale scores with the placebo (P<0.001). More patients reported adequate anesthesia following lidocaine-tetracaine compared to placebo (73 vs 31%). Fifty-nine percent of patients indicated adequate pain relief with lidocaine-tetracaine and not the placebo, and 15% reported adequate pain relief with the placebo and not lidocaine-tetracaine (P=0.002). More patients indicated they would use lidocaine-tetracaine again compared to placebo (70 vs 33%). Fifty-one percent of patients reported that they would use lidocaine-tetracaine again but not the placebo, and 15% reported that they would use the placebo again but not lidocaine-tetracaine (P=0.006). Investigators rated 63% of patients as having no pain with lidocaine-tetracaine treatment compared to 33% of patients with the placebo treatment. Investigators considered 46% of patients to have less pain with lidocaine-tetracaine than placebo, and 15% of patients to have less pain with the placebo than lidocaine-tetracaine (P=0.021). Independent observers rated 68% of patients having no pain with lidocaine-tetracaine compared to 38% with the placebo. The independent observers considered 46% of patients to have less pain with lidocaine-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				tetracaine than placebo, and 15% of patients to have less pain with the placebo than lidocaine-tetracaine (P=0.015). For the overall rating, the investigators considered more patients to have adequate anesthesia with lidocaine-tetracaine compared to placebo (60 vs 23%). They considered 54% of patients to have adequate anesthesia with lidocaine-tetracaine and not the placebo, and considered 15% of patient to have adequate anesthesia with the placebo and not lidocaine-tetracaine (P=0.004). Secondary: Not reported
George et al.[58] (2008) Lidocaine-tetracaine patch applied for 20 minutes followed by saline infiltration vs placebo patch applied for 20 minutes followed by infiltration with lidocaine 2%	RCT Women ≥18 years of age who were considering labor epidural analgesia	N=33 1 day	Primary: Provider and patient assessment of discomfort with epidural needle insertion (using a verbal rating scale); ease of epidural insertion Secondary: Not reported	Primary: The patients' recorded verbal rating scale, with epidural placement, was significantly higher in the lidocaine-tetracaine group (P<0.001), as was the anesthesia providers' verbal rating scale of perceived pain (P<0.01) compared to placebo. A greater number of lidocaine-tetracaine patients required additional deep infiltration (P=0.02). The four-point scale, used to subjectively estimate the quality of patient cooperation during epidural placement, was not significantly different between groups. The patients' recorded verbal rating scale and the anesthesiologists' verbal rating scale rating scores were similar in the two groups. Secondary: Not reported
Masud et al.[59] (2010) Lidocaine-tetracaine patch with controlled heat applied 20 minutes before	DB, MC, RCT Healthy adult volunteers undergoing venipuncture	N=250 1 day	Primary: Patient-reported pain intensity using a visual analog scale, skin reactions and adverse events	Primary: The mean pain intensity scores for patients who received the heated patch was significantly lower than patients who received the unheated patch (14.7 and 23.5 mm, respectively; P=0.04). More patients who received the heated patch reported adequate anesthesia compared to those who received unheated patches (71 vs 53%; P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intravenous cannulation vs lidocaine-tetracaine patch applied 20 minutes before intravenous cannulation (with no heat)			Secondary: Not reported	The percentage of patients who responded positively to the questions, ‘‘Did the local anesthetic provide adequate pain relief for the vascular access procedure?’’ and ‘‘Would you have this form of local anesthesia administered again if given the option?’’ did not differ significantly when compared by heated vs unheated patch. Five patients who received the heated patch and two who received the unheated patch experienced an adverse reaction. Six of these seven events were mild skin reactions (erythema) that resolved within a day without treatment. One patient reported a purple-green discoloration during the 24-48 hour follow-up conversation that, on investigator evaluation, was noted as an ecchymosis of mild severity, unrelated to the study. No arrhythmias, seizures, or respiratory difficulties were reported. Secondary: Not reported
Sawyer et al.[60] (2009) Lidocaine-tetracaine patch applied for 10, 20, 30, or 60 minutes before intravenous cannulation vs lidocaine-prilocaine cream applied for 10, 20, 30, or 60 minutes before intravenous cannulation All patients received both	DB, RCT Healthy adult volunteers undergoing venipuncture	N=82 1 day	Primary: Patient-reported pain intensity using a 100 mm visual analog scale Secondary: Patient evaluation of effectiveness, investigator evaluation of the patient’s pain intensity and overall impression, and adverse events	Primary: Median visual analog scale scores were significantly lower for the lidocaine-tetracaine patch than for lidocaine-prilocaine cream in the 10 minute (P=0.010), 20 minute (P=0.042), and 30 minute (P=0.001) application groups. There was no difference between treatments in the 60 minute group (P=0.887). Secondary: Significantly more patients using the lidocaine-tetracaine patch said they would use the product again compared to lidocaine-prilocaine cream at 10 minutes (80 vs 47%; P=0.008), 20 minutes (95 vs 70%; P=0.025), and 30 minutes (100 vs 64%; P=0.005). There was no difference among the treatment groups at 60 minutes (90 vs 95%; P=0.317). For those patients who reported no pain associated with the vascular access procedure, significantly more patients in the 20 and 30 minute groups reported that the lidocaine-tetracaine patch eliminated pain compared to lidocaine-prilocaine cream (P=0.014 and P=0.020, respectively). After the 10 minute application of the lidocaine-tetracaine patch, 65% of patients reported no pain, but the difference compared to the lidocaine-prilocaine cream was not significant (P=0.059). There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatments.				difference between treatments in the 60 minute group. Investigator ratings of patient pain intensity were significantly lower for lidocaine-tetracaine patch applications in the 10 minute group (P=0.046). The pain intensity ratings for the remaining groups and the investigator's evaluation of the general effectiveness of the treatments were not significantly different between the lidocaine-tetracaine patch and lidocaine-prilocaine cream. Secondary: The lidocaine-tetracaine patch was associated with significantly more erythema than lidocaine-prilocaine cream at 20, 30, and 60 minutes, whereas lidocaine-prilocaine cream produced more blanching than the lidocaine-tetracaine patch at 30 and 60 min. No arrhythmias, seizures, or respiratory difficulties were reported.
Bourolias et al.[61] (2010) Tetracaine 2% solution applied locally vs lidocaine 10% spray applied locally	RCT Patients undergoing transnasal fiber-optic laryngoscopy of the inferior turbinate	N=48 Single dose	Primary: Severity of pain Secondary: Not reported	Primary: There was a significantly lower mean nasal discomfort score in favor of the tetracaine group (2.29 vs 3.04; P<0.001). No complications or side effects regarding the intranasal use of tetracaine or lidocaine were observed. Secondary: Not reported

Drug regimen abbreviations: QID=four times daily
Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Skin and Mucous Membrane Antipruritics and Local Anesthetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Doxepin	cream	Prudoxin®, Zonalon®	$$$$	N/A
Ethyl chloride	spray	N/A	N/A	$
Lidocaine	cream, lotion, ointment, solution, transdermal patch	Lidoderm®*, Pre-attached LTA	$$$$$	$$$$
Combination Products				
Hydrocortisone and lidocaine	rectal cream, rectal gel, rectal kit	N/A	N/A	$$$$$
Hydrocortisone, lidocaine, and aloe vera	rectal gel, rectal kit	N/A	N/A	$$$-$$$$
Lidocaine and prilocaine	cream, kit	N/A	$$$	N/A
Lidocaine and tetracaine	transdermal patch	Synera®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The skin and mucous membrane antipruritics and local anesthetics have a variety of uses, including relief of itching and pain caused by insect bites, minor burns and sunburns, atopic dermatitis, lichen simplex chronicus and hemorrhoids.[1-8] They are also used to prevent and treat pain due to postherpetic neuralgia, venipuncture, intravenous cannulation, minor operative/dermatological procedures, endoscopic/diagnostic procedures, as well as other procedures.[1-8] Due to the variety of products, dosage forms and Food and Drug Administration (FDA)-approved indications, direct comparisons of agents within this class is difficult. There are also few clinical guidelines available that provide recommendations regarding the use of these agents. Several of the products are available in a generic formulation.

When used appropriately, the topical anesthetics can effectively relieve pain. Clinical trials have demonstrated that lidocaine, lidocaine and prilocaine and lidocaine and tetracaine are more effective at relieving pain than placebo.[32, 35, 38-41, 45, 48-49, 52-58] There are relatively few studies that directly compare the topical anesthetics. There was no difference in pain relief with lidocaine and prilocaine cream compared to lidocaine (cream, ointment and transdermal injection).[46,50-51] In one study, pain intensity associated with venipuncture was lower following the use of a lidocaine and tetracaine patch compared to lidocaine and prilocaine cream.[60] The FDA remains concerned about the potential for topical anesthetics to cause life-threatening adverse events such as arrhythmias, seizures, respiratory difficulties, coma and death.[23] If a topical anesthetic is prescribed, patients should use the least amount that will relieve the pain, apply the product sparingly to the area where pain exists or is expected to occur, and do not apply the product to broken or irritated skin. If wrapping or covering the skin is being considered, this can increase the chance of serious adverse events, as can applying heat to the treated area while the medication is still present.[23]

Doxepin cream is approved for the short-term management of moderate pruritus in patients with atopic dermatitis and lichen simplex chronicus. For the treatment of atopic dermatitis, emollients are considered the standard of care.[9-14] They are steroid-sparing and are useful for both prevention and maintenance therapy. Topical corticosteroids provide symptomatic relief and are safe to use in the short term. Although the short-term use of topical doxepin relieves pruritus, adverse events may limit its usefulness.[14] In clinical trials, doxepin was found to be more effective than placebo at controlling pruritus.[24-26]

Topical application of ethyl chloride effectively controls pain. Two clinical trials evaluated the efficacy and safety of ethyl chloride as an anesthetic prior to intravenous cannulation.[28,30] Robinson et al. demonstrated that intradermal lidocaine was more effective than ethyl chloride at reducing the pain of intravenous cannulation.[30] Ramsook et al. found no difference in pain scores with ethyl chloride when compared to isopropyl alcohol.[28]

For the treatment of hemorrhoids, adequate fiber intake and water is the cornerstone of therapy.[16-17] Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge or fecal seepage. A literature search did not reveal any published studies evaluating the use of lidocaine/hydrocortisone combination products for the treatment of hemorrhoids or other disorders.

There is insufficient evidence to support that one brand skin and mucous membrane antipruritic or local anesthetic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antipruritics and local anesthetics within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antipruritic or local anesthetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Nov 23]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Nov 23]. Available from: http://www.thomsonhc.com/.
3. Lexi-Comp Online [database on the internet], Hudson (OH): Lexi-Comp, Inc.; 2013 [cited 2013 Nov 23]. Available from: http://www.lexi.com.
4. Prudoxin® [package insert]. San Antonio, TX: Healthpoint, Ltd; Not dated.
5. Zonalon® [package insert]. Fairfield, NJ: Doak Dermatologics; 2011 Oct.
6. Lidoderm® [package insert]. Chadds Ford, PA: Endo Pharmaceuticals, Inc.; 2013 Jan.
7. EMLA® [package insert]. Wilmington, DE: AstraZeneca LP; 2006 Apr.
8. Synera® [package insert]. Salt Lake City, UT: ZARS Pharma, Inc.; 2013 Sep.
9. Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care. Edinburgh: SIGN; (SIGN publication no. 125). 2011 [cited 2013 Nov 23]. Available from: http://www.sign.ac.uk/pdf/sign125.pdf.
10. Primary Care Dermatology Society & British Association of Dermatologists. Guidelines for the management of atopic eczema. 2009 [cited 2013 Nov 23]. Available from: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PCDS-BAD%20Eczema%20reviewed%202010.pdf.
11. Darsow U, Wollenberg A, Simon D, et al. Position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol. 2009;24:317-28.
12. National Collaborating Centre for Women's and Children's Health. Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Dec. 39 p. [cited 2013 Nov 23]. Available from: http://www.nice.org.uk/nicemedia/live/11901/38597/38597.pdf.
13. Schneider L, Tiles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: A practice parameter update 2012. J Allergy Clin Immunol. 2013;131:295-9.
14. Hanifin J, Cooper K, Ho V, et al. Guidelines of care for atopic dermatitis. J Am Acad Dermatol. 2004;50(3):391-404.
15. Bourke J, Coulson I, English J. British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of contact dermatitis: an update. Br J Dermatol. 2009;160:946-54.
16. American Gastroenterological Association medical position statement: Diagnosis and treatment of hemorrhoids. Clinical Practice Committee. Gastroenterology. 2004;126:1461-2.
17. American Gastroenterological Association. Technical review on the diagnosis and treatment of hemorrhoids. Gastroenterology. 2004;126:1463-73.
18. Attal N, Cruccu G, Haanpää M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol. 2006;13:1153-69.
19. Centre for Clinical Practice. Neuropathic pain. The pharmacological management of neuropathic pain in adults in non-specialist settings. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Mar. 155 p. (Clinical guideline; no. 96) [cited 2013 Nov 23]. Available from: http://www.nice.org.uk/nicemedia/live/12948/47949/47949.pdf.
20. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, et al. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. Mayo Clin Proc. 2010;85(3)(suppl):s3-s14.
21. Dworkin RH, Johnson RW, Breuer J, Gnann JW, et al. Recommendations for the management of herpes zoster. Infectious Diseases Society of America. Clin Infect Dis. 2007;44 Suppl 1:S1-26.
22. Dubinsky R, Kabbani H, El-Chami Z, Boutwell C, Ali H, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2004;63:959-65.
23. FDA Public Health Advisory Potential Hazards of Skin Products Containing Numbing Ingredients for Relieving Pain from Mammography and Other Medical Tests and Conditions 2009 [cited 2013 Nov 23]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm110625.htm.

24. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. J Am Acad Dermatol. 1994;31:613-6.
25. Drake L, Millikan L. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Arch Dermatol. 1995;131:1403-8.
26. Breneman D, Dunlop F, Monroe E, et al. Doxepin cream relieves eczema associated pruritis within 15 minutes and is not accompanied by a risk of rebound upon discontinuation. J Dermatol Treat. 1997;8:161-8.
27. Berberian BJ, Breneman DL, Drake LA, et al. The addition of topical doxepin to corticosteroid therapy: an improved treatment regimen for atopic dermatitis. Int J Dermatol. 1999;38:145-8.
28. Ramsook C, Kozinetz C, Moro-Sutherland D. Efficacy of ethyl chloride as a local anesthetic for venipuncture and intravenous cannula insertion in a pediatric emergency department. Pediatric Emergency Care. 2001;17(5):341-3.
29. Davies E, Molloy A. Comparison of ethyl chloride spray with topical anaesthetic in children experiencing venipuncture. Pediatric Nursing. 2006;18:39-43.
30. Robinson P, Carr S, Pearson S, et al. Lignocaine is a better analgesic than either ethyl chloride or nitrous oxide for peripheral intravenous cannulation. Emerg Med Australas. 2007;19:427-32.
31. Celik G, Ozbek O, Yilmaz M, Duman I, Ozbek S, Apiliogullari S. Vapocoolant spray vs lidocaine/prilocaine cream from reducing the pain of venipuncture in hemodialysis patients: A randomized, placebo-controlled, crossover study. Int J Med Sci 2011;8(7):623-627.
32. Kokinsky E, Cassuto J, Sinclair R, Rubensson A, Nilsson K, Larsson L. Topical wound anesthesia in children—a temporary postoperative pain relief. Acta Anaesthesiol Scand. 1999;43:225-9.
33. Corkill A, Lavender T, Walkinshaw S, Alfirevic Z. Reducing postnatal pain from perineal tears by using lignocaine gel: a double-blind randomized trial. Birth. 2001;28(1):22-7.
34. Minassian V, Jazayeri A, Prien S, Timmons R, Stumbo K. Randomized trial of lidocaine ointment vs placebo for the treatment of postpartum perineal pain. Obstetrics and Gynecology. 2002;100(6):1239-43.
35. Habib AS, Polascik TJ, Weizer AZ, et al. Lidocaine patch for postoperative analgesia after radical retropubic prostatectomy. Anesth Analg. 2009;108:1950-3.
36. Ingalls NK, Horton ZA, Bettendorf M, et al. Randomized, double-blind, placebo-controlled trial using lidocaine patch 5% in traumatic rib fractures. J Am Coll Surg. 2010;210:205-9.
37. Cheville AL, Sloan JA, Northfelt DW, et al. Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). Support Care Cancer. 2009;17:451-60.
38. Galer B, Rowbotham M, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain. 1999;80:533-8.
39. Meier T, Wasner G, Faust M et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain. 2003;106:151-8.
40. Galer B, Jensen M, Ma T, Davies P, Rowbotham M. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, three-week efficacy study with use of the neuropathic pain scale. Clin J Pain. 2002;18(5):297-301.
41. Lin PL, Fan SZ, Huang CH, et al. Analgesic effect of lidocaine patch 5% in the treatment of acute herpes zoster: a double-blind and vehicle-controlled study. Reg Anesth Pain Med. 2008;33:320-5.
42. Katz N, Gammaitoni A, Davis M, et al. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. Pain Medicine. 2002;3:324-32.
43. Devers A, Galer B. Topical lidocaine patch relieves a variety of neuropathic pain conditions: and open-label study. Clin J Pain. 2000;16(3):205-8.
44. Fleming JA, O'Connor BD. Use of lidocaine patches for neuropathic pain in a comprehensive cancer center. Pain Res Manag. 2009;14:381-8.
45. Affaitati G, Fabrizio A, Savini A, et al. A randomized, controlled study comparing a lidocaine patch, a placebo patch, and anesthetic injection for treatment of trigger points in patients with myofascial pain syndrome: evaluation of pain and somatic pain thresholds. Clin Ther. 2009;31:705-20.
46. Luhmann J, Hurt S, Shootman M, Kennedy R. A comparison of buffered lidocaine vs ELA-Max before peripheral intravenous catheter insertions in children. Pediatrics. 2004;113(3):217-20.
47. Gursoy A, Ertugrul D, Sahin M, et al. The analgesic efficacy of lidocaine/prilocaine (EMLA) cream during fine-needle aspiration biopsy of thyroid nodules. Clin Endocrinol. 2007;66:691-4.
48. Shaikh FM, Naqvi SA, Grace PA, et al. The influence of a eutectic mixture of lidocaine and prilocaine on minor surgical procedures: a randomized controlled double-blind trial. Dermatol Surg. 2009;35:948-51.
49. McCluskey A, Currer B, Sayeed I. The efficacy of 5% lidocaine-prilocaine (EMLA) cream on pain during intravenous injection of propofol. Anesth Analg. 2003;97:713-4.

50. Koh J, Harrison D, Myers R et al. A randomized, double-blind comparison study of EMLA® and ELA-Max® for topical anesthesia in children undergoing intravenous insertion. Pediatric Anesthesia. 2004;14:977-82.
51. Kuvaki B, Gokmen N, Gunenc F et al. EMLA® does not permit pain-free retrobulbar injection. Acta Anaesthesiol Scand. 2003;47:739-41.
52. Usmani H, Pal Singh S, Quadir A, et al. A comparison between EMLA cream application vs lidocaine infiltration for postoperative analgesia after inguinal herniotomy in children. Reg Anesth Pain Med. 2009;34:106-9.
53. Berman B, Flores J, Pariser D et al. Self-warming lidocaine/tetracaine patch effectively and safely induces local anesthesia during minor dermatologic procedures. Dermatol Surg. 2005;31:135-8.
54. Schecter A, Pariser D, Pariser R et al. Randomized, double-blind, placebo-controlled study evaluating the lidocaine/tetracaine patch for induction of local anesthesia prior to minor dermatologic procedures in geriatric patients. Dermatol Surg. 2005;31:287-91.
55. Sethna N, Verghese S, Hannallah R, et al. A randomized controlled trial to evaluate S-Caine Patch for reducing pain associated with vascular access in children. Anesthesiology. 2005;102:403-8.
56. Singer A, Taira B, Chisena E, et al. Warm lidocaine/tetracaine patch vs placebo before pediatric intravenous cannulation: a randomized controlled trial. Ann Emerg Med. 2008;52:41-7.
57. Curry S, Finkel J. Use of the Synera patch for local anesthesia before vascular access procedures: a randomized, double-blind, placebo-controlled study. Pain Med. 2007;8:497-502.
58. George R, Habib A, Allen T, et al. Brief report: a randomized controlled trial of Synera vs lidocaine for epidural needle insertion in laboring parturients. Can J Anaesth. 2008;55:168-71.
59. Masud S, Wasnich RD, Ruckle JL, et al. Contribution of a heating element to topical anesthesia patch efficacy prior to vascular access: results from two randomized, double-blind studies. J Pain Symptom Manage. 2010;40:510-9.
60. Sawyer J, Febbraro S, Masud S, et al. Heated lidocaine/tetracaine patch (Synera, Rapydan) compared to lidocaine/prilocaine cream (EMLA) for topical anaesthesia before vascular access. Br J Anaesth. 2009;102:210-5.
61. Bourolias C, Gkotsis A, Kontaxakis A, et al. Lidocaine spray vs tetracaine solution for transnasal fiber-optic laryngoscopy. Am J Otolaryngol. 2010;31:114-6.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Astringents
AHFS Class 841200
February 12, 2014

I. Overview

Aluminum chloride is the only skin and mucous membrane astringent that is currently available. It is used as an aid in the management of hyperhidrosis.[1,2] Hyperhidrosis is a chronic idiopathic condition, which is characterized by excessive sweating in amounts greater than physiologically needed for thermoregulation.[3,45] Idiopathic (primary) hyperhidrosis usually affects the axillae, palms and soles. The onset of symptoms generally present in childhood or adolescence, and the condition persists throughout adult life.[4] Episodes of excessive sweating usually occur at least once per week and do not occur during periods of sleep. Generalized (secondary) hyperhidrosis is often due to medications or a systemic illness. Unlike primary hyperhidrosis, episodes of excessive sweating occur during sleep with secondary hyperhidrosis.[4]

Treatment options for hyperhidrosis include topical aluminum chloride, systemic medications, iontophoresis, botulinum toxin and surgery. It is thought aluminum chloride mechanically obstructs the sweat gland ducts or causes atrophy of the secretory cells.[4]

The skin and mucous membrane astringents that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Astringents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aluminum chloride	solution	Drysol®, Hypercare®, Xerac AC®	aluminum chloride

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane astringents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Astringents

Clinical Guideline	Recommendation(s)
International Hyperhidrosis Society: **Primary Focal Hyperhidrosis Clinical Guideline[5] (2012)**	General • For generalized secondary hyperhidrosis, the underlying cause should be treated with adjustments to medications as needed. • If response is not adequate, systemic medications (i.e., anticholinergics [e.g., glycopyrrolate, oxybutynin, propantheline], propranolol, clonidine, diltiazem) may be considered. • If desired response is not reached, re-evaluation of medical conditions or concurrent medications (prescription and over-the-counter) is recommended. Axillary • Topical aluminum chloride antiperspirants are the first-line of treatment for axillary hyperhidrosis. • If excessive sweating symptoms occur during, or are exacerbated by, known anxiety-provoking situations, the patient may be treated prior to such events with an anticholinergic or a short course benzodiazepine. • If a patient does not adequately respond to topical antiperspirant therapy or if the side effects of such therapy are intolerable,

Clinical Guideline	Recommendation(s)
	onabotulinumtoxinA (BTX-A) injections are the next line of treatment. • If there is not a good response to BTX-A, then local sweat ablation or systemic medications (i.e., anticholinergics [e.g., glycopyrrolate, oxybutynin, propantheline], propranolol, clonidine, diltiazem) can be considered. • The last option for treatment for axillary hyperhidrosis.is endoscopic thoracic sympathectomy after patients have been educated to fully understand the limited efficacy compared to the risks of complications. <u>Craniofacial</u> • Topical aluminum chloride antiperspirants are first-line. • If a good response is not achieved, BTX-A are considered second-line. • The next option when patients do not respond to BTX-A is systemic medications (i.e., anticholinergics [e.g., glycopyrrolate, oxybutynin, propantheline], propranolol, clonidine, diltiazem) can be considered. <u>Gustatory hyperhidrosis (Frey's syndrome)</u> • First-line therapy for Gustatory hyperhidrosis is either topical aluminum chloride antiperspirants or BTX-A. • If response is not achieved, treatment with the other first-line agents should be considered. • If both first-line treatments do not have response, systemic medications (i.e., anticholinergics [e.g., glycopyrrolate, oxybutynin, propantheline], propranolol, clonidine, diltiazem) are recommended. <u>Palmar</u> • Topical aluminum chloride antiperspirants are often considered the first-line of treatment for palmar hyperhidrosis. A higher concentration of active ingredients (up to 30%) is often required. • Many experts also consider tap water iontophoresis to be a first-line treatment for palmar sweating. • If excessive sweating symptoms occur during, or are exacerbated by, known anxiety-provoking situations, the patient may be treated prior to such events with an anticholinergic or a short course benzodiazepine. • If symptoms do not resolve with topical antiperspirants, iontophoresis, or short course oral medications (if appropriate), the remaining options to consider are: BTX-A injections, on-going use of systemic medications (i.e., anticholinergics [e.g., glycopyrrolate, oxybutynin, propantheline], propranolol, clonidine, diltiazem), or endoscopic thoracic sympathectomy. • Systemic medications are often associated with side effects precluding long-term treatment. endoscopic thoracic sympathectomy is invasive and associated with high rates of compensatory hyperhidrosis. Therefore, BTX-A is often recommended first and repeated as necessary to control symptoms. <u>Plantar</u> • An important first step in the care of the plantar hyperhidrosis patient is to provide education regarding good foot hygiene (to keep the feet as dry as possible). Useful plantar hygienic products include: absorbent foot powder, absorbent insoles for shoes, and moisture-wicking socks. Patients should also be encouraged to wear nonocclusive footwear and to change their shoes and socks frequently. • Topical aluminum chloride antiperspirants are often considered the first-line of treatment for plantar hyperhidrosis (keeping in mind that a

Clinical Guideline	Recommendation(s)
	higher concentration of active ingredients [up to 30%] than is used to treat axillary hyperhidrosis is often required). • Many experts also consider tap water iontophoresis to be a first-line treatment for plantar sweating. • Patients may also be treated with BTX-A. If the patient does not respond to BTX-A, the last therapeutic option to consider is the use of a systemic medication (i.e., anticholinergics [e.g., glycopyrrolate, oxybutynin, propantheline], propranolol, clonidine, diltiazem). • Additionally, if symptoms are exacerbated in known anxiety-provoking situations, short-term expectant use of a benzodiazepine or anticholinergic may be considered.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane astringents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Astringents[1,2]

Indication	Aluminum Chloride
Management of hyperhidrosis	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane astringents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Astringents[1,2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aluminum chloride	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

There are no significant drug interactions with the skin and mucous membrane astringents.

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane astringents are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Astringents[1,2]

Adverse Events	Aluminum Chloride
Dermatological	
Burning sensation	✔
Prickling sensation	✔
Skin irritation	✔
Transient itching or stinging	✔

✔ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane astringents are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Astringents[1,2]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aluminum chloride	Management of hyperhidrosis: Solution: apply to the affected area once daily at bedtime	Safety and efficacy in children have not been established.	Solution: 6.25% 20%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane astringents are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Astringents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rayner et al.[6] (1980) Aluminum chloride 20% applied on alternate nights vs placebo	DB, PC, XO Patients 18 to 41 years of age with axillary hyperhidrosis	N=36 6 months	Primary: Symptomatic relief, avoidance of surgery Secondary: Adverse effects	Primary: After two weeks, 24 patients had achieved considerable relief, six patients showed no improvement, two patients obtained relief with placebo, and four patients obtained relief with both solutions. After six months of treatment, 68% opted for surgery. Secondary: Significant local reaction was seen in 55% of the patients.
Scholes et al.[7] (1978) Aluminum chloride 20% applied at night	MC Patients 14 to 51 years of age with axillary hyperhidrosis	N=65 15 months	Primary: Symptomatic relief Secondary: Adverse effects	Primary: Sixty four patients (98%) achieved complete control of axillary sweating with periodic use of the solution. Secondary: Irritation of the axillary skin was reported in 45% of the patients, of which all but one patient achieved relief with 1% hydrocortisone cream. One patient discontinued treatment due to intolerable irritation.
Goh[8] (1990) Aluminium chloride 20% applied at night	SB Patients with symptomatic idiopathic palmar hyperhidrosis	N=12 4 weeks of treatment and 2 weeks of follow-up	Primary: Skin water vapor loss Secondary: Adverse events	Primary: The mean skin water vapor loss of treated palms was significantly lower than untreated palms at one, two, and four weeks (P=0.049, P=0.007 and P=0.004, respectively). There was no significant difference between treated palms and untreated palms during week three. The mean skin water vapor loss of treated palms returned to baseline at week five. Secondary: Four patients developed skin irritation from treatment; in three this disappeared after one week and therapy was continued.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Flanagan et al.[9] (2008) Aluminum chloride 20% applied at night vs BTX-A 50 unites injected in each axillae bilaterally once at baseline	OL, PG, RCT, SC, XO Patients >18 years of age with moderate to severe primary idiopathic axillary hyperhidrosis	N=25 12 weeks	Primary: Treatment response by an improvement ≥2 grades on the hyperhidrosis disease severity scale from baseline to week four Secondary: Treatment response at week eight and week 12 using hyperhidrosis disease severity scale scores, patient satisfaction, irritation	Primary: At week four, 91.7% of the subjects in the BTX-A group achieved treatment response compared to 33.3% of the subjects in the aluminum chloride group (P<0.0001). At weak four, 71% of subjects in the aluminum chloride group did not tolerate treatment and/or did not achieve an improvement ≥2 points in their hyperhidrosis disease severity scale score, and crossed over to BTX-A. Secondary: At week eight, 88% of subjects remained in the BTX-A group and 90.9% were treatment responders. At week eight, 24% of aluminum chloride patients were evaluable and 83% continued to be responders. At week 12, 77.3% of subjects in the BTX-A group continued to be treatment responders. There were seven evaluable subjects in the aluminum chloride group and 100% were treatment responders. There was no difference in treatment response between the BTX-A and aluminum chloride. At week four, 87.5% of patients in the BTX-A group were “very satisfied” with their treatment compared to 33.3% of patients in the aluminum chloride group (P<0.003). At week 12, 81.1% of patients in the BTX-A group were “very satisfied” with their treatment compared to 83.3% of patients who remained in the aluminum chloride group, which did not differ significantly from the BTX-A group. The BTX-A group sustained very few side effects of irritation, but the aluminum chloride group reported significant complaints of irritation across all categories assessed.

Study abbreviations: DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, SB=single-blind, SC=single-center, XO=crossover
Miscellaneous abbreviations: BTX-A=onabotulinumtoxinA

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Astringents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aluminum chloride	solution	Drysol®, Hypercare®, Xerac AC®	$	$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Aluminum chloride is the only skin and mucous membrane astringent that is currently available. It is approved for the treatment of hyperhidrosis and is available in a generic formulation. According to the International Hyperhidrosis Society guidelines, topical aluminum chloride is recommended as initial therapy for axillary, palmar and plantar hyperhidrosis.[5] If a patient does not adequately respond to topical antiperspirant therapy, or if adverse events are intolerable, onabotulinumtoxinA (BTX-A), systemic medications and surgery are also treatment options.[5]

Although aluminum chloride has been available for many years, there are very few clinical trials assessing the efficacy and safety of this agent. It has been shown to be effective in reducing axillary and palmar hyperhidrosis; however, clinical trials have enrolled small numbers of patients.[6-9] Flanagan et al. compared treatment with aluminum chloride and BTX-A in patients with moderate to severe axillary hyperhidrosis.[9] BTX-A was more effective than aluminum chloride and provided greater patient satisfaction after four weeks of therapy. Rayner et al. reported that 68% of study patients opted for surgery after six months of treatment with aluminum chloride.

The use of aluminum chloride is often associated with skin irritation; however, this can be managed by applying the product on dry skin at bedtime and washing it off in the morning.[4] Other strategies include the use of a hair dryer to quickly dry the application site, the use of baking soda in the morning to neutralize the aluminum chloride, or the use of a low potency corticosteroid cream to relieve irritation.[4]

There is insufficient evidence to support that one brand skin and mucous membrane astringent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane astringents within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane astringent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Aluminum chloride hexahydrate: drug information. In Basdow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Dec 9]. Available from: http://www.utdol.com/utd/index.do.
2. Micromedex® Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Healthcare. Updated periodically [cited 2013 Dec9]. Available from: http://www.thomsonhc.com/.
3. Stolman LP. Treatment of hyperhidrosis. Dermatol Clin. 1998;16(4):863-9.
4. Smith CC and Pariser D. Primary focal hyperhidrosis. In: Basdow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Dec 9]. Available from: http://www.utdol.com/utd/index.do.
5. International Hyperhidrosis Society. Primary focal hyperhidrosis clinical guideline [guideline on the internet]. Quakertown (PA): International Hyperhidrosis Society 2013 [cited 2013 Dec 9] Available from http://www.sweathelp.org/English/HCP_Hyperhidrosis_Clinical_Primary_Focal.asp.
6. Rayner CRW, Ritchie ID, Stark GP. Axillary hyperhidrosis, 20% aluminum chloride hexahydrate, and surgery. BMJ. 1980;280(6224):1168.
7. Scholes KT, Crow KD, Ellis JP, et al. Axillary hyperhidrosis treated with alcoholic solution of aluminum chloride hexahydrate. BMJ. 1978;2:84-5.
8. Goh CL. Aluminum chloride hexahydrate vs palmar hyperhidrosis. Evaporimeter assessment. Int J Dermatol. 1990;29:368-70.
9. Flanagan K, King R, Glaser D. Botulinum toxin type a vs topical 20% aluminum chloride for the treatment of moderate to severe primary focal axillary hyperhidrosis. J Drugs Dermatol. 2008;7:221-7.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Keratolytic Agents
AHFS Class 842800
February 12, 2014

I. Overview

The skin and mucous membrane keratolytic agents are approved for the treatment of a variety of hyperkeratotic skin conditions, including calluses, corns, cutaneous warts, eczema, ichthyosis, psoriasis, xerosis, as well as others.[1-4] Some of the agents are also approved for the treatment of damaged, ingrown and devitalized nails.[1-4] Cutaneous warts are caused by the human papilloma virus (HPV) and have a variable clinical presentation based on the skin surface location and morphology.[5] Eczema is a chronic inflammatory skin condition characterized by redness, edema, pruritus, dryness, crusting, flaking, blistering, cracking, oozing and bleeding.[6] Ichthyosis is a genetic hyperkeratotic skin disorder characterized by dry and scaly skin.[7-8] Psoriasis is a chronic, immune-mediated disorder which results in hyperproliferation and abnormal differentiation of the epidermis.[9] It is characterized by erythematous plaques which appear as silvery scales. Xerosis, or excessive dryness of the skin, is characterized by redness, scaling and fissures.[7]

The stratum corneum is the outermost layer of the epidermis. It is composed of stacked layers of corneocytes, which are held together by a lipid-based intercellular matrix that serves as a tough, yet flexible, protective barrier against excessive water loss.[7] Normal skin contains more than 10% hydration.[7] When the water content is less than 10%, disruption in the stratum corneum can occur, leading to scaling, cracking and irritation. Salicylic acid and urea hydrate and dissolve the intracellular matrix of the stratum corneum, which causes the cornified tissue to swell, soften, macerate and desquamate.[1-4] Urea also hydrates and dissolves the intercellular matrix of the nail plate, which can result in the softening and debridement of the nail plate.[1-4]

The skin and mucous membrane keratolytic agents that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Products solely indicated for the treatment of acne and/or rosacea are not covered by Alabama Medicaid. Therefore, these products are not included in this review. All of the products included in this review are available in a generic formulation. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Keratolytic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Salicylic acid	cream, gel, liquid, lotion, shampoo	Salex®*	salicylic acid
Urea	cream, emulsion, foam, gel, lotion, suspension	Aluvea®*, Remeven®*, Umecta®*, Umecta PD®, Uramaxin®*, Uramaxin GT®*, X-viate®*	urea
Combination Products			
Urea, lactic acid, and salicylic acid†	suspension	N/A	urea, lactic acid, and salicylic acid
Urea, lactic acid, and zinc undecylenate†	emulsion	N/A	urea, lactic acid, and zinc undecylenate

*Generic is available in at least one dosage form or strength.
†No current clinical significant information was identified.
N/A=not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane keratolytic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Keratolytic Agents

Clinical Guideline	Recommendation(s)
American Academy of Dermatology: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapies[10] (2009)**	• Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. • Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include vitamin D analogs, tazarotene, tacrolimus, pimecrolimus, nonmedicated topical moisturizers, salicylic acid, anthralin, coal tar and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific Food and Drug Administration (FDA)-approved indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid; however, the agent is typically used in combination with other topical therapies. • Coal tar products are often poorly tolerated by patients because of cosmetic issues, including staining of clothes and the tar odor that is present in almost all products. • Coal tar is carcinogenic in animals; however, in humans there are no convincing data proving carcinogenicity, and epidemiologic studies fail to show increased risk of skin cancer in patients who use coal tar.

British Association of Dermatologists/Primary Care Dermatology Society: **Recommendations for the Initial Management of Psoriasis[11] (2009)**	• Emollients should be used to soften scaling and reduce any irritation.
	• For localized plaque psoriasis (e.g., on the elbows or knees), one or more of the following topical preparations can be tried. The sequence of choice will vary according to the extent and pattern of psoriasis, and patient preference:
	  o A tar-based cream, or a tar/corticosteroid mixture.
	  o A moderate potency topical corticosteroid (e.g. 0.05% clobetasone butyrate); stronger agents can be used on palms and soles or on the scalp (use of topical steroids may lead to rebound exacerbation when treatment is discontinued).
	  o A vitamin D analog (e.g.; calcipotriol, calcitriol or tacalcitol). The latter two tend to be less irritant and are more suitable for face or flexures, but should still be used with caution.
	  o Calcipotriol with betamethasone dipropionate as a combination product (long-term data regarding relapse rates is not yet established).
	  o A vitamin A analog (tazarotene).
	  o A dithranol preparation, usually used as a short-contact treatment (these are effective but more difficult to use, especially if there are many small lesions).
	• For more widespread plaque psoriasis (e.g., on the trunk or the limbs), the same treatments may be appropriate.
	  o Dithranol is often impracticable to apply to multiple small lesions and will irritate flexures.
	  o Topical corticosteroids may be inappropriate for use in widespread psoriasis, particularly more potent agents if used on a long-term

Clinical Guideline	Recommendation(s)
	basis. • For scalp psoriasis, a tar-based shampoo should be tried first. This can be combined with salicylic acid (2 to 5% preparation), a coconut oil/tar/salicylic acid combination ointment, a potent topical corticosteroid preparation (e.g., 0.1% betamethasone valerate), calcipotriol scalp application, or more than one of these. • In palm and sole psoriasis, both hyperkeratosis and inflammation are usually present and may require separate treatments. Hyperkeratosis usually needs to be treated with a keratolytic agent. Topical steroids (usually potent, due to the thick skin at this site), tars and vitamin D analogs may all be useful. • In general, milder agents are used for flexures. These include low potency topical steroids, mild tar preparations, and tacalcitol or calcitriol (not calcipotriol, this is usually irritant in flexures). • In facial psoriasis, use mild agents: emollients, mild corticosteroids, calcitriol, tacalcitol, mild tars.
Finnish Medical Society Duodecim: **Seborrheic Dermatitis[12] (2007)**	General considerations • Treatment does not cure the disease. Therefore, it must be repeated when the symptoms recur, or even prophylactically. Removing the thick scales and decreasing the amount of sebum • The scales can be softened with a cream containing salicylic acid and sulfur (but not Vaseline) or by wetting and washing. • Seborrheic skin should be washed more often than usual. Decreasing fungal growth • Washing the scalp with ketoconazole shampoo or selenium sulfide shampoo. • Topical treatment with creams containing imidazole derivatives. • Antimycotic on skin creases (rarely necessary). • Sometimes ultraviolet light therapy. Symptomatic topical treatment • Corticosteroid liniments for the scalp (from mild to potent). • Corticosteroid creams for other parts of the body (from mild to potent). • Moisturizing emollients after washing. • Ketoconazole shampoo and corticosteroid liniments must often be combined in therapy-resistant cases.
British Association of Dermatologists: **Guidelines for the Management of Cutaneous Warts[13] (2001)**	• There is no single treatment that is 100% effective and different types of treatment may be combined. • Salicylic acid alone has been shown to produce clearance in 67% of patients with hand warts and 84% in those with plantar warts in 12 weeks. • There are many commercially available preparations, but there is limited information to enable comparisons to be made between products. • Comparisons between salicylic acid-containing paints, monotherapy with glutaraldehyde, fluorouracil, podophyllin, benzalkonium or liquid nitrogen cryotherapy, failed to find any preparation more effective than salicylic acid.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane keratolytic agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Keratolytic Agents[1-4]

Indication	Salicylic Acid	Urea
Hyperkeratotic Skin Disorders		
A topical aid in the removal of excessive keratin in hyperkeratotic skin disorders, including common and plantar warts, psoriasis, calluses and corns	✔	
For softening, smoothing and removing rough scaling hyperkeratotic skin in conditions such as xerosis, ichthyosis, skin cracks and fissures, dermatitis, eczema, psoriasis, keratosis and calluses		✔ *
For debridement and promotion of normal healing of hyperkeratotic surface lesions, particularly where healing is retarded by local infection, necrotic tissue, fibrinous or purulent debris, or eschar; urea is useful for the treatment of hyperkeratotic conditions, such as dry, rough skin; dermatitis; psoriasis; xerosis; ichthyosis; eczema; keratosis; keratoderma; and corns and calluses; as well as damaged, ingrown, and devitalized nails		✔ †
For moisturizing and softening dry, cracked, calloused rough and hardened skin of feet, hands, or elbows		✔ ‡
For softening, smoothing, and removing rough scaling hyperkeratotic skin in conditions such as xerosis, ichthyosis, skin cracks and fissures, dermatitis, eczema, psoriasis, keratoses, and calluses		✔ §

*42% concentrations.
†40% concentrations, 40% (foam), 35% (foam), 45% (cream), and 50% concentrations.
‡10 and 20% concentrations.
§30% (foam): concentrations.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane keratolytic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Keratolytic Agents[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Salicylic acid	Not reported	Not reported	Not reported	Not reported	Not reported
Urea	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane keratolytic agents, no significant drug interactions have been reported.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane keratolytic agents are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Keratolytic Agents[1-4]

Adverse Events	Salicylic Acid	Urea
Central Nervous System		
Dizziness	✔	-
Headache	✔	✔
Mental confusion	✔	✔
Dermatological		
Burning	✔	✔
Erythema	✔	-

Adverse Events	Salicylic Acid	Urea
Itching	-	✔
Irritation	✔	✔
Peeling	✔	-
Pruritus	✔	-
Scaling	✔	-
Stinging	✔	✔
Other		
Diarrhea	✔	-
Hyperpnea	✔	-
Hyperventilation	✔	-
Lethargy	✔	-
Loss of hearing	✔	-
Nausea	✔	✔
Syncope	-	✔
Tinnitus	✔	-
Vomiting	✔	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane keratolytic agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Keratolytic Agents[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Salicylic acid	Hyperkeratotic skin disorders: Cream: apply to affected area three to four times daily; apply to clean, dry skin; some products may be left in place overnight Foam: apply to affected area twice daily; rub into skin until completely absorbed Gel or liquid: apply to each wart and allow to dry; may repeat once or twice daily, up to 12 weeks; apply to clean dry area Gel: apply to affected area once daily, generally used at night and rinsed off in the morning Liquid (27.5%): apply to each wart; allow to dry then apply a second application; may repeat two-application process once or twice daily, up to six weeks Shampoo: massage into wet hair or affected area; leave in place for several minutes; rinse thoroughly; labeled for over the counter use two to three times a week, or as	Hyperkeratotic skin disorders: Cream: apply to affected area three to four times daily; apply to clean, dry skin; some products may be left in place overnight Foam: apply to affected area twice daily; rub into skin until completely absorbed Gel or liquid: apply to each wart and allow to dry; may repeat once or twice daily, up to 12 weeks; apply to clean dry area Gel: apply to affected area once daily, generally used at night and rinsed off in the morning Liquid (27.5%): apply to each wart; allow to dry then apply a second application; may repeat two-application process once or twice daily, up to six weeks Shampoo: massage into wet hair or affected area; leave in place for several minutes; rinse thoroughly; labeled for over the counter use two to three times a week, or as directed	Cream: 6% Foam: 6% Gel: 6% Liquid: 26% Liquid-film: 27.5% Lotion: 6% Shampoo: 6%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	directed by healthcare provider; some products may be left in place overnight	by healthcare provider; some products may be left in place overnight	
Urea	Hyperkeratotic skin disorders: All formulations: apply to the affected area twice daily	Hyperkeratotic skin disorders: All formulations: apply to the affected area twice daily	Cream: 39% 40% 45% 50% Emulsion: 40% Foam: 20% 40% Gel: 40% 45% Lotion: 40% 45% Suspension: 40%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane keratolytic agents are summarized in Table 7. Although the keratolytic agents have been available for many years, there are limited clinical trials evaluating their use.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Keratolytic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hyperkeratotic Skin Disorders				
Carroll et al.[14] (2005) Salicylic acid 6% gel applied twice daily on half of the body for 8 weeks vs salicylic acid 6% gel and tacrolimus 0.1% ointment applied on the other half of the body for 8 weeks	RCT Adult patients with symmetrical plaque-type psoriasis	N=30 12 weeks	Primary: Difference in the sum of the erythema, scale, and thickness scores from baseline to end of treatment Secondary: Global assessments and pruritus	Primary: There were significant differences between the two treatment groups at weeks one, two, and eight, with the tacrolimus plus salicylic acid–treated side of the body showing greater improvement in the target lesions than the vehicle plus salicylic acid–treated side (P<0.05). At week eight, there was greater improvement on the tacrolimus-treated side than on the placebo-treated side in erythema, scaling, and pruritus (P=0.04, P=0.04, and P=0.02, respectively). Thickness improved more on the tacrolimus plus salicylic acid–treated side, but the difference was not significant (P=0.07). Secondary: The tacrolimus plus salicylic acid treatment resulted in greater improvement according to the investigators' global evaluation of scaling and thickness (P=0.01 and P=0.02, respectively). The subjects' global evaluations showed a trend toward decreased severity of disease on the tacrolimus-treated side of the body, but the differences were not significant (P=0.19).
Ademola et al.[15] (2002) Urea 40% cream applied twice daily for 14 days vs	DB, PG, RCT Patients 18 to 65 years of age with a clinical diagnosis of dry skin of at least grade 2 (moderate to severe) on the plantar surface of	N=25 28 days	Primary: Investigators' clinical observations, instrumental measurements, and subjects' self-assessment	Primary: At the end of the second week of treatment, ammonium lactate lotion decreased skin roughness, scaling, fissures, thickness and dryness by 0.2, 0.7, 0.3, 0.4 and 0.6 units from baseline, respectively. These parameters were decreased from baseline by 0.3, 0.5, 0.5, 0.7, and 0.9, respectively by urea cream during the same treatment period. After the second week of treatment, urea cream was associated with statistically significant improvement (P<0.05) in skin roughness, fissures,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ammonium lactate 12% lotion applied twice daily for 14 days	both feet		Secondary: Not reported	thickness and dryness compared to ammonium lactate lotion. At the end of the two week treatment period, there was no significant difference in transepidermal water loss between the two treatment groups. Changes in skin hydration (as measured by corneometer) were significantly higher in the urea treatment arm compared to ammonium lactate (P<0.05). Urea cream treated surfaces demonstrated a significant (P<0.05) increased desquamation index over baseline at the second week of treatment, compared to the ammonium lactate lotion plantar surfaces. There was no significant difference between ammonium lactate lotion or urea cream by patient self-assessment. A preference questionnaire completed by the patients at the end of the 14th day indicated that patients significantly preferred ammonium lactate over urea cream, primarily for its effect on skin texture (P<0.05). Both therapies showed sustaining benefit between day 14 and day 28 were associated with similar scores for roughness, scaling, fissure, thickness and skin dryness and at levels that remained lower than baseline (P<0.05). Patient self-assessments also indicated that by day 28, therapeutic differences disappeared. Secondary: Not reported
Goldstein et al.[16] (2008) Urea 30% emollient foam	OL, OS, PRO, SC Patients ≥18 years of age with hyperkeratosis with a specified symptom skin score ≥5 and not receiving	N=10 28 days	Primary: Clinical assessment of specified symptom skin score from baseline to day 14 and day 28	Primary: Significant improvements in clinicians' specified symptom skin score scores were noted at the day 14 and day 28 visits compared to baseline (P=0.007 and <0.001, respectively). Secondary: There was a 64.3% improvement in aggregate quality of life scores with comparable improvements noted for symptoms (63.4%), emotions

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	any other treatments		Secondary: Frequency and types of adverse events, patient quality of life assessments, patients' subjective ratings of their skin condition recorded on the Likert scale (5-point), patient/clinician ratings of satisfaction with the product on the Liker scale (5-point)	(65.0%), and functioning (63.8%) at day 28. Patients' reported noticeable improvements in their skin condition with a mean score of 3.2 on day 14 and 4.0 on day 28. The use of urea 30% resulted in no adverse events at any point during the study and all patients completed the 28-day treatment course. Patient satisfaction ratings for urea 30% at day 28 were favorable with mean ratings of 4.9 for odor, 4.7 for ease of application, 4.6 for product feel, 4.3 for overall product satisfaction, and 4.2 for absence of sticky residue. Mean clinician satisfaction rating for urea 30% at day 28 was 4.0.
Kwok et al.[17] (2011) Topical treatment of cutaneous warts (salicylic acid, cryotherapy, duct tape, bleomycin, 5-flurourocil, dinitrochlorobenzene, interferon or photodynamic therapy)	MA Studies evaluating the topical treatment of cutaneous warts	N=77 trials Duration varied	Primary: Cure rate Secondary: Not reported	Primary: Salicylic acid was more efficacious compared to placebo. Cryotherapy was not statistically better than placebo but aggressive cryotherapy was significantly better than gentle cryotherapy. Combined therapy of salicylic acid and cryotherapy had a higher cure rate than either agent alone. The results of the pooled analysis found a cure rate of 23% (5 to 73%) in placebo trials, 52% (0 to 87%) in salicylic acid trials, 49% (0 to 69%) in cryotherapy trials, 54% (45 to 75%) in aggressive cryotherapy trials and 58% (38 to 78%) in the combined cryotherapy and SA trials. Secondary: Not reported

Study abbreviations: DB=double-blind, MA=meta-analysis, OL=open-label, OS=observational, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SC=single center

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Keratolytic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Salicylic acid	cream, gel, liquid, lotion, shampoo	Salex®*	$$$$	$$
Urea	cream, emulsion, foam, gel, lotion, suspension	Aluvea®*, Remeven®*, Umecta®*, Umecta PD®, Uramaxin®*, Uramaxin GT®*, X-viate®*	$	$
Combination Products				
Urea, lactic acid, and salicylic acid†	suspension	N/A	N/A	$$$-$$$$
Urea, lactic acid, and zinc undecylenate†	emulsion	N/A	N/A	$$$$

*Generic is available in at least one dosage form or strength.
†No current clinical significant information was identified.
N/A=Not available

X. Conclusions

Salicylic acid and urea are used to treat a variety of hyperkeratotic skin conditions, including psoriasis, xerosis, ichthyosis, eczema, corns and calluses.[1-4] Salicylic acid is also approved for the treatment of cutaneous warts. Urea is approved for the treatment of damaged, ingrown and devitalized nails. Salicylic acid and urea are available in a generic formulation.

There are numerous topical and systemic therapies available for the treatment of psoriasis. The selection of therapy should take into consideration the disease severity, location of the lesions, and patient preference. Patients with mild to moderate disease can often be treated with a topical agent, while those with moderate to severe disease may need systemic therapy.[10-11] Topical preparations that are effective include corticosteroids, tar-based products, dithranol preparations, vitamin A analogs and vitamin D analogs. Salicylic acid may be combined with other topical therapies, including corticosteroids and topical immunomodulators. Emollients should also be used to soften scaling and reduce irritation. Guidelines do not give preference to one topical agent over another.[10-11] For the treatment of seborrheic dermatitis, the FMSD guidelines recommend the use of salicylic acid to soften scales.[12] Topical corticosteroids, antifungal agents and moisturizing emollients are also frequently prescribed to decrease fungal growth and control symptoms. For the management of cutaneous warts, salicylic acid is recommended as one of several initial treatment options.[13] There are no recommendations regarding the use of urea in the guidelines.[10-12]

Although the keratolytic agents have been available for many years, there are relatively few studies evaluating the efficacy of these agents.[14-16] There were no studies found in the medical literature that directly compared salicylic acid and urea.

There is insufficient evidence to support that one brand skin and mucous membrane keratolytic agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane keratolytic agents within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane keratolytic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2010 [cited 2013 Sept]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Sept]. Available from: http://www.thomsonhc.com/.
3. Salicylic acid: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Sept]. Available from: http://www.utdol.com/utd/index.do.
4. Urea: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Sept]. Available from: http://www.utdol.com/utd/index.do.
5. Goldstein BG, Goldstein AO. Cutaneous warts. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Sept]. Available from: http://www.utdol.com/utd/index.do.
6. Weston WL, Howe W. Epidemiology, clinical manifestations, and diagnosis of atopic dermatitis (eczema). In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Sept]. Available from: http://www.utdol.com/utd/index.do.
7. Bikowski J. Hyperkeratosis of the heels: treatment with salicylic acid in a novel delivery system. Skinmed. 2004;3(6):350-1.
8. Grekin JL, Basler RSW. New treatments for ichthyosis. Cutis. 1980;25:432-4.
9. Feldman SR, Pearce DJ. Epidemiology, clinical manifestations, and diagnosis of psoriasis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Sept]. Available from: http://www.utdol.com/utd/index.do.
10. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009 Apr;60(4):643-59.
11. British Association of Dermatologists & Primary Care Dermatology Society. Recommendations for the initial management of psoriasis. Available at: http://www.eguidelines.co.uk/eguidelinesmain/guidelines/summaries/skin/bad_pcds_psoriasis.php?page=3. Accessed September 2013.
12. Finnish Medical Society Duodecim. "Seborrheic dermatitis." In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007 Apr 19 [Various].
13. Sterling JC, Handfield-Jones S, Hudson PM; British Association of Dermatologists. Guidelines for the management of cutaneous warts. Br J Dermatol. 2001;144(1):4-11.
14. Carroll CL, Clarke J, Camacho F, et al. Topical tacrolimus ointment combined with 6% salicylic acid gel for plaque psoriasis treatment. Arch Dermatol 2005;141:43-6.
15. Ademola J, Frazier C, Kim SJ, et al. Clinical evaluation of 40% urea and 12% ammonium lactate in the treatment of xerosis. Am J Clin Dermatol. 2002;3:217-22.
16. Goldstein JA, Gurge RM. Treatment of hyperkeratosis with Kerafoam emollient foam (30% urea) to assess effectiveness and safety within a clinical setting: a case study report. J Drugs Dermatol. 2008;7:159-62.
17. Kwok CS, Holland R and Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. British Association of Dermatologists. 2011;165:233-46.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Keratoplastic Agents
AHFS Class 843200
February 12, 2014

I. Overview

As of October 1, 2013, Alabama Medicaid no longer covers over-the-counter (OTC) medications for adults and children. The only exceptions are insulin, 2nd generation antihistamines, and specialized nutritional products. Currently there are no prescription medications classified by American Hospital Formulary Service (AHFS) as keratoplastic agents.

II. Conclusions

There are no prescription medications available in the keratoplastic agents class (AHFS Class 843200).

III. Recommendations

No brand skin and mucous membrane keratoplastic agent is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 843200 in the Preferred Drug List (PDL) screening process. If new prescription keratoplastic agents are added, it is recommended that this class be re-reviewed.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Agents, Miscellaneous
AHFS Class 849200
February 14, 2014

I. Overview

The miscellaneous skin and mucous membrane class includes a diverse group of products used to treat many skin conditions, including actinic keratoses, atopic dermatitis, basal cell carcinoma, cutaneous T-cell lymphoma, Kaposi's sarcoma, mucositis, pain associated with anal fissure, postherpetic neuralgia, psoriasis, warts and wounds.[1-29] The wide variety of products, as well as the range of Food and Drug Administration (FDA)-approved indications, makes direct comparisons difficult. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous skin and mucous membrane agents.

Acitretin, alitretinoin, bexarotene and tazarotene bind to retinoid receptors, which controls cellular differentiation and proliferation.[3,4,6,,28] Becaplermin promotes the chemotactic recruitment and proliferation of cells involved in wound repair.[5] Calcipotriene and calcitriol are vitamin D analogs, which regulate skin cell production and proliferation.[7-10] Capsaicin is a transient receptor potential vanilloid 1(TRPV1) receptor agonist. Topical administration provides pain relief, which is thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings.[11] Collagenase can digest collagen in necrotic tissue, which contributes to the formation of granulation tissue and epithelialization.[12] Diclofenac reversibly inhibits cyclooxygenase-1 and 2 enzymes, which result in decreased formation of prostaglandin precursors.[12] Fluorouracil is an antineoplastic antimetabolite that interferes with synthesis of deoxyribonucleic acid (DNA), and to a lesser extent, inhibits the formation of ribonucleic acid (RNA).[14-16] Imiquimod is an immune response modifier, which induces cytokines, including interferon-alpha and others.[18,19] Ingenol mebutate induces cell death of actinic keratosis; however, the exact mechanism of action is unknow.[20] Mucositis, stomatitis combination adheres to the mucosal surface of the mouth and forms a protective coating over irritate areas and lesions.[21] Nitroglycerin stimulates guanylate cyclase causing an increase in cyclic guanosine 3'5' monophosphate, regulating the contractile state in smooth muscle and leading to vasodilation and analgesia.[22] Pimecrolimus and tacrolimus bind to the intracellular protein FKBP-12, inhibiting calcineurin, which blocks cytokine transcription and inhibits T-cell activation.[23,27] Podophyllin resin is a cytotoxic agent that arrests mitosis in metaphase.[25] Podofilox is an active component of podophyllin resin.[24] Sinecatechins is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis (L.) O Kuntze* and is a mixture of catechins and other green tea components. The mechanism of action of sinecatechins for the treatment of anogenital warts is unknown.[26] The thrombin/fibrinogen/aprotinin/calcium chloride product is a two-component fibrin sealant made from pooled human plasma, which mimics the final stage of the blood coagulation cascade.[29]

The miscellaneous skin and mucous membrane agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Acitretin, calcipotriene, calcitriol, fluorouracil, imiquimod and podofilox are available in a generic formulation. This class was last reviewed in November 2011.

Table 1. Skin and Mucous Membrane Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Acitretin	oral capsule	Soriatane®*	acitretin
Alitretinoin	gel	Panretin®	none
Becaplermin	gel	Regranex®	none
Bexarotene	gel	Targretin®	none
Calcipotriene	cream, foam, ointment, solution	Dovonex®*, Sorilux®	calcipotriene
Calcitriol	ointment	Vectical®*	calcitriol
Collagenase	ointment	Santyl®	none
Diclofenac	gel	Solaraze®	none
Fluorouracil	cream, solution	Carac®, Efudex®*	fluorouracil

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Formaldehyde	solution	N/A	formaldehyde
Imiquimod	cream	Aldara®*, Zyclara®	imiquimod
Ingenol mebutate	gel	Picato®	none
Nitroglycerin	ointment	Rectiv®	none
Pimecrolimus	cream	Elidel®	none
Podofilox	gel, solution	Condylox®*	podofilox
Podophyllum resin	liquid	Podocon-25®	none
Sinecatechins	ointment	Veregen®	none
Tacrolimus	ointment	Protopic®	none
Tazarotene	cream, gel	Tazorac®	none
Combination Products			
Calcipotriene and betamethasone	ointment, suspension	Taclonex®	none
Capsaicin and skin cleanser	kit	Qutenza®	none
Mucositis, stomatitis combination	wafer	Mucotrol®	none
Thrombin, fibrinogen, aprotinin, and calcium chloride	kit, syringe	Artiss®, Artiss® Duploject	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous skin and mucous membrane agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Agents, Miscellaneous

Clinical Guideline	Recommendation(s)
British Association of Dermatologists: **Guidelines for the Management of Actinic Keratoses[30] (2007)**	General considerations • When treatment is warranted, cryosurgery or one of the many topical therapies can be employed taking into consideration the specifics of the situation. • If there is diagnostic concern or failure to respond to first-line treatment, a histological specimen, such as obtained at curettage with cautery or formal excision, may be both diagnostic and curative. • Where actinic keratoses are multiple or confluent, at sites of poor healing or with poor response to standard therapies, photodynamic therapy may be helpful. Treatment recommendations • No therapy, or emollient, is a reasonable option for mild actinic keratoses. • Sun block applied twice daily for seven months may protect against development of actinic keratoses. • 5-Fluorouracil cream used twice daily for six weeks is effective for up to 12 months in clearance of the majority of actinic keratoses. Due to side-effects of soreness, less aggressive regimens are often used, which may be effective, but have not been fully evaluated. • Diclofenac gel has moderate efficacy with low morbidity in mild actinic keratoses. There are few follow-up data to indicate the duration of benefit. • Imiquimod 5% cream has been demonstrated to be effective over a 16-week course of treatment but only eight weeks of follow up. It has similar side effects as 5-fluorouracil. • Topical tretinoin has some efficacy on the face, but may need to be used for up

Clinical Guideline	Recommendation(s)
	to a year at a time to optimize benefit. • Cryosurgery is effective for up to 75% of lesions in trials comparing it with photodynamic therapy. It may be particularly superior for thicker lesions, but may leave scars. • Photodynamic therapy is effective in up to 91% of actinic keratoses in trials comparing it with cryotherapy, with consistently good cosmetic result. It may be particularly good for superficial and confluent actinic keratoses. It is of particular value where actinic keratoses are numerous or when located at sites of poor healing such as the lower leg. • There are no studies of curettage or excisional surgery, but both are of value in determining the exact histological nature of proliferative or atypical actinic keratoses unresponsive to other therapies, where invasive squamous cell carcinoma is possible.
Scottish Intercollegiate Guidelines Network: **Management of Atopic Eczema in Primary Care[31] (2011)**	Emollient therapy • Patients with atopic eczema should receive ongoing treatment with emollients. Topical corticosteroid therapy • Patients should continue with emollient therapy during treatment with topical corticosteroids. • Patients with atopic eczema should be advised to apply topical corticosteroids once daily. • Twice weekly maintenance therapy with a topical corticosteroid should be considered in patients with moderate to severe atopic eczema experiencing frequent relapses. • There is no good quality evidence to assist in the choice of topical corticosteroid potency in the treatment of atopic eczema. • The choice of topical corticosteroid potency should be tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed. For delicate areas of skin, such as the face and flexures, only mild or moderately potent preparations should be used. On the face, especially in children, it is reasonable to start with a mildly potent topical corticosteroid. • Topical corticosteroids should be used with caution in the periocular region. Topical calcineurin inhibitors • Tacrolimus should be considered for short-term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids, or if there is a serious risk of important adverse effects from further topical corticosteroid use (e.g., skin atrophy). • Topical calcineurin inhibitors should not be applied to skin which appears actively infected. • Due to long-term safety issues, topical calcineurin inhibitors should not be used as first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Antihistamines • Short-term bedtime use of sedating antihistamines should be considered in patients with atopic eczema when there is sleep disturbance.
Primary Care Dermatology Society/British Association of Dermatologists: **Guidelines for the Management of Atopic Eczema[32]**	Emollients • Most patients have dry skin and require the general use of emollients. • Emollients should be applied as liberally and frequently as possible. They are best applied when the skin is moist but they can and should be applied at other times as well. Emollients should be applied every four hours or at least three to four times per day. • Continual treatment with complete emollient therapy (combinations of cream, ointment, bath oil and emollient soap substitute) will help provide maximal

Clinical Guideline	Recommendation(s)
(2009)	effect. • Intensive use of emollients will reduce the need for topical steroids. <u>Topical steroids</u> • Topical steroids provide symptomatic relief and are safe in the short term. • The potency should be matched to the disease severity and the affected site. Weaker corticosteroids should be used on the face and flexures. • The weakest steroid that controls the disease effectively should be chosen. • Steroid use should be limited to a few days to a week for acute eczema and up to four to six weeks to gain initial remission for chronic eczema. • Very potent corticosteroids may rarely be indicated in resistant severe eczema on the hands and feet of adults. • Patients using moderate and potent steroids must be kept under review for both local and systemic side-effects, including the use of growth charts for children. • Topical steroids should not be used to provide an emollient effect. Emollients should not be applied shortly after application of a topical steroid. <u>Immunomodulatory treatments</u> • Immunomodulatory agents (e.g., tacrolimus or pimecrolimus) are an alternative to topical steroids. • They should only be considered if the patient is intolerant to or has failed with conventional corticosteroid therapy. • They do not cause skin atrophy. • The long-term adverse effects of tacrolimus and pimecrolimus are unknown. • Treatment with tacrolimus or pimecrolimus should be initiated only by physicians with experience in dermatology, after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options. <u>Other treatments</u> • Sedating antihistamines may be used to reduce pruritus. Non-sedating antihistamines have very limited benefit. • Third-line treatments include phototherapy and various immunosuppressive agents.
European Academy of Dermatology and Venereology: **Position Paper on Diagnosis and Treatment of Atopic Dermatitis[33] (2009)**	• Topical corticosteroids are a first-line anti-inflammatory therapy. Application two to three times monthly with emollients should suffice in mild disease. • Topical calcineurin inhibitors have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Tacrolimus 0.1% ointment is similar to an intermediately potent topical corticosteroid and an intermediately potent topical corticosteroid is more active than pimecrolimus 1% cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and pre-clinical data do not indicate an increased risk for photo carcinogenicity, though ultraviolet protection is advised. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma over a period of six years or photo carcinogenicity for topical calcineurin inhibitors. But since the continuous oral administration of the cyclosporine is associated with an increased photo carcinogenicity risk in solid organ transplant patients, ultraviolet protection e.g. with sunscreens has been advised.
National Institute for Health and Clinical	<u>General considerations</u> • A stepped approach should be used for managing atopic eczema in children.

Clinical Guideline	Recommendation(s)

Excellence:
Management of Atopic Eczema in Children From Birth Up to the Age of 12 Years[34]
(2007)
	Treatment should be tailored based on the severity of the atopic eczema.
	• Emollients should always be used, even when the atopic eczema is clear. Treatment can be stepped up or down, according to the severity of symptoms, with the addition of the other treatments as necessary as follows:
	  o Mild atopic eczema: emollients and mild potency topical corticosteroids.
	  o Moderate atopic eczema: emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages.
	  o Severe atopic eczema: emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy.
	
	<u>Emollients</u>
	• Emollients should be used on the whole body when the atopic eczema is clear and while using all other treatments.
	
	<u>Topical corticosteroids</u>
	• Use mild potency topical corticosteroids on the face and neck, except for short-term (three to five days) use of moderate potency agents for severe flares.
	• Use moderate or potent topical corticosteroids for short periods only (seven to 14 days) for flares in sites such as axillae and groin.
	• Do not use very potent preparations in children without specialist dermatological advice.
	• Topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily.
	• In children ≥12 months of age, potent topical corticosteroids should be used for the shortest amount of time as possible; no longer than 14 days. They should not be used on the face or neck. Potent topical corticosteroids should not be used in children <12 months of age without specialist dermatological supervision.
	• Consider treating problem areas with topical corticosteroids for two consecutive days per week to prevent flares, rather than treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled.
	• A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected.
	
	<u>Topical calcineurin inhibitors</u>
	• Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.
	• Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
	• Pimecrolimus is recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged two to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
	• Treatment with tacrolimus or pimecrolimus should only be initiated by physicians (including general practitioners) with a special interest and experience in dermatology.
	• For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical

Clinical Guideline	Recommendation(s)
	calcineurin inhibitors. Antihistamines • Oral antihistamines should not be used routinely in the management of atopic eczema in children. • A one-month trial of a nonsedating antihistamine should be offered to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every three months. • A seven to 14 day trial of an age-appropriate sedating antihistamine should be offered to children aged six months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful. Phototherapy and systemic treatments • Phototherapy or systemic treatments should be considered for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life.
American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma and Immunology/Joint Council on Allergy, Asthma and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter[35] (2012)**	General considerations • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. Skin hydration • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. Topical corticosteroids • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. Topical calcineurin inhibitors • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and

Clinical Guideline	Recommendation(s)
	skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. Tar preparations • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. Antihistamines • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. Vitamin D • Patients with atomic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. Dilute bleach baths • The addition of dilute bleach baths twice weekly may reduce the severity of atomic dermatitis, especially in patients with recurrent skin infections. Microbes • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atomic dermatitis, and patients with moderate-to-severe atomic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atomic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atomic dermatitis and might contribute to exacerbations. Systemic Immunomodulating Agents • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. Phototherapy • Ultraviolet therapy can be a useful treatment for recalcitrant atomic dermatitis.

Clinical Guideline	Recommendation(s)
	Allergen immunotherapy • Select patients with atomic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for Atopic Dermatitis[36] (2004)**	Topical agents • Topical corticosteroids are the standard of care for the treatment of atopic dermatitis. • Cutaneous complications such as striae, atrophy, and telangiectasia limit the long-term use of these agents. • Despite the extensive use of topical corticosteroids, there are limited data regarding optimal corticosteroid concentrations, duration and frequency of therapy, and quantity of application; similarly, data supporting the perception that long-term corticosteroid use is not associated with extracutaneous adverse effects are lacking. • Altering the local environment by hydration and/or occlusion as well as varying the vehicle can impact the absorption and effect of the topical corticosteroid administered. • The use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies. • Emollients are a standard of care, steroid-sparing, and useful for prevention and maintenance therapy. • Pimecrolimus and tacrolimus have been shown to reduce the extent, severity, and symptoms of atopic dermatitis in adults and children. • Tar may be associated with therapeutic benefits, but is limited by compliance. • Short-term adjunctive use of topical doxepin may reduce pruritus, but adverse events may limit its usefulness. Antibiotics and antiseptics • Patients with atopic dermatitis are commonly colonized with *Staphylococcus aureus*. Systemic and topical antibiotics temporarily reduce *Staphylococcus aureus* colonization on the skin. • Topical antibiotics can be effective when infection is present; however, development of resistance is a concern. Oral antihistamines • For patients with significant sleep disruption due to itch, allergic dermatographism, or allergic rhinoconjunctivitis, sedating antihistamines may be useful. • Many patients with atopic dermatitis may also have allergic rhinoconjunctivitis, urticaria, and dermatographism and may benefit from the use of antihistamines.
National Comprehensive Cancer Network: **Basal Cell and Squamous Cell Skin Cancers[37] (2013)**	Actinic keratoses • Actinic keratoses should be treated aggressively at first development. • Accepted treatment modalities include cryosurgery, topical 5-fluorouracil, topical imiquimod, photodynamic therapy, and curettage and electrodessication. • Other modalities that may be considered include topical diclofenac chemical peel (trichloroacetic acid) and ablative skin resurfacing. • Actinic keratoses are most commonly treated with cryotherapy, or topical treatment with 5-fluorouracil or imiquimod. Basal cell carcinoma • The goal of primary treatment of basal cell skin cancer is the cure of the tumor and the maximal preservation of function and cosmesis. • Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, and patient preference may lead to choosing radiation therapy as primary treatment in order

Clinical Guideline	Recommendation(s)
	to achieve optimal overall results. • In patients with low-risk superficial basal cell skin cancer, where surgery or radiation is contraindicated or impractical, topical therapies such as 5-fluorouracil, imiquimod, photodynamic therapy (e.g., porfimer sodium, topical amino levulinic acid) or vigorous cryotherapy may be considered, even though cure rate may be lower.
British Association of Dermatologists: **Guidelines for the Management of Basal Cell Carcinoma[38] (2008)**	General considerations • The goal of treatment is to eradicate the tumor in a manner likely to result in a cosmetic outcome that will be acceptable to the patient. • Cryosurgery, curettage, radiotherapy and photodynamic therapy are generally used to treat low-risk tumors, although radiotherapy also has an important role in the management of high-risk basal cell carcinoma. • Surgical excision is widely used to treat both low- and high-risk basal cell carcinoma, and is generally considered to have the lowest overall failure rate in basal cell carcinoma treatment. • There are few randomized controlled studies comparing different skin cancer treatments, and much of the published literature on the treatment of basal cell carcinoma consists of open studies, some with low patient numbers and relatively short follow-up periods. Evidence level • Mohs micrographic surgery is a good treatment for high-risk primary basal cell carcinoma and recurrent basal cell carcinoma. • Curettage and cautery is a good treatment for low-risk basal cell carcinoma. It is a poor treatment for high-risk primary basal cell carcinoma and recurrent basal cell carcinoma. • Topical imiquimod appears effective in the treatment of primary small superficial basal cell carcinoma. It may possibly have a role in the treatment of primary nodular basal cell carcinoma. • Photodynamic therapy is a good treatment for primary superficial basal cell carcinoma. It is a reasonable treatment for primary low-risk nodular basal cell carcinoma. • Radiotherapy is a good treatment for primary basal cell carcinoma and recurrent basal cell carcinoma.
National Comprehensive Cancer Network: **Non-Hodgkin's Lymphomas[39] (2013)**	Cutaneous T-cell lymphomas • Initial treatment in patients with patch/plaque disease consists of skin-directed therapies (localized or generalized), with the addition of systemic biologic therapy for refractory or progressive disease. • Patients with unfavorable prognostic factors may have systemic biologic therapies introduced earlier in the treatment algorithm. • Patients, who do not respond to biologic therapy, or those with very aggressive or extracutaneous disease, may be treated with chemotherapy. • Localized skin-directed treatments include topical therapy with corticosteroids, mechlorethamine hydrochloride, carmustine, topical bexarotene or topical imiquimod. • Topical corticosteroids are effective especially for the treatment of patch-stage mycosis fungoides, producing a cure rate of >90%. However, long-term use of topical steroids may lead to skin atrophy or striae formation and the risk worsens with increased potency of the steroid. • Topical chemotherapy with nitrogen mustard or carmustine has been used for the management of mycosis fungoides for many decades. • Synthetic retinoids (bexarotene and tazarotene) and imiquimod have been used as topical therapy for the treatment of patients with mycosis fungoides and Sézary syndrome. Only bexarotene is approved for topical therapy in patients with mycosis fungoides and Sézary syndrome.

Clinical Guideline	Recommendation(s)
	• Patients with minimal stage IA mycosis fungoides may be managed effectively with local superficial radiotherapy without adjuvant therapy. • Generalized skin-directed therapies (phototherapy) and total skin electronic beam therapy are indicated in patients with widespread skin involvement. • Phototherapy with ultraviolet B and photochemotherapy with psoralen and ultraviolet A are effective alternative treatment options for patients with early stage mycosis fungoides. • Systemic therapies with extracorporeal photopheresis, interferons, systemic retinoids, denileukin diftitox or vorinostat are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies. • Patients with Stage IA have an excellent prognosis using skin-directed therapies alone. Treatment options include topical corticosteroids, nitrogen mustard or carmustine, topical retinoids (bexarotene or tazarotene), topical imiquimod, phototherapy with ultraviolet B for patch or thin plaques or psoralen combined with ultraviolet A for thicker plaques. • Patients with Stage IB-IIA disease require generalized skin treatment. Topical retinoids are not recommended for generalized skin involvement since they can cause a lot of irritation.
British Association of Dermatologists/United Kingdom Cutaneous Lymphoma Group: **Guidelines for the Management of Primary Cutaneous T-Cell Lymphomas[40] (2003)**	• Skin-directed therapy (topical therapy, superficial radiotherapy and phototherapy) is appropriate treatment for patients with early stages of mycosis fungoides (stages IA–IIA) with the choice of therapy dependent on the extent of cutaneous disease and plaque thickness. • Combined psoralen combined with ultraviolet A and a-interferon therapy can be effective for patients with resistant early-stage disease (stage IB–IIA). • Patients with later stages of mycosis fungoides (stage IIB or higher) will require some form of systemic therapy. • New agents such as bexarotene offer important therapeutic alternatives which are currently being evaluated.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain[41] (2010)**	<u>Postherpetic neuralgia</u> • Tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line therapy of postherpetic neuralgia. • Topical lidocaine may be considered as first-line therapy in the elderly, especially if there are concerns regarding the central nervous system side effects of oral medications. A two to four week trial is recommended before starting other therapy. • Strong opioids and capsaicin cream are recommended as second-line therapy. • Capsaicin patches are promising, but the long-term effects of repeated applications particularly on sensation are not clarified.

National Institute for Health and Clinical Excellence: **Pharmacological Management of Neuropathic Pain in Adults in Non-Specialist Settings[42] (2010)**	• When selecting pharmacological treatments, take into account:
	  ○ Adverse effects.
	  ○ Safety considerations and contraindications.
	  ○ Patient preference.
	  ○ Lifestyle factors (such as occupation).
	  ○ Mental health problems (such as depression and/or anxiety).
	  ○ Concomitant medications.
	• Amitriptyline or pregabalin are recommended as first-line therapy.
	• For patients with painful diabetic neuropathy, duloxetine is recommended as first-line therapy. If duloxetine is contraindicated, oral amitriptyline is an alternative agent.
	• If pain reduction is not achieved with first-line treatment, switching to another agent or use of combination therapy should be considered.
	  ○ If first-line treatment was with amitriptyline (or imipramine or nortriptyline), switch to or combine with oral pregabalin.
	  ○ If first-line treatment was with pregabalin, switch to or combine with oral amitriptyline (or imipramine or nortriptyline).

Clinical Guideline	Recommendation(s)

	• For patients with painful diabetic neuropathy:
	  ○ If first-line treatment was with duloxetine, switch to amitriptyline or pregabalin, or combine with pregabalin.
	  ○ If first-line treatment was with amitriptyline, switch to or combine with pregabalin.
	• If satisfactory pain reduction is not achieved with second-line treatment:
	  ○ Consider tramadol as third-line treatment instead of or in combination with the second-line treatment.
	  ○ Consider topical lidocaine for treatment of localized pain for people who are unable to take oral medication because of medical conditions and/or disability.
	  ○ Do not start treatment with opioids other than tramadol without an assessment by a specialist pain service.

International Association for the Study of Pain: **Pharmacologic Management of Neuropathic Pain: Evidence-Based Recommendations[43] (2010)**	<u>General treatment considerations</u>
	• Medication selection should be individualized, considering side effects, comorbidities, and onset of pain relief.
	• Recommended first-line treatments include tricyclic antidepressants (nortriptyline, desipramine) and selective serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine), calcium channel α2-δ ligand (gabapentin and pregabalin), and topical lidocaine.
	• Opioid analgesics and tramadol are recommended as second-line treatments that can be considered for first-line use in select clinical circumstances.
	• Other medications that would be used as third-line treatments include certain antiepileptic (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine, N-methyl-D-aspartate receptor antagonists, and topical capsaicin.
	
	<u>Stepwise pharmacologic management of neuropathic pain</u>
	Step 1:
	• Assess pain and establish the diagnosis of neuropathic pain.
	• Establish and treat the cause of neuropathic pain.
	• Identify comorbidities that might be relieved or exacerbated by neuropathic pain treatment, or that might require dosage adjustment or additional monitoring of therapy.
	Step 2:
	• Initiate therapy of the disease causing neuropathic pain, if applicable.
	• Initiate symptom treatment with one or more of the following:
	  ○ Tricyclic antidepressant (nortriptyline, desipramine) or a selective serotonin and norepinephrine reuptake inhibitor (duloxetine, venlafaxine).
	  ○ Calcium channel α2-δ ligand (gabapentin or pregabalin).
	  ○ Topical lidocaine used alone or in combination with one of the other first-line therapies for patients with localized peripheral neuropathic pain.
	  ○ Opioid analgesics or tramadol alone or in combination with one of the first-line therapies for patients with acute neuropathic pain, neuropathic cancer pain, or exacerbations of severe pain.
	Step 3:
	• Reassess pain and quality of life frequently.
	• If substantial pain relief (average pain reduced to ≤3/10) and tolerable side effects, continue treatment.
	• If partial pain relief (average pain remains ≥4/10) after an adequate trial, add one of the other first-line medications.
	• If no or inadequate pain relief (<30% reduction) at target dosage after an adequate trial, switch to an alternative first-line medication.

Clinical Guideline	Recommendation(s)
	Step 4: • If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center.
Infectious Diseases Society of America: **Recommendations for the Management of Herpes Zoster[44] (2007)**	• Antiviral therapy does not prevent postherpetic neuralgia in all patients. • The combination of antiviral therapy with effective relief of acute pain may lessen the risk of postherpetic neuralgia beyond that achieved with antiviral therapy alone. • Effective relief of acute pain is a desirable treatment goal. The choice of therapy depends on pain severity, comorbidities, and prior response to therapy. • Patients with mild to moderate pain may be managed with acetaminophen or non-steroidal antiinflammatory drugs, alone or in combination with a weak opioid analgesic or tramadol. • For pain that is moderate to severe in intensity, treatment with a strong opioid analgesic is recommended. • If moderate to severe pain has not responded to treatment with an opioid analgesic, the addition of one of the following three classes of oral medications in combination with the opioid analgesic should be considered: (1) gabapentin or pregabalin; (2) tri-cyclic antidepressants, especially nortriptyline; or (3) corticosteroids (e.g., prednisone), if there are no contraindications. • For patients with moderate or severe pain who are unable to tolerate an opioid analgesic, treatment with these three classes of medications, alone and in combination, can be considered. • Although topical capsaicin may have benefit in some patients with postherpetic neuralgia, there is no basis for its use in patients with herpes zoster, in whom it can be expected to exacerbate pain.
American Academy of Neurology: **Treatment of Postherpetic Neuralgia[45] (2004)**	• Tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of postherpetic neuralgia. • Aspirin in cream is possibly effective in the relief of pain in patients with postherpetic neuralgia but the magnitude of benefit is low, as is seen with capsaicin.

British Association of Dermatologists: **Guidelines on the Efficacy and Use of Acitretin in Dermatology[46] (2010)**	<u>In which conditions should acitretin be used?</u>
	• Severe psoriasis, or psoriasis with severe effects on quality of life, meriting systemic therapy, which is resistant to topical therapy, phototherapy or is unsuitable for these treatments.
	  ○ Acitretin is recommended as a combination with psoralen combined with ultraviolet A therapy or narrowband phototherapy.
	  ○ Acitretin is recommended with hydroxycarbamide.
	  ○ Acitretin is recommended in combination with calcipotriol ointment.
	  ○ The following combinations are not recommended: 1) acitretin with cyclosporine; and 2) acitretin with methotrexate.
	• Palmoplantar pustular psoriasis.
	• Hyperkeratotic hand eczema.
	• Severe Darier disease (keratosis follicularis).
	• Severe congenital ichthyosis.
	• Keratoderma.
	• There is evidence that patients with lichen planus benefit from acitretin.

American Academy of Dermatology: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapies[47]**	• Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. • Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences.

Clinical Guideline	Recommendation(s)
(2009)	• Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include vitamin D analogs, tazarotene, tacrolimus, pimecrolimus, nonmedicated topical moisturizers, salicylic acid, anthralin, coal tar and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific Food and Drug Administration (FDA)-approved indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid; however, the agent is typically used in combination with other topical therapies. • Coal tar products are often poorly tolerated by patients because of cosmetic issues, including staining of clothes and the tar odor that is present in almost all products. • Coal tar is carcinogenic in animals; however, in humans there are no convincing data proving carcinogenicity, and epidemiologic studies fail to show increased risk of skin cancer in patients who use coal tar.

British Association of Dermatologists/Primary Care Dermatology Society: **Recommendations for the Initial Management of Psoriasis[48] (2009)**	• Emollients should be used to soften scaling and reduce any irritation.
	• For localized plaque psoriasis (e.g., on the elbows or knees), one or more of the following topical preparations can be tried. The sequence of choice will vary according to the extent and pattern of psoriasis, and patient preference:
	  o A tar-based cream, or a tar/corticosteroid mixture.
	  o A moderate potency topical corticosteroid (e.g. 0.05% clobetasone butyrate); stronger agents can be used on palms and soles or on the scalp (use of topical steroids may lead to rebound exacerbation when treatment is discontinued).
	  o A vitamin D analog (e.g.; calcipotriol, calcitriol or tacalcitol). The latter two tend to be less irritant and are more suitable for face or flexures, but should still be used with caution.
	  o Calcipotriol with betamethasone dipropionate as a combination product (long-term data regarding relapse rates is not yet established).
	  o A vitamin A analog (tazarotene).
	  o A dithranol preparation, usually used as a short-contact treatment (these are effective but more difficult to use, especially if there are many small lesions).
	• For more widespread plaque psoriasis (e.g., on the trunk or the limbs), the same treatments may be appropriate.
	  o Dithranol is often impracticable to apply to multiple small lesions and will irritate flexures.
	  o Topical corticosteroids may be inappropriate for use in widespread psoriasis, particularly more potent agents if used on a long-term basis.
	• For scalp psoriasis, a tar-based shampoo should be tried first. This can be combined with salicylic acid (2 to 5% preparation), a coconut oil/tar/salicylic acid combination ointment, a potent topical corticosteroid preparation (e.g., 0.1% betamethasone valerate), calcipotriol scalp application, or more than one of these.
	• In palm and sole psoriasis, both hyperkeratosis and inflammation are usually present and may require separate treatments. Hyperkeratosis usually needs to be treated with a keratolytic agent. Topical steroids (usually potent, due to the thick skin at this site), tars and vitamin D analogs may all be useful.
	• In general, milder agents are used for flexures. These include low potency topical steroids, mild tar preparations, and tacalcitol or calcitriol (not calcipotriol, this is usually irritant in flexures).
	• In facial psoriasis, use mild agents: emollients, mild corticosteroids, calcitriol, tacalcitol, mild tars.

Centers for Disease	Genital herpes

Clinical Guideline	Recommendation(s)
Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines[49] (2010)**	• Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir 200 mg orally five times daily for seven to 10 days, famciclovir 250 mg orally three times daily for seven to 10 days or valacyclovir 1,000 mg orally twice daily for seven to 10 days. Treatment can be extended if healing is incomplete after 10 days of therapy. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • The safety and efficacy of suppressive therapy have been documented among patients receiving daily therapy with acyclovir for as long as six years and with famciclovir or valacyclovir for one year. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy. • Recommended regimens for suppressive therapy of genital herpes include acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily, valacyclovir 500 mg orally once daily or valacyclovir 1,000 mg orally once daily. • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms being. • Recommended regimens for episodic treatment of genital herpes include acyclovir 400 mg orally three times daily for five days, acyclovir 800 mg orally twice daily for five days, acyclovir 800 mg orally three times daily for two days,

Clinical Guideline	Recommendation(s)

	famciclovir 125 mg orally twice daily for five days, famciclovir 1,000 mg orally twice daily for one day, famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days, valacyclovir 500 mg orally twice daily for three days or valacyclovir 1,000 mg orally once daily for five days.
	• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.
	• The sex partners of patients who have genital herpes can benefit from evaluation and counseling.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with human immunodeficiency virus (HIV) include acyclovir 400 to 800 mg orally twice daily, famciclovir 500 mg orally twice daily or valacyclovir 500 mg orally twice daily.
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV include acyclovir 400 mg orally three times daily for five to 10 days, famciclovir 500 mg orally twice daily for five to 10 days or valacyclovir 1,000 mg orally twice daily for five to 10 days.
	• The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established.
	• Infants exposed to HSV during birth should be followed carefully in consultation with a pediatric infectious disease specialist.
	
	<u>Pediculosis pubis (pubic lice infestation)</u>
	• Recommended regimens:
	  o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  o Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  o Ivermectin 250 µg/kg orally and repeated in two weeks.
	
	<u>Scabies</u>
	• Recommended regimens:
	  o Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  o Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Alternative regimens:
	  o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	
	<u>Bacterial vaginosis</u>
	• Recommended regimens for nonpregnant women include:
	  o Metronidazole 500 mg orally twice a day for seven days.
	  o Metronidazole 0.75% gel 5 g intravaginally for five days.
	  o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.
	• Alternative regimens for nonpregnant women include:
	  o Tinidazole 2 g orally once daily for two days.
	  o Tinidazole 1 g orally once daily for five days.
	  o Clindamycin 300 mg orally twice daily for seven days.
	  o Clindamycin 100 mg ovules intravaginally once at bedtime for three days.
	• Additional regimens include metronidazole (750 mg extended-release tablets once daily for seven days), or a single dose of clindamycin intravaginal cream,

Clinical Guideline	Recommendation(s)

	although data on these alternative regimens are limited.
	
	<u>Uncomplicated vulvovaginal candidiasis</u>
	• Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women.
	• Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis.
	• The topically applied azole drugs are more effective than nystatin.
	• Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy.
	• Recommended regimens include:
	  ○ Butoconazole 2% cream 5 g intravaginally for three days.
	  ○ Butoconazole 2% cream 5 g single intravaginal application.
	  ○ Clotrimazole 1% cream 5 g intravaginally for seven to 14 days.
	  ○ Clotrimazole 2% cream 5 g intravaginally for three days. Miconazole 2% cream 5 g intravaginally for seven days.
	  ○ Miconazole 4% cream 5 g intravaginally for three days.
	  ○ Miconazole 100 mg vaginal suppository for seven days.
	  ○ Miconazole 200 mg vaginal suppository for three days.
	  ○ Miconazole 1,200 mg vaginal suppository, for one day.
	  ○ Nystatin 100,000-unit vaginal tablet, one tablet for 14 days.
	  ○ Tioconazole 6.5% ointment 5 g single intravaginal application.
	  ○ Terconazole 0.4% cream 5 g intravaginally for seven days.
	  ○ Terconazole 0.8% cream 5 g intravaginally for three days.
	  ○ Terconazole 80 mg vaginal suppository for three days.
	  ○ Fluconazole 150 mg oral tablet in single dose.
	
	<u>Complicated vulvovaginal candidiasis</u>
	• Complicated vulvovaginal candidiasis is defined as recurrent (four or more episodes in one year) or severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with uncontrolled diabetes, debilitation or immunosuppression.
	• Treatment: Each individual episode of recurrent vulvovaginal candidiasis caused by *Candida albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen.
	• Maintenance regimens: Oral fluconazole weekly for six months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.
	
	<u>Severe vulvovaginal candidiasis</u>
	• Severe vulvovaginitis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	<u>Non-albicans vulvovaginal candidiasis</u>
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. Options include longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered

Clinical Guideline	Recommendation(s)

	vaginally once daily for two weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.
	
	<u>Genital warts</u>
	• Treatment of genital warts should be guided by the preference of the patient, the available resources, and the experience of the health-care provider.
	• No definitive evidence suggests that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that influence selection of treatment include wart size, wart number, location of the wart, wart morphology, patient preference, convenience, adverse effects, and provider experience.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens (patient-applied):
	  o Podofilox 0.5% solution or gel.
	  o Imiquimod 5% cream.
	  o Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  o Cryotherapy with liquid nitrogen or cryoprobe.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	  o Surgical removal
	• Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.
	
	<u>Cervical warts</u>
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	
	<u>Vaginal warts</u>
	• Recommended regimens:
	  o Cryotherapy with liquid nitrogen.
	  o Trichloroacetic acid or bichloracetic acid 80 to 90%.
	
	<u>Urethral meatus warts</u>
	• Recommended regimens:
	  o Cryotherapy with liquid nitrogen.
	  o Podophyllin resin 10 to 15% in a compound tincture of benzoin.
	
	<u>Anal warts</u>
	• Recommended regimens:

Clinical Guideline	Recommendation(s)
	○ Cryotherapy with liquid nitrogen. ○ Trichloroacetic acid or bichloracetic acid 80 to 90%. ○ Surgical removal.
British Association for Sexual Health and Human Immunodeficiency Virus: **United Kingdom National Guideline on the Management of Anogenital Warts[50] (2007)**	<u>Genital warts</u> • Treatment choice depends on the morphology, number, and distribution of warts and patient preference. • Treatment decisions should be made after discussing the appropriate options with the patient, taking into account their preference and convenience. • The evidence base to direct first and second line treatments is not strong. • All treatments have significant failure and relapse rates. • Soft non-keratinized warts respond well to podophyllin, podophyllotoxin, and trichloroacetic acid. • Keratinized lesions are better treated with physical ablative methods such as cryotherapy, excision, or electrocautery. • Imiquimod may be suitable for both keratinized and non-keratinized warts. • People with a small number of low volume warts, irrespective of type, are best treated with ablative therapy from the outset. • Podophyllotoxin, for four week cycles, and imiquimod for up to 16 weeks are suitable for home treatment by patients. • No treatment is an option at any site and may apply particularly to warts in the vagina and anal canal. <u>Intravaginal warts</u> • Cryotherapy, electrosurgery and trichloroacetic acid are recommended treatments. <u>Cervical warts</u> • Cryotherapy, electrosurgery, trichloroacetic acid, laser ablation and excision are recommended treatments. <u>Urethral meatus warts</u> • If base of lesions seen, treatment with cryotherapy, electrosurgery, laser ablation, podophyllotoxin or imiquimod. • Lesions deeper in the urethra should be surgically ablated under direct vision. <u>Intra-anal warts</u> • Treatment options include trichloroacetic acid, cryotherapy, electrosurgery, and laser ablation. • There have been anecdotal reports of successful use of intra-anal imiquimod.
British Association of Dermatologists: **Guidelines for the Management of Cutaneous Warts[51] (2001)**	• There is no single treatment that is 100% effective and different types of treatment may be combined. • Salicylic acid alone has been shown to produce clearance in 67% of patients with hand warts and 84% in those with plantar warts in 12 weeks. • There are many commercially available preparations, but there is limited information to enable comparisons to be made between products. • Comparisons between salicylic acid-containing paints, monotherapy with glutaraldehyde, fluorouracil, podophyllin, benzalkonium or liquid nitrogen cryotherapy, failed to find any preparation more effective than salicylic acid.
International Working Group on the Diabetic Foot: **Practical Guidelines on the Management and Prevention of the Diabetic Foot[52]**	<u>Principles of ulcer treatment</u> • Relief of pressure and protection of the ulcer. • Restoration of skin perfusion. • Treatment of infection. • Metabolic control and treatment of comorbidity. • Local wound care.

Clinical Guideline	Recommendation(s)
(2007)	○ Frequent wound inspection. ○ Frequent wound debridement with scalpel. ○ Control of exudate and maintenance of moist environment. ○ Consideration of negative pressure therapy in postoperative wounds. • The following treatments are not established in routine management: ○ Biological active products (collagen, growth factors, bioengineered tissue) in neuropathic ulcers. ○ Systemic hyperbaric oxygen treatment. ○ Silver or other anti-microbial agents containing dressings.
American College of Foot and Ankle Surgeons: **Diabetic Foot Disorders: A Clinical Practice Guideline[53] (2006)**	<u>Debridement</u> • Debridement of necrotic tissue is an integral component in the treatment of chronic wounds since they will not heal in the presence of unviable tissue, debris, or critical colonization. • Enzymatic debridement consists of the application of exogenous proteolytic enzymes manufactured specifically for wound debridement. Various enzymes have been developed, including bacterial collagenase, plant derived papain/urea, fibrinolysin/DNAse, trypsin, streptokinase-streptodornase combination. • Collagenases are enzymes that are isolated from *Clostridium histolyticum*. These display high specificity for the major collagen types (I and II), but they not active against keratin, fat, or fibrin. <u>Moisture balance</u> • Moisture accelerates re-epithelialization in a wound. A moist wound environment promotes granulation and autolytic processes. Effective management of chronic wound fluids is an essential part of wound bed preparation. <u>Inflammation and infection</u> • In chronic wounds, inflammation persists due to recurrent tissue trauma and the presence of contaminants. • The presence of infection must be ascertained and identified as local, ascending, and/or systemic. <u>Advanced wound care modalities</u> • Chronic ulcers have demonstrated benefit from becaplermin, a recombinant DNA platelet-derived growth factor. It has been shown to stimulate chemotaxis and mitogenesis of neutrophils, fibroblasts, monocytes and other components that form the cellular basis of wound healing. • Bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers. • Extracellular matrices (nonliving) are generally derived from devitalized tissue to produce an immunologically inert acellular dermal matrix. <u>Adjunctive modalities</u> • Regenerative tissue matrix is a new therapy used in diabetic foot ulcers. The allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and vascularization. • Hyperbaric oxygen therapy has shown promise in the treatment of diabetic foot wounds with hypoxia severe enough to interfere with healing. • Several ultrasound devices are being used to both debride the wound and provide ultrasonic therapy. • Negative pressure wound therapy has become a common adjunctive treatment modality for diabetic foot ulcerations.

Clinical Guideline	Recommendation(s)
	Pressure relief-off-loading • The reduction of pressure to the diabetic foot ulcer is essential to treatment. Proper off-loading and pressure reduction prevents further trauma and promotes healing.
American Diabetes Association (ADA): **Consensus Development Conference on Diabetic Foot Wound Care**[54] **(1999)**	• Six approaches to the treatment of diabetic ulcers are supported by clinical trials or well-established principles of wound healing and include off-loading, debridement, dressings, management of infection, vascular reconstruction, and amputation. • Becaplermin (recombinant platelet-derived growth factor) for the topical treatment of diabetic foot ulcers shows a modest benefit if used with adequate off-loading, debridement, and control of infection. • Becaplermin is not a substitute for comprehensive wound care.
Multinational association of Supportive Care in Cancer/Society of Oral Oncology: **Mucositis (2013)**[55]	• Oral care protocols are suggested to be used to prevent oral mucositis in all patients. • Thirty minutes of oral cryotherapy is recommended to be using to prevent oral mucositis in patients receive bolus 5-flurouracil chemotherapy. Oral cryotherapy is suggested to be used for prevention of oral mucositis in patients receiving high-dose melphalan with or without total body irradiation as conditioning for hematopoietic stem cell transplantation. • Recombinant human keratinocyte growth factor-1 is recommended to be using to prevent oral mucositis in patients receiving high-dose chemotherapy and total body irradiation followed by autologous stem cell transplantation for al hematological malignancy. • Low-level laser therapy is recommended to prevent oral mucositis in patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy with or without total body irradiation, and suggested in patient undergoing radiotherapy with or without concomitant chemotherapy for head and neck cancer. • Benzydamine mouthwash is recommended to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation without concomitant chemotherapy. • To treat pain due to oral mucositis, patient-controlled analgesia with morphine is recommended in patients undergoing hematopoietic stem cell transplantation; transdermal fentanyl is suggested as may be effective in patient receiving conventional and high-dose chemotherapy, with or without total body irradiation; 2% morphine mouthwash is suggested as may be effective in patients receiving radiation therapy for head and neck cancer; and 0.5% doxepin mouthwash is suggested as may be effective for oral mucositis pain.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous skin and mucous membrane agents are noted in Tables 3 to 5. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs A-F)[1-8,10,12-17]

Indication	Acitretin	Ali-tretinoin	Bexa-rotene	Becaplermin	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	Formaldehyde
Cutaneous Lesions										
Treatment of actinic keratoses								✔		
Treatment of multiple actinic keratoses									✔ *	
Treatment of actinic keratoses of the face and scalp									✔ †	
Treatment of cutaneous lesions in patients with acquired immunodeficiency syndrome-related Kaposi's sarcoma		✔								
Treatment of cutaneous lesions in patients with cutaneous T-cell lymphoma (Stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies			✔							
Superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites									✔ †	
Psoriasis										
Treatment of plaque psoriasis					✔ ‡					

Indication	Acitretin	Ali-tretinoin	Bexa-rotene	Becaplermin	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	Formaldehyde
Treatment of mild to moderate plaque psoriasis						✔				
Treatment of severe psoriasis	✔									
Treatment of moderate to severe psoriasis of the scalp					✔ §					
Treatment of plaque psoriasis of the scalp and body					✔ ‖					
Warts										
Drying agent for pre and post surgical removal of warts or for non-surgical laser removal of warts where dryness is required										✔
Wound Care										
Debriding chronic dermal ulcers and severely burned areas							✔			
Treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply				✔						
Miscellaneous										
Management of oral mucosal pain caused by oral mucositis/stomatitis (resulting from chemotherapy or radiation therapy), irritation due to oral surgery, traumatic ulcers caused by										✔

Indication	Acitretin	Ali-tretinoin	Bexa-rotene	Becaplermin	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	Formaldehyde
braces/ill-fitting dentures or disease, diffuse aphthous ulcers										

*1, 2 and 5% formulations.
†0.5% formulation.
‡Cream/ointment formulations.
§Solution formulation.
‖Foam formulation.

Table 4. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs I-P)[1,2,18-20,22-28]

Indication	Imiquimod	Ingenol mebutate	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum	Sinecatechins	Tacrolimus	Tazarotene
Cutaneous Lesions									
Treatment of actinic keratoses		✔							
Treatment of actinic keratoses of the face and scalp	✔ *†								
Treatment of biopsy-confirmed, superficial basal cell carcinoma with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate	✔ *								
Dermatitis									
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those				✔					

Indication	Imiquimod	Ingenol mebutate	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum	Sinecatechins	Tacrolimus	Tazarotene
treatments are not advisable									
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable								✔	
Warts									
Treatment of external genital and perianal warts	✔ *†								
Removal of soft genital warts						✔			
Treatment of external genital/perianal warts					✔ ‡				
Treatment of external genital warts					✔ §		✔		
Miscellaneous									
Treatment of moderate to severe pain associated with chronic anal fissure			✔						
Treatment of plaque psoriasis									✔ ‖¶
Treatment of acne vulgaris									✔ ¶

*5% formulation.
†3.75% formulation.
‡Gel formulation.
§Solution formulation.
‖0.05% formulation.
¶0.1% formulation.

Table 5. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous Combination Agents[1,2,9,11,21,29]

Indication	Calcipotriene and Betamethasone	Capsaicin and Skin Cleanser	Mucositis, stomatitis Combination	Thrombin, Fibrinogen, Aprotinin and Calcium Chloride
Psoriasis				
Treatment of plaque psoriasis	✔ *			
Treatment of plaque psoriasis of the scalp and body	✔ †			
Wound Care				
To adhere autologous skin grafts to surgically prepared wound beds resulting from burns				✔
To adhere to tissue flaps during rhytidectomy				✔
Miscellaneous				
Management of neuropathic pain associated with postherpetic neuralgia		✔		
Management of oral mucosal pain caused by oral mucositis/stomatitis (resulting from chemotherapy or radiation therapy), irritation due to oral surgery, traumatic ulcers caused by braces/ill-fitting dentures or disease, diffuse aphthous ulcers			✔	

*Ointment formulations.
†Suspension formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous skin and mucous membrane agents are listed in Table 6.

Table 6. Pharmacokinetic Parameters of the Skin and Mucous Membrane Agents, Miscellaneous[1-29]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Acitretin	59	>99	Not reported	Renal (34 to 54) Feces (16 to 53)	49
Alitretinoin	Minimal	Not reported	Liver	Not reported	1 to 3
Becaplermin	Not reported	Not reported	Not reported	Not reported	Not reported
Bexarotene	Minimal	>99	Not reported	Renal (<1)	7
Calcipotriene	Minimal to 6	Not reported	Liver	Not reported	Not reported
Calcitriol	Not reported	Not reported	Kidney	Renal	5 to 8
Capsaicin	Not reported	Not reported	Not reported	Not reported	Not reported
Collagenase	Not reported	Not reported	Not reported	Not reported	Not reported
Diclofenac	6	>99	Liver	Renal	1 to 2
Fluorouracil	Minimal	Not reported	Liver	Renal (7 to 20)	6 to 22 minutes
Formaldehyde	Not reported	Not reported	Not reported	Not reported	Not reported
Imiquimod	Minimal	Not reported	Not reported	Renal (0.08 to 2.41)	20.0 to 24.1
Ingenol mebutate	Not reported	Not reported	Not reported	Not reported	Not reported
Nitroglycerin	0.2	60	Liver	Not reported	1.5 to 7.5 minutes
Pimecrolimus	Minimal	Not reported	Liver	Feces (80)	Not reported
Podofilox	Not reported	Not reported	Not reported	Not reported	1.0 to 4.5 hours
Podophyllum resin	Not reported	Not reported	Not reported	Not reported	Not reported
Sinecatechins	Not reported	Not reported	Not reported	Not reported	Not reported
Tacrolimus	Minimal	99	Liver	Renal, Bile	71 to 112
Tazarotene	2 to 3	99	Liver	Bile	18
Combination Products					
Calcipotriene and betamethasone	Not reported	Not reported	Liver	Not reported	Not reported
Capsaicin and skin cleanser	Not reported	Not reported	Not reported	Not reported	Not reported
Mucositis, stomatitis combination	Not reported	Not reported	Not reported	Not reported	Not reported
Thrombin, fibrinogen, aprotinin, and calcium	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Significant drug interactions with the miscellaneous skin and mucous membrane agents are listed in Table 7.

Table 7. Significant Drug Interactions with the Skin and Mucous Membrane Agents, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Acitretin	1	Oral contraceptives	Use of acitretin with oral contraceptives may interfere with the contraceptive effects

Generic Name(s)	Significance Level	Interaction	Mechanism
			of low-dose progestin contraceptives.
Acitretin	1	Tetracyclines	Concurrent administration may increase the risk for development of pseudotumor cerebri.
Acitretin	1	Methotrexate	Coadministration of these agents may increase the risk of hepatotoxicity.
Bexarotene	1	Disulfiram	The combination may produce acute alcohol intolerance.
Diclofenac	1	Anticoagulants	Coadministration of these agents may increase the risk of bleeding.
Diclofenac	1	Heparin and factor Xa inhibitors	The risk of bleeding may be increased by coadministration of these agents.
Diclofenac	1	Methotrexate	Plasma concentrations and toxic effects of methotrexate may be increased by diclofenac.
Nitroglycerin	1	Phosphodiesterase-5 Inhibitors	Concurrent administration may result in potentiation of hypotensive effects.
Acitretin	2	Vitamin A	Use of acitretin with vitamin A has been reported to increase the risk of toxic effects.
Bexarotene	2	Furazolidine	The combination of bexarotene and furazolidone may produce acute alcohol intolerance.
Bexarotene	2	Metronidazole	The combination of bexarotene and metronidazole may produce acute alcohol intolerance.
Diclofenac	2	Angiotensin converting enzyme inhibitors	The antihypertensive effects of may be decreased by diclofenac.
Diclofenac	2	Antiplatelet agents	Use of diclofenac with antiplatelet agents may increase the risk of bleeding.
Diclofenac	2	Direct thrombin inhibitors	Coadministration of these agents may increase the risk of bleeding.
Diclofenac	2	Nucleotide reverse transcriptase inhibitors	Pharmacologic and toxic effects of nucleotide reverse transcriptase inhibitors may be increased by diclofenac. Increased nephrotoxicity may result.
Diclofenac	2	Serotonin reuptake blockers	Toxic effects may be increased with coadministration of diclofenac and serotonin reuptake blockers.
Diclofenac	2	Aspirin	Regular use of diclofenac may decrease the antiplatelet effects of aspirin.
Diclofenac	2	Cyclosporine	Coadministration of these agents may increase the risk of renal impairment.
Diclofenac	2	Lithium	Pharmacologic effects of lithium may be increased by diclofenac.
Diclofenac	2	Probenecid	Pharmacologic and toxic effects of diclofenac may be increased by Probenecid.
Diclofenac	2	Quinolones	Risk of central nervous system stimulation and seizures from quinolones may be increased by the addition of diclofenac.
Nitroglycerin	2	Ergotamine	Nitroglycerin decreases first-pass metabolism of ergotamine.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous skin and mucous membrane agents are listed in Tables 8 to 10. The boxed warnings for the miscellaneous skin and mucous membrane agents are listed in Tables 11 to 13.

Table 8. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs A-F)[1-8,10,12-17]

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Bexarotene	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	For-maldehyde
Cardiovascular										
Chest pain	<1	-	-	-	-	-	-	1 to 2	-	-
Cyanosis	<1	-	-	-	-	-	-	-	-	-
Flushing	1 to 10	-	-	-	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-	-	1 to 2	-	-
Increased bleeding time	<1	-	-	-	-	-	-	-	-	-
Peripheral ischemia	<1	-	-	-	-	-	-	-	-	-
Central Nervous System										
Abnormal gait	<1	-	-	-	-	-	-	-	-	-
Anxiety	<1	-	-	-	-	-	-	-	-	-
Asthenia	-	-	-	6	-	-	-	-	-	-
Chills	-	-	-	-	-	-	-	1 to 2	-	-
Depression	1 to 10	-	-	-	-	-	-	-	-	-
Dizziness	<1	-	-	-	-	-	-	-	-	-
Emotional upset	-	-	-	-	-	-	-	-	✔	-
Fever	<1	-	-	-	-	-	-	-	-	-
Headache	1 to 10	-	-	14	-	-	-	7	✔	-
Hyperesthesia	-	-	-	-	-	-	-	3	-	-
Hyperkinesia	-	-	-	-	-	-	-	2	-	-
Insomnia	1 to 10	-	-	-	-	-	-	-	✔	-
Irritability	-	-	-	-	-	-	-	-	✔	-
Migraine	<1	-	-	-	-	-	-	1	-	-
Nervousness	<1	-	-	-	-	-	-	-	-	-
Neuritis	<1	-	-	-	-	-	-	-	-	-
Pain	1 to 10	0 to 34	-	30	-	-	-	-	-	-
Paresthesia	10 to 25	3 to 22	-	6	-	-	-	≤20	-	-
Pseudotumor cerebri	<1	-	-	-	-	-	-	-	-	-
Rigors	10 to 25	-	-	-	-	-	-	-	-	-
Somnolence	<1	-	-	-	-	-	-	-	-	-
Dermatological										
Abnormal hair texture	1 to 10	-	-	-	-	-	-	-	-	-
Abnormal skin odor	1 to 10	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Bexarotene	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	For-maldehyde
Acne	<1	-	-	-	-	-	-	1	-	-
Alopecia	50 to 75	-	-	-	-	-	-	1 to 2	✔	-
Blistering	-	-	-	-	-	-	-	-	✔	-
Bullous eruption	1 to 10	-	-	-	-	-	-	-	-	-
Bullous pemphigoid	-	-	-	-	-	-	-	-	✔	-
Burning	-	-	-	-	10 to 23	✔	✔	-	✔	-
Cold/clammy skin	1 to 10	-	-	-	-	-	-	-	-	-
Contact dermatitis	-	-	-	14	-	-	-	4 to 33	-	-
Crusting	-	-	-	-	-	-	-	-	✔	
Dermatitis	1 to10	-	-	-	1 to 10	✔	-	-	-	✔
Dry skin	25 to 50	-	-	-	1 to 10	-	-	≤27	✔	-
Eczema	<1	-	-	-	-	-	-	-	-	-
Edema	1 to 10	3 to 8	-	10	-	-	-	-	✔	-
Erythema	-	-	<1	-	1 to 10	✔	✔	-	✔	-
Exfoliation	-	3 to 9	-	6	-	-	-	-	-	-
Exfoliative dermatitis	-	-	-	-	-	-	-	6 to 24	-	-
Exuberant granulation tissue	-	-	<1	-	-	-	-	-	-	-
Folliculitis	-	-	-	-	<1	-	-	-	-	-
Fungal dermatitis	<1	-	-	-	-	-	-	-	-	-
Furunculosis	<1	-	-	-	-	-	-	-	-	-
Hair discoloration	<1	-	-	-	-	-	-	-	-	-
Herpes simplex	<1	-	-	-	-	-	-	2	✔	-
Hyperesthesia	10 to 25	-	-	-	-	-	-	-	-	-
Hyperkeratosis	<1	-	-	-	-	-	-	-	-	-
Hyperpigmentation	-	-	-	-	<1	-	-	-	✔	-
Hypertrichosis	<1	-	-	-	-	-	-	-	-	-
Hypoesthesia	<1	-	-	-	-	-	-	-	-	-
Ichthyosis	-	-	-	-	-	-	-	-	✔	-
Impaired healing	<1	-	-	-	-	-	-	-	-	-
Irritation	-	-	-	-	>10	-	✔	-	✔	-
Nail disorder	25 to 50	-	-	-	-	-	-	-	-	-
Pain (local)	-	-	<1	-	3	-	✔	15 to 26	✔	-
Paronychia	10 to 25	-	-	-	-	-	-	-	-	-
Peeling	50 to 75	-	-	-	1 to 10	-	-	2	✔	-
Photosensitivity	<1	-	-	-	-	-	-	-	-	-
Pruritus	25 to 50	8 to 11	-	6 to 40	1 to 10	1 to 3	-	≤52	✔	-
Psoriasis form rash	1 to 10	-	-	-	-	-	-	-	-	-
Purpura	1 to 10	-	-	-	-	-	-	-	-	-
Pyogenic granuloma	1 to 10	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Bexarotene	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	For-maldehyde
Rash	1 to 10	25 to 77	2	14 to 72	>10	-	-	35 to 46	✔	-
Scaling	-	-	-	-	-	-	-	-	✔	-
Scarring	-	-	-	-	-	-	-	-	✔	-
Scleroderma	<1	-	-	-	-	-	-	-	-	-
Seborrhea	1 to 10	-	-	-	-	-	-	-	-	-
Sensitivity reaction	-	-	-	-	-	-	-	-	-	✔
Skin atrophy	1 to 10	-	-	-	<1	-	-	-	-	-
Skin carcinoma	-	-	-	-	-	-	-	-	2	-
Skin discomfort	-	-	-	-	-	3	-	-	-	-
Skin disorder	1 to 10	<8	-	-	-	-	-	-	-	-
Skin inflammation	<1	-	-	-	-	-	-	-	-	-
Skin nodule	<1	-	-	-	-	-	-	-	-	-
Skin stickiness	10 to 25	-	-	-	-	-	-	-	-	-
Skin ulcer	-	-	<1	-	-	-	-	1 to 2	✔	-
Soreness	-	-	-	-	-	-	-	-	✔	-
Stinging	-	-	-	-	>10	-	-	-	-	-
Sunburn	1 to 10	-	-	-	-	-	-	-	-	-
Suppuration	-	-	-	-	-	-	-	-	✔	-
Sweat gland disorder	<1	-	-	-	-	-	-	-	-	-
Sweating	<1	-	-	6	-	-	-	-	-	-
Telangiectasia	-	-	-	-	-	-	-	-	✔	-
Tenderness	-	-	-	-	-	-	-	-	✔	-
Tingling	-	-	-	-	>10	-	-	-	-	-
Tunneling of ulcer	-	-	<1	-	-	-	-	-	-	-
Urticaria	<1	-	-	-	-	-	-	-	✔	-
Verrucae	<1	-	-	-	-	-	-	-	-	-
Worsening of psoriasis	<1	-	-	-	1 to 10	-	-	-	-	-
Endocrine and Metabolic										
Breast pain	<1	-	-	-	-	-	-	-	-	-
Decreased high-density lipoprotein	40	-	-	-	-	-	-	-	-	-
Hypercalcemia	-	-	-	-	<1	≤24	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	-	1	-	-
Hyperlipidemia	-	-	-	10	-	-	-	1	-	-
Increased cholesterol	33	-	-	-	-	-	-	-	-	-
Increased triglycerides	66	-	-	-	-	-	-	-	-	-
Jaundice	<1	-	-	-	-	-	-	-	-	-
Gastrointestinal										
Abdominal pain	1 to 10	-	-	-	-	-	-	1 to 2	-	-
Altered saliva	<1	-	-	-	-	-	-	-	-	-
Anal disorder	<1	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Bexarotene	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	For-maldehyde
Anorexia	1 to 10	-	-	-	-	-	-	-	-	-
Constipation	<1	-	-	-	-	-	-	-	-	-
Diarrhea	1 to 10	-	-	-	-	-	-	2	-	-
Dyspepsia	<1	-	-	-	-	-	-	2 to 3	-	-
Esophagitis	<1	-	-	-	-	-	-	-	-	-
Gastritis	<1	-	-	-	-	-	-	-	-	-
Gastroenteritis	<1	-	-	-	-	-	-	-	-	-
Gingival bleeding	1 to 10	-	-	-	-	-	-	-	-	-
Gingivitis	1to 10	-	-	-	-	-	-	-	-	-
Glossitis	<1	-	-	-	-	-	-	-	-	-
Gum hyperplasia	<1	-	-	-	-	-	-	-	-	-
Hemorrhoids	<1	-	-	-	-	-	-	-	-	-
Increased appetite	1 to 10	-	-	-	-	-	-	-	-	-
Medicinal taste	-	-	-	-	-	-	-	-	✔	-
Melena	<1	-	-	-	-	-	-	-	-	-
Nausea	<1	-	-	-	-	-	-	-	-	-
Stomatitis	1 to 10	-	-	-	-	-	-	-	✔	-
Taste loss/perversion	1 to 10	-	-	-	-	-	-	-	-	-
Tenesmus	<1	-	-	-	-	-	-	-	-	-
Tongue disorder	<1	-	-	-	-	-	-	-	-	-
Tongue ulceration	<1	-	-	-	-	-	-	-	-	-
Ulcerative stomatitis	1 to 10	-	-	-	-	-	-	-	-	-
Xerostomia	10 to 25	-	-	-	-	-	-	-	-	-
Genitourinary										
Abnormal urine	<1	-	-	-	-	-	-	-	-	-
Atrophic vaginitis	<1	-	-	-	-	-	-	-	-	-
Dysuria	<1	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	-	-	-	2	-	-
Hypercalciuria	-	-	-	-	-	3	-	-	-	-
Kidney stones	-	-	-	-	-	✔	-	-	-	-
Leukorrhea	<1	-	-	-	-	-	-	-	-	-
Libido alterations	<1	-	-	-	-	-	-	-	-	-
Urine abnormality	-	-	-	-	-	4	-	-	-	-
Vaginal moniliasis	<1	-	-	-	-	-	-	-	-	-
Hematologic										
Leukopenia	-	-	-	6	-	-	-	-	-	-
Leukocytosis	-	-	-	-	-	-	-	-	✔	-
Lymphadenopathy	-	-	-	6	-	-	-	-	-	-
Thrombocytosis	✔	-	-	-	-	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	-	-	-	✔	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Bexarotene	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	For-maldehyde
Hepatic										
Increased alanine aminotransferase	✔	-	-	-	-	-	-	-	-	-
Increased aspartate aminotransferase	✔	-	-	-	-	-	-	-	-	-
Increased gamma-glutamyltransferase	✔	-	-	-	-	-	-	-	-	-
Increased Lactate dehydrogenase	✔	-	-	-	-	-	-	-	-	-
Musculoskeletal										
Arthralgia	10 to 25	-	-	-	-	-	-	2	-	-
Arthritis	1 to 10	-	-	-	-	-	-	-	-	-
Arthrosis	1 to 10	-	-	-	-	-	-	2	-	-
Back pain	1 to 10	-	-	-	-	-	-	2 to 4	-	-
Bone disorder	<1	-	-	-	-	-	-	-	-	-
Hypertonia	1 to 10	-	-	-	-	-	-	-	-	-
Myalgia	1 to 10	-	-	-	-	-	-	2 to 3	-	-
Neck pain	-	-	-	-	-	-	-	2	-	-
Osteodynia	1 to 10	-	-	-	-	-	-	-	-	-
Spinal/peripheral joint hyperostosis	1 to 25	-	-	-	-	-	-	-	-	-
Tendonitis	<1	-	-	-	-	-	-	-	-	-
Weakness	-	-	-	-	-	-	-	1 to 10	-	-
Respiratory										
Asthma	-	-	-	-	-	-	-	2	-	-
Cough	<1	-	-	6	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	2	-	-
Laryngitis	<1	-	-	-	-	-	-	-	-	-
Nasal irritation	-	-	-	-	-	-	-	-	✔	✔
Nasopharyngitis	-	-	-	-	-	-	-	-	-	-
Pharyngitis	<1	-	-	6	-	-	-	2	-	-
Pneumonia	-	-	-	-	-	-	-	2	-	-
Respiratory tract irritation	-	-	-	-	-	-	-	-	-	✔
Rhinitis	25 to 50	-	-	-	-	-	-	2	-	-
Sinusitis	<1	-	-	-	-	-	-	2	2 to 5	-
Special Senses										
Abnormal vision	1 to 10	-	-	-	-	-	-	-	-	-
Blepharitis	1 to 10	-	-	-	-	-	-	-	-	-
Conjunctival hemorrhage	<1	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Bexarotene	Calcipotriene	Calcitriol	Collagenase	Diclofenac	Fluoro-uracil	For-maldehyde
Conjunctival reaction	-	-	-	-	-	-	-	-	✔	-
Conjunctivitis	1 to 10	-	-	-	-	-	-	2 to 4	-	-
Corneal epithelial abnormality	1 to 10	-	-	-	-	-	-	-	-	-
Corneal ulceration	<1	-	-	-	-	-	-	-	-	-
Decreased night vision/ blindness	1 to 10	-	-	-	-	-	-	-	-	-
Diplopia	<1	-	-	-	-	-	-	-	-	-
Ear pain	1 to 10	-	-	-	-	-	-	-	-	-
Ectropion	<1	-	-	-	-	-	-	-	-	-
Eye irritation	-	-	-	-	-	-	-	-	✔	-
Eye pain	1 to 10	-	-	-	-	-	-	2	-	-
Lacrimation	<1	-	-	-	-	-	-	-	✔	-
Otitis media	<1	-	-	-	-	-	-	-	-	-
Papilledema	<1	-	-	-	-	-	-	-	-	-
Photophobia	1to 10	-	-	-	-	-	-	-	-	-
Xerophthalmia	10 to 25	-	-	-	-	-	-	-	-	-
Other										
Accidental injury	-	-	-	-	-	-	-	4	-	-
Alcohol intolerance	<1	-	-	-	-	-	-	-	-	-
Allergic reaction	-	-	-	-	-	-	-	1	1 to 3	-
Birth defect	✔	-	-	-	-	-	-	-	✔	-
Ceruminosis	<1	-	-	-	-	-	-	-	-	-
Chalazion	<1	-	-	-	-	-	-	-	-	-
Cheilitis	>75	-	-	-	-	-	-	-	-	-
Common cold	-	-	-	-	-	-	-	-	2 to 5	-
Cyst	<1	-	-	-	-	-	-	-	-	-
Epistaxis	25 to 50	-	-	-	-	-	-	-	-	-
Fatigue	1 to 10	-	-	-	-	-	-	-	-	-
Flu symptoms	<1	-	-	-	-	-	-	1 to 10	-	-
Hemorrhage	<1	-	-	-	-	-	-	-	-	-
Hot flashes	1 to 10	-	-	-	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	-	✔	-	-	-
Infection	1 to 10	-	-	18	-	-	-	4	-	-
Increased saliva	<1	-	-	-	-	-	-	-	-	-
Malaise	<1	-	-	-	-	-	-	-	-	-
Miscarriage	-	-	-	-	-	-	-	-	✔	-
Thirst	1 to 10	-	-	-	-	-	-	-	-	-
Toxic granulation	-	-	-	-	-	-	-	-	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 9. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs I-T) [1,2,18-20,22-28]

Adverse Events	Imiquimod	Ingenol-mebutate	Nitro-glycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Sinecatechins	Tacrolimus	Tazarotene
Cardiovascular									
Arrhythmias	✔	-	-	-	-	-	-	-	-
Atrial fibrillation	1	-	-	-	-	-	-	-	-
Bradycardial	-	-	-	-	-	-	-	-	-
Capillary leak syndrome	✔	-	-	-	-	-	-	-	-
Cardiac arrest	-	-	-	-	-	-	-	-	-
Cardiac failure	✔	-	-	-	-	-	-	-	-
Cardiomyopathy	✔	-	-	-	-	-	-	-	-
Chest pain	1	-	-	-	-	-	-	<1	-
Hypertension	-	-	-	-	-	-	-	1 to 2	-
Hypotension	-	-	✔	-	-	-	-	-	-
Ischemia	✔	-	-	-	-	-	-	-	-
Myocardial infarction	✔	-	-	-	-	-	-	-	-
Peripheral edema	-	-	-	-	-	-	-	1 to 4	1 to 10
Pulmonary edema	✔	-	-	-	-	-	-	-	-
Seizure	-	-	-	-	-	-	-	✔	-
Syncope	✔	-	-	-	-	-	-	<1	-
Tachycardia	-	-	-	-	-	-	-	<1	-
Valvular heart disease	-	-	-	-	-	-	-	<1	-
Vasodilation	-	-	-	-	-	-	-	<1	-
Central Nervous System									
Abnormal thinking	-	-	-	-	-	-	-	<1	-
Agitation	✔	-	-	-	-	-	-	-	-
Anxiety	1	-	-	-	-	-	-	<1	-
Asthenia	-	-	-	-	-	-	-	1 to 3	-
Cerebrovascular accident	✔	-	-	-	-	-	-	-	-
Chills	-	-	-	-	-	-	-	<1	-
Coma	-	-	-	-	-	✔	-	-	-
Convulsions	✔	-	-	-	-	-	-	-	-
Depression	✔	-	-	-	-	-	-	1 to 2	-
Dizziness	1	-	6	-	<5	-	-	<1	-
Fatigue	1 to 2	-	-	-	-	-	-	-	-
Fever	1 to 5	-	-	1 to 13	-	✔	-	1 to 21	-
Headache	4 to 8	2	79	7 to 25	7	-	-	5 to 20	-
Hyperesthesia	-	-	-	-	-	-	-	3 to 7	-
Hypertonia	-	-	-	-	-	-	-	<1	-
Insomnia	✔	-	-	-	<5	-	-	1 to 4	-

Adverse Events	Imiquimod	Ingenol-mebutate	Nitro-glycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Sinecatechins	Tacrolimus	Tazarotene
Malaise	-	-	-	-	-	-	-	<1	-
Migraine	-	-	-	-	-	-	-	<1	-
Multiple sclerosis aggravation	✔	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	✔	-	1 to 3	-
Polyneuritis	-	-	-	-	-	✔	-	-	-
Rigors	1	-	-	-	-	-	-	-	-
Suicide	✔	-	-	-	-	-	-	-	-
Vertigo	-	-	-	-	-	-	-	<1	-
Dermatological									
Acne	-	-	-	≤2	-	-	-	2 to 7	-
Alopecia	✔	-	-	-	-	-	-	1	-
Bleeding	2 to 3	-	-	-	1 to 19	-	2	-	1 to 10
Blistering	-	-	-	-	✔	-	-	-	1 to 10
Burning	6 to 26	-	-	2 to 26	12 to 78	-	67	20 to 58	10 to 30
Cellulitis	-	-	-	-	-	-	-	1	-
Chafing	-	-	-	-	<5	-	-	-	-
Cheilitis	-	-	-	-	-	-	-	-	1 to 10
Contact dermatitis	-	-	-	-	-	-	-	2 to 4	1 to 10
Cutaneous moniliasis	-	-	-	-	-	-	-	<1	-
Crusting	83 to 93	74 to 80	-	-	<5	-	-	-	-
Cyst	-	-	-	-	-	-	-	1 to 3	-
Dermal cyst	-	-	-	-	-	-	-	-	-
Desquamation	-	-	-	-	-	-	5	-	1 to 30
Discharge	-	-	-	-	-	-	3	-	-
Dry skin	-	-	-	-	<5	-	<1	1 to 3	1 to 30
Eczema	2	-	-	-	-	-	<1	1 to 2	1 to 10
Eczema herpeticum	-	-	-	1 to 2	-	-	-	1 to 2	-
Edema	12 to 78	-	-	-	<5	-	45	<1	-
Erosion	30 to 66	56 to 98	-	-	9 to 67	-	49	-	-
Erythema	2 to 100	92 to 94	-	≤2	5	-	70	7 to 28	10 to 30
Excoriation	18 to 26	-	-	-	-	-	-	-	-
Exfoliative dermatitis	-	-	✔	-	-	-	-	1 to 3	-
Facial edema	-	-	-	<1	-	-	-	1 to 2	-
Fissure	-	-	-	-	✔	-	-	-	1 to 10
Flaking	91 to 93	85 to 90	-	-	-	-	-	-	-
Flushing	-	-	✔	<1	-	-	-	3 to 7	-
Folliculitis	-	-	-	1 to 6	-	-	-	2 to 6	-
Fungal dermatitis	-	-	-	-	-	-	-	1 to 4	-
Furunculosis	-	-	-	-	-	-	-	<1	-

Adverse Events	Imiquimod	Ingenol-mebutate	Nitro-glycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Sinecatechins	Tacrolimus	Tazarotene
Herpes simplex	✔	-	-	≤4	-	-	-	3 to 4	-
Hyperesthesia	-	-	-	-	-	-	<1	1 to 7	-
Hyperkeratosis	1 to 8	-	-	-	-	-	-	-	-
Hyperpigmentation	✔	-	-	-	-	-	-	-	-
Hypopigmentation	>1	-	-	-	-	-	-	-	-
Impetigo	-	-	-	2 to 4	-	-	-	✔	-
Induration	2 to 84	-	-	-	-	-	35	-	-
Inflammation	-	-	-	-	9 to 71	-	-	-	1 to 10
Irritation	1 to 2	4	-	≤6	-	-	1	-	1 to 30
Leukoderma	-	-	-	-	-	-	-	<1	-
Molluscum contagiosum	-	-	-	≤2	-	-	-	-	-
Necrosis	-	-	-	-	-	-	<1	-	-
Pain	1 to 8	2 to 15	-	-	12 to 72	-	56	1 to 2	-
Papules	2	-	-	-	-	-	<1	-	-
Peeling	-	-	-	-	<5	-	-	-	-
Photosensitivity	1	-	-	-	-	-	-	<1	1 to 10
Pruritus	16 to 32	8	-	1 to 6	8 to 65	-	69	19 to 46	10 to 30
Pustular vasculitis	44 to 56	-	-	-	-	-	-	-	-
Rash	>1	-	✔	-	✔	-	1 to 20	2 to 7	1 to 10
Rosacea	-	-	-	-	-	-	-	✔	-
Scabbing	4 to 86	-	-	-	✔	-	-	-	-
Scaling	91 to 93	85 to 90	-	-	-	-	-	-	-
Scarring	-	-	-	-	<5	-	1	-	-
Seborrhea	-	-	-	-	-	-	-	<1	-
Skin carcinoma	-	-	-	-	-	-	-	<1	-
Skin discoloration	-	-	-	<1	✔	-	<1	<1	1 to 10
Skin disorder	-	-	-	-	-	-	-	1 to 4	-
Skin hypertrophy	-	-	-	-	-	-	-	<1	-
Skin infection	-	-	-	2 to 6	-	-	-	5 to 16	-
Skin papilloma (warts)	-	-	-	≤3	-	-	-	-	-
Skin ulcer	-	-	-	-	-	-	-	<1	-
Soreness	<3	-	-	-	✔	-	-	-	-
Squamous carcinoma	4	-	-	-	-	-	-	-	-
Stinging	3	-	-	-	7	-	-	2 to 8	1 to 10
Sunburn	-	-	-	-	-	-	-	1 to 2	-
Sweating	-	-	-	-	-	-	-	<1	-
Swelling	-	64 to 79	-	-	-	-	-	-	-
Tenderness	1 to 2	-	-	-	<5	-	-	-	-
Tinea cruris	>1	-	-	-	-	-	-	-	-
Tingling	-	-	-	-	✔	-	-	1 to 8	-

Adverse Events	Imiquimod	Ingenol-mebutate	Nitro-glycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Sinecatechins	Tacrolimus	Tazarotene
Ulceration	4 to 40	56 to 98	-	-	<5		49	-	-
Urticaria	-	-	-	≤1	-	-	-	1 to 6	-
Vesicles	2 to 31	-	-	-	<5	-	-	-	-
Weeping/exudate	22	-	-	-	-	-	-	-	-
Worsening of psoriasis	-	-	-	-	-	-	-	-	10 to 30
Endocrine/Metabolic									
Dehydration	-	-	-	-	-	-	-	<1	-
Dysmenorrhea	-	-	-	1 to 2	-	-	-	1 to 4	-
Hypertriglyceridemia	-	-	-	-	-	-	-	-	1 to 10
Hypothyroidism	-	-	-	-	-	-	-	<1	-
Thyroiditis	✔	-	-	-	-	-	-	-	-
Gastrointestinal									
Anorexia	-	-	-	-	-	-	-	<1	-
Abdominal pain	✔	-	-	≤4	-	-	-	1 to 3	-
Colitis	-	-	-	-	-	-	-	<1	-
Constipation	-	-	-	≤4	-	-	-	<1	-
Cramps	-	-	-	-	-	-	-	<1	-
Diarrhea	>1	-	-	1 to 8	-	-	-	3 to 5	-
Dyspepsia	2 to 3	-	-	-	-	-	-	1 to 4	-
Gastritis	-	-	-	-	-	-	-	<1	-
Gastroenteritis	-	-	-	≤7	-	-	-	2 to 4	-
Hernia	-	-	-	-	-	-	-	<1	-
Mouth ulceration	-	-	-	-	-	-	-	<1	-
Oral moniliasis	-	-	-	-	-	-	-	<1	-
Nausea	1	-	-	-	-	-	-	1 to 3	-
Paralytic ileus	-	-	-	-	-	✔	-	-	-
Perianal infection	-	-	-	-	-	-	<1-	-	-
Periodontal abscess	-	-	-	-	-	-	-	1	-
Stomatitis	-	-	-	-	-	-	-	<1	-
Taste perversion	-	-	-	-	-	-	-	<1	-
Tooth disorder	-	-	-	-	-	-	-	1 to 2	-
Vomiting	1	-	-	9	<5	-	-	1 to 6	-
Genitourinary									
Acute renal failure	-	-	-	-	-	-	-	✔	-
Cystitis	-	-	-	-	-	-	-	<1	-
Dysuria	✔	-	-	-	-	-	-	-	-
Foreskin retraction	-	-	-	-	<5	-	-	-	-
Hematuria	-	-	-	-	<5	-	-	-	-
Moniliasis	-	-	-	-	-	-	-	<1	-
Pain with intercourse	-	-	-	-	<5	-	-	-	-

Adverse Events	Imiquimod	Ingenol-mebutate	Nitro-glycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Sinecatechins	Tacrolimus	Tazarotene
Pelvic pain	-	-	-	-	-	-	<1	-	-
Proteinuria	✔	-	-	-	-	-	-	-	-
Urethritis	-	-	-	-	-	-	<1	-	-
Urinary retention	✔	-	-	-	-	-	-	-	-
Urinary tract infection	1	-	-	-	-	-	-	1 to 2	-
Vaginal moniliasis	-	-	-	-	-	-	-	<1	-
Vaginitis	-	-	-	-	-	-	-	<1	-
Vulvitis	-	-	-	-	-	-	<1	-	-
Hematologic									
Anemia	-	-	-	-	-	-	-	<1	-
Bilirubinemia	-	-	-	-	-	-	-	<1	-
Ecchymosis	-	-	-	-	-	-	-	<1	-
Erythropenia	✔	-	-	-	-	-	-	-	-
Hypercholesterolemia	-	-	-	-	-	-	-	<1	-
Leukopenia	-	-	-	-	-	✔	-	-	-
Lymphadenopathy	3	-	-	-	-	-	-	-	-
Methemoglobinemia	-	-	✔	-	-	-	-	-	-
Thrombocytopenia	✔	-	-	-	-	✔	-	-	-
Musculoskeletal									
Arthralgia	✔	-	-	-	-	-	-	1 to 3	-
Arthrosis	-	-	-	-	-	-	-	<1	-
Back pain	1 to 4	-	-	-	-	-	-	1 to 3	-
Bone disorder	-	-	-	-	-	-	-	<1	-
Bursitis	-	-	-	-	-	-	-	<1	-
Joint disorder	-	-	-	-	-	-	-	<1	-
Myalgia	1	-	-	-	-	-	-	1 to 3	-
Neck disorder	-	-	-	-	-	-	-	<1	-
Tendon disorder	-	-	-	-	-	-	-	<1	-
Weakness	-	-	-	-	-	-	-	2 to 3	-
Respiratory									
Asthma	-	-	-	1 to 4	-	-	-	4 to 13	-
Bronchitis	-	-	-	≤11	-	-	-	2 to 4	-
Cough	1 to 3	-	-	2 to 16	-	-	-	1 to 18	-
Dry mouth/nose	-	-	-	-	-	-	-	<1	-
Dyspnea	✔	-	-	≤2	-	-	-	<1	-
Epistaxis	-	-	-	≤3	-	-	-	<1	-
Laryngitis	-	-	-	-	-	-	-	<1	-
Lung disorder	-	-	-	-	-	-	-	<1	-
Nasal congestion	-	-	-	1 to 3	-	-	-	-	-
Nasopharyngitis	-	2	-	8 to 27	-	-	-	-	-

Adverse Events	Imiquimod	Ingenol-mebutate	Nitro-glycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Sinecatechins	Tacrolimus	Tazarotene
Pharyngitis	1	-	-	1 to 8	-	-	-	3 to 12	-
Pneumonia	-	-	-	≤2	-	-	-	1 to 3	-
Rhinitis	2 to 3	-	-	13	-	-	-	2 to 6	-
Rhinorrhea	-	-	-	≤2	-	-	-	-	-
Sinusitis	2 to 7	-	-	1 to 3	-	-	-	2 to 7	-
Upper respiratory infection	3 to 15	-	-	4 to 19	-	-	-	-	-
Wheezing	-	-	-	≤1	-	-	-	-	-
Special Senses									
Abnormal vision	-	-	-	-	-	-	-	<1	-
Blepharitis	-	-	-	-	-	-	-	<1	-
Cataract	-	-	-	-	-	-	-	<1	-
Conjunctival edema	-	-	-	-	-	-	-	<1	-
Conjunctivitis	3	-	-	-	-	-	-	1 to 3	-
Dry eyes	-	-	-	-	-	-	-	<1	-
Ear disorder	-	-	-	-	-	-	-	<1	-
Ear infection	-	-	-	1 to 6	-	-	-	-	-
Eye infection	-	-	-	≤1	-	-	-	-	-
Eye irritation	-	-	-	<1	-	-	-	-	-
Eye pain	-	-	-	-	-	-	-	1	-
Otitis externa	-	-		-	-	-	-	<1	-
Otitis media	-	-	-	1 to 3	-	-	-	1 to 12	-
Periorbital edema	-	7	-	-	-	-	-	-	-
Other									
Abscess	-	-	-	-	-	-	-	<1	-
Abnormal liver function	✔	-	-	-	-	-	-	-	-
Alcohol intolerance	-	-	-	-	-	-	-	3 to 7	-
Allergic reaction	-	-	-	-	-	-	-	4 to 13	-
Anaphylaxis	-	-	-	<1	-	-	-	<1	-
Angioedema	✔	-	-	-	-	-	-	-	-
Angioneurotic edema	-	-	-	<1	-	-	-	-	-
Bacterial infection	-	-	-	1 to 2	-	-	-	-	-
Basal cell carcinoma	-	-	-	<1	-	-	-	✔	-
Breast neoplasm benign	-	-	-	-	-	-	-	<1	-
Death	-	-	-	-	-	✔	-	-	-
Flu symptoms	1	-	-	-	-	-	-	22 to 34	-
Fungal infection	2 to 11	-	-	-	-	-	-	-	-
Hypersensitivity	-	-	-	3 to 5	-	-	2	-	-
Impaired healing	-	-	-	-	-	-	-	-	-
Infection	1	8	-	-	-	-	-	1 to 10	-
Influenza	-	-	-	3 to 11	-	-	-	-	-

Adverse Events	Imiquimod	Ingenol-mebutate	Nitro-glycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Sinecatechins	Tacrolimus	Tazarotene
Lymphadenitis	-	-	-	-	-	-	3	-	-
Lymphadenopathy	-	-	-	<1	-	-	-	1 to 3	-
Lymphoma	-	-	-	<1	-	-	-	✔	-
Malignant melanoma	-	-	-	<1	-	-	-	✔	-
Malodor	-	-	-	-	<5	-	-	-	-
Osteomyelitis	-	-	-	-	-	-	-	✔	-
Phimosis	-	-	-	-	-	-	3	-	-
Septicemia	-	-	-	-	-	-	-	✔	-
Skin graft failure	-	-	-	-	-	-	-	-	-
Skin neoplasm benign	-	-	-	-	-	-	-	1 to 2	-
Squamous cell carcinoma	-	-	-	<1	-	-	-	✔	-
Staphylococcemia	-	-	-	-	-	-	<1	-	-
Tonsillitis	-	-	-	≤6	-	-	-	-	-
Varicella/herpes zoster	-	-	-	-	-	-	-	1 to 5	-
Viral infection	1	-	-	≤7	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 10. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous Combination Products[1,2,9,11,21,29]

Adverse Events	Calcipotriene and Betamethasone	Capsaicin and Skin Cleanser	Mucositis, Stomatitis Combination	Thrombin, Fibrinogen, Aprotinin and Calcium Chloride
Cardiovascular				
Bradycardial	-	-	-	≤10
Cardiac arrest	-	-	-	<1
Edema	-	-	-	<1
Hypertension	-	2	-	<1
Hypotension	-	-	-	<1
Shock	-	-	-	<1
Tachycardia	-	-	-	<1
Central Nervous System				
Dizziness	-	<1	-	-
Fever	-	-	-	6
Headache	-	<1	-	-
Pain	-	42	-	-
Paresthesia	-	<1	-	-
Peripheral sensory neuropathy	-	<1	-	-
Dermatological				
Acne	<1	-	-	-

Adverse Events	Calcipotriene and Betamethasone	Capsaicin and Skin Cleanser	Mucositis, Stomatitis Combination	Thrombin, Fibrinogen, Aprotinin and Calcium Chloride
Bruising	-	<1	-	-
Burning	<1	<1	-	-
Contact dermatitis	<1	-	-	-
Dermal cyst	-	-	-	<1
Dermatitis	<1	<1	-	-
Dry skin	<1	2	-	-
Edema	-	4	-	-
Erythema	2	63	-	-
Exfoliation	-	<1	-	-
Facial edema	<1	-	-	-
Folliculitis	<1	-	-	-
Hyperesthesia	-	<1	-	-
Hyperpigmentation	<1	-	-	-
Hypopigmentation	<1	-	-	-
Inflammation	-	<1	-	-
Irritation	1	-	-	-
Papules	-	6	-	-
Pruritus	4	6	-	≤1
Rash	1	-	-	-
Skin atrophy	<1	-	-	-
Skin order	-	<1	-	-
Skin pain	<1	-	-	-
Telangiectasia	<1	-	-	-
Urticaria	-	<1	-	-
Worsening of psoriasis	<1	-	-	-
Endocrine/Metabolic				
Hypercalcemia	<1	-	-	-
Gastrointestinal				
Dysgeusia	-	<1	-	-
Throat irritation	-	<1	-	-
Vomiting	-	3	-	-
Genitourinary				
Hypercalciuria	<1	-	-	-
Respiratory				
Bronchitis	-	2	-	-
Cough	-	<1	-	-
Nasopharyngitis	-	4	-	-
Sinusitis	-	3	-	-
Special Senses				
Burning sensation in mouth	-	-	✔	-

Adverse Events	Calcipotriene and Betamethasone	Capsaicin and Skin Cleanser	Mucositis, Stomatitis Combination	Thrombin, Fibrinogen, Aprotinin and Calcium Chloride
Eye irritation	<1	-	-	-
Inflammation/stinging of oral cavity	-	-	✔	-
Otitis externa	<1	-	-	-
Other				
Hypersensitivity	-	-	-	<1
Impaired healing	-	-	-	<1
Seroma	-	-	-	<1
Skin graft failure	-	-	-	3
Thromboembolic complications	-	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 11. Boxed Warning for Acitretin[3]

WARNING

Acitretin causes birth defects. Female patients must not get pregnant.

Acitretin must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least three years following discontinuation of therapy. Acitretin also must not be used by females who may not use reliable contraception while undergoing treatment or for at least three years following discontinuation of treatment. Acitretin is a metabolite of etretinate, and major human fetal abnormalities have been reported with the administration of etretinate and acitretin. Potentially, any fetus exposed can be affected.

Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with acitretin or for two months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification.

Acitretin has been shown to be embryotoxic or teratogenic in rabbits, mice, and rats at doses of 0.6, 3.0, and 15.0 mg/kg, respectively. These doses are approximately 0.2, 0.3, and 3.0 times the maximum recommended therapeutic dose, respectively, based on a mg/m^2 comparison.

Major human fetal abnormalities associated with acitretin or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactylies, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, cardiovascular malformation, and alterations of the skull and cervical vertebrae.

Acitretin should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity.

WARNING

Important information for women of childbearing potential:
Acitretin should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.

Females of reproductive potential must not be given a prescription for acitretin until pregnancy is excluded. Acitretin is contraindicated in females of reproductive potential unless the patient meets all of the following conditions:

- Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial acitretin prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue acitretin therapy. The second pregnancy test (a confirmation test) should be done during the first five days of the menstrual period immediately preceding the beginning of acitretin therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using two effective forms of contraception [birth control] simultaneously). Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment.
- Must have selected and have committed to use two effective forms of contraception (birth control) simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly postmenopausal.
- Patients must use two effective forms of contraception (birth control) simultaneously for at least one month prior to initiation of acitretin therapy, during acitretin therapy, and for at least three years after discontinuing acitretin therapy. An acitretin patient referral form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a regular basis by the prescriber. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed. Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include the following: Tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each secondary form must be used with a spermicide. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception (birth control) simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it has been established that acitretin interferes with the contraceptive effect of microdosed progestin preparations. Microdosed “minipill” progestin preparations are not recommended for use with acitretin. It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy. Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's wort.
- Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to acitretin, about contraceptive failure, and about the fact that they must not ingest beverages or products containing ethanol while taking acitretin and for two months after acitretin treatment has been discontinued.

If pregnancy does occur during acitretin therapy or at any time for at least three years following discontinuation of acitretin therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows:

Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established

WARNING

when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least three years after stopping treatment with acitretin, based on the following considerations:

- In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within two months, assuming a mean elimination half-life of 49 hours.
- In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol, greater than 98% of the etretinate formed would be eliminated in two years, assuming a mean elimination half-life of 120 days, and greater than 98% of the etretinate formed would be eliminated in three years, based on the longest demonstrated elimination half-life of 168 days. However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin therapy.
- Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred after the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.
- There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred after the last dose of etretinate (103 cases), acitretin (126) or both (nine). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, gastrointestinal malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and five cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least one year but less than two years after the last dose. There were three reports of abnormal outcomes out of these 43 cases (involving limb malformation, gastrointestinal tract malformations and premature birth). There were only four cases where conception occurred at least two years after the last dose but there were no reports of birth defects in these cases.
- There is also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are three reports of birth defects when the conception occurred at least one year but less than two years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and four reports of birth defects when conception occurred two or more years after the last dose of acitretin (including foot malformation, cardiac malformations [two cases] and unspecified neonatal and infancy disorder). There were three additional abnormal outcomes in cases where conception occurred two or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia, and stillbirth).
- Females who have taken etretinate must continue to follow the contraceptive recommendations for etretinate. Etretinate is no longer marketed in the United States; for information, call the manufacturer at 1-800-526-6367.
- Patients should not donate blood during and for at least three years following the completion of acitretin therapy because women of childbearing potential must not receive blood from patients being treated with acitretin.

Important information for males taking acitretin:
Patients should not donate blood during and for at least three years following acitretin therapy because women of childbearing potential must not receive blood from patients being treated with acitretin.

WARNING

Samples of seminal fluid from three male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows:

There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, nine reports were retrospective and four were prospective (meaning the pregnancy was reported prior to knowledge of the outcome).

- When acitretin treatment was given at time of conception, there were five deliveries of healthy neonates (four of five cases were prospective), five spontaneous abortions, and one induced abortion.
- When acitretin was discontinued approximately four weeks prior to conception, there was one induced abortion (with malformation pattern not typical of retinoid embryopathy [bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus]).
- When acitretin was discontinued approximately six to eight months prior to conception, there was one spontaneous abortion.

For all patients: An acitretin medication guide must be given to the patient each time acitretin is dispensed, as required by law.

Hepatotoxicity:
Of the 525 patients treated in United States clinical trials, two had clinical jaundice with elevated serum bilirubin and transaminases considered related to acitretin treatment. Liver function test results in these patients returned to normal after acitretin was discontinued. Two of the 1,289 patients treated in European clinical trials developed biopsy-confirmed toxic hepatitis. A second biopsy in one of these patients revealed nodule formation suggestive of cirrhosis. One patient in a Canadian clinical trial of 63 patients developed a three-fold increase of transaminases. A liver biopsy of this patient showed mild lobular disarray, multifocal hepatocyte loss and mild triaditis of the portal tracts compatible with acute reversible hepatic injury. The patient's transaminase levels returned to normal two months after acitretin was discontinued.

The potential of acitretin therapy to induce hepatotoxicity was prospectively evaluated using liver biopsies in an open-label study of 128 patients. Pretreatment and posttreatment biopsies were available for 87 patients. A comparison of liver biopsy findings before and after therapy revealed 49 (58%) patients showed no change, 21 (25%) improved and 14 (17%) patients had a worsening of their liver biopsy status. For six patients, the classification changed from class 0 (no pathology) to class I (normal fatty infiltration; nuclear variability and portal inflammation; both mild); for seven patients, the change was from class I to class II (fatty infiltration, nuclear variability, portal inflammation and focal necrosis; all moderate to severe); and for one patient, the change was from class II to class IIIb (fibrosis, moderate to severe). No correlation could be found between liver function test result abnormalities and the change in liver biopsy status, and no cumulative dose relationship was found.

Elevations of aspartate aminotransferase, alanine transaminase, gamma-glutamyl transpeptidase (gamma-glutamyl transpeptidase) or lactate dehydrogenase have occurred in approximately one in three patients treated with acitretin. Of the 525 patients treated in clinical trials in the United States, treatment was discontinued in 20 (3.8%) due to elevated liver function test results. If hepatotoxicity is suspected during treatment with acitretin, the drug should be discontinued and the etiology further investigated.

Ten of 652 patients treated in United States clinical trials of etretinate, of which acitretin is the active metabolite, had clinical or histologic hepatitis considered to

WARNING
be possibly or probably related to etretinate treatment. There have been reports of hepatitis-related deaths worldwide; a few of these patients had received etretinate for one month or less before presenting with hepatic symptoms or signs.

Table 12. Boxed Warning for Becaplermin[5]

WARNING
An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of becaplermin in a postmarketing retrospective cohort study. Use becaplermin only when the benefits can be expected to outweigh the risks. Use becaplermin with caution in patients with known malignancy.

Table 13. Boxed Warning for Pimecrolimus[22]

WARNING
Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy (e.g., skin malignancy, lymphoma) have been reported in patients treated with topical calcineurin inhibitors including pimecrolimus. Therefore, • Avoid continuous, long-term use of topical calcineurin inhibitors, including pimecrolimus, in any age group, and limit application to areas of involvement with atopic dermatitis. • Pimecrolimus is not indicated for use in children younger than two years of age.

Table 14. Boxed Warning for Tacrolimus[26]

WARNING
Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy (i.e., skin cancer and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including tacrolimus ointment. Therefore: • Avoid continuous long-term use of topical calcineurin inhibitors, including tacrolimus ointment, in any age group, and limit application to areas of involvement with atopic dermatitis. • Tacrolimus ointment is not indicated for use in children younger than two years of age. Only tacrolimus 0.03% ointment is indicated for use in children two to 15 years of age.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous skin and mucous membrane agents are listed in Table 15.

Table 15. Usual Dosing Regimens for the Skin and Mucous Membrane Agents, Miscellaneous[1-29]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Acitretin	Severe psoriasis: Capsule: 25 to 50 mg per day, given as a single dose with the main meal	Safety and efficacy in children have not been established.	Capsules: 10 mg 17.5 mg 25 mg
Alitretinoin	Treatment of cutaneous lesions in patients with acquired immunodeficiency syndrome-related Kaposi's sarcoma: Gel: apply to lesions two times daily; may increase to three to four times daily as tolerated	Safety and efficacy in children have not been established.	Gel: 0.1%
Becaplermin	Diabetic neuropathic ulcers: Gel: apply once daily to ulcer until complete healing has occurred	Safety and efficacy in children have not been established.	Gel: 0.01%
Bexarotene	Treatment of cutaneous lesions in patients with cutaneous T-cell lymphoma (Stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies: Gel: apply once every other day for first week, then increase as tolerated to once daily for one week, then two times daily for one week, then three times daily for one week, then four times daily	Safety and efficacy in children have not been established.	Gel: 1%
Calcipotriene	Plaque psoriasis: Cream: apply to the affected area twice daily Ointment: apply to the affected area one to two times daily Moderate to severe psoriasis of the scalp: Solution: apply to the affected scalp area twice daily Plaque psoriasis of the scalp and body: Foam: apply to the affected area twice daily	Safety and efficacy in children have not been established.	Cream: 0.005% Foam: 0.01% Ointment: 0.005% Solution: 0.005%
Calcitriol	Mild to moderate plaque psoriasis: Ointment: apply to the	Safety and efficacy in children have not been established.	Ointment: 3 µg/g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	affected area twice daily		
Collagenase	Debriding chronic dermal ulcers and severely burned areas: Ointment: apply to the affected area once daily	Safety and efficacy in children have not been established.	Ointment: 250 units/g
Diclofenac	Actinic keratosis: Gel: apply to the affected area twice daily	Safety and efficacy in children have not been established.	Gel: 3%
Fluorouracil	Actinic keratoses of the face and scalp: 0.5%cream: apply to the affected area once daily Multiple actinic keratosis: 1% cream, 2% solution and 5% cream and solution: apply to the affected area twice daily Superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites: 5% cream and solution: apply to the affected area twice daily	Safety and efficacy in children have not been established.	Cream: 0.5% 5% Solution: 2% 5%
Formaldehyde	Drying agent for pre and post-surgical removal of warts or for non-surgical laser removal of warts where dryness is required; management of oral mucosal pain caused by oral mucositis/stomatitis (resulting from chemotherapy or radiation therapy), irritation due to oral surgery, traumatic ulcers caused by braces/ill-fitting dentures or disease, diffuse aphthous ulcers:: Solution: apply to the affected area once daily	Safety and efficacy in children have not been established.	Solution: 10%
Imiquimod	Actinic keratosis of the face and scalp: Cream 2.5 and 3.75%: apply to the affected area once daily Cream 5%: apply to the affected area twice weekly External genital and perianal warts: Cream 3.75%: apply to the affected area once daily Cream 5%: apply to the affected area three times per	External genital and perianal warts for individuals ≥12 years of age: Cream: apply to the affected area three times per week	Cream: 2.50% 3.75% 5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	week Treatment of biopsy-confirmed, superficial basal cell carcinoma with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate: Cream 5%: apply to the affected area five times per week		
Ingenol mebutate	Actinic keratosis : Gel: apply to affected area once daily	Safety and efficacy in children have not been established.	Gel: 0.02% 0.05%
Nitroglycerin	Moderate to severe pain associated with chronic anal fissure: Ointment: apply one inch of ointment every 12 hours	Safety and efficacy in children have not been established.	Ointment: 0.4%
Pimecrolimus	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable: Cream: apply to the affected area twice daily	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable for individuals ≥2 years of age: Cream: apply to the affected area twice daily	Cream: 1%
Podofilox	External genital/perianal warts: Gel: apply twice daily for three consecutive days, then discontinue for four consecutive days; this one week cycle of treatment may be repeated until there is no visible wart tissue or for a maximum of four cycles External genital warts: Solution: apply twice daily for three consecutive days, then discontinue for four consecutive days; this one week cycle of treatment may be repeated until there is no visible wart tissue or for a maximum of four cycles	Safety and efficacy in children have not been established.	Gel: 0.5% Solution: 0.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Podophyllum resin	Removal of soft genital warts: Liquid: apply to the affected area for one to four hours	Safety and efficacy in children have not been established.	Liquid: 25%
Sinecatechins	External genital warts: Ointment: apply to the affected area three times daily	Safety and efficacy in children have not been established.	Ointment: 15%
Tacrolimus	Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable: Ointment: apply to the affected area twice daily	Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable for individuals ≥2 years of age: Ointment: apply to the affected area twice daily	Ointment: 0.03% 0.1%
Tazarotene	Acne vulgaris: 0.1% formulations: apply to the affected area once daily in the evening Plaque psoriasis: 0.05 and 0.1% formulations: apply to the affected area once daily in the evening	Acne vulgaris in individuals ≥12 years of age: 0.1% formulations: apply to the affected area once daily in the evening	Cream: 0.05% 0.1% Gel: 0.05% 0.1%
Combination Products			
Calcipotriene and betamethasone	Plaque psoriasis: Ointment: apply to the affected area once daily Plaque psoriasis of the scalp and body: Suspension: apply to the affected area once daily	Safety and efficacy in children have not been established.	Ointment: 0.005%-0.064% Suspension: 0.005%-0.064%
Capsaicin and skin cleanser	Neuropathic pain associated with postherpetic neuralgia: Patch kit: apply up to four patches as a single 60 minute application; repeat no more frequently than every three months	Safety and efficacy in children have not been established.	Kit: 8%
Mucositis, stomatitis combination	Management of oral mucosal pain caused by oral mucositis/stomatitis (resulting from chemotherapy or radiation therapy), irritation due to oral surgery, traumatic ulcers caused by braces/ill-fitting dentures or disease, diffuse aphthous ulcers: Wafer: dissolve one wafer by swishing around in mouth three times daily or as needed	Safety and efficacy in children have not been established.	Wafer

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Thrombin, fibrinogen, aprotinin, and calcium chloride	To adhere autologous skin grafts to surgically prepared wound beds resulting from burns; to adhere to tissue flaps during rhytidectomy: The aerosolized sealant should be applied to the wound in a painting motion from side to side to achieve a single thin application; the skin graft should be attached to the wound bed immediately after product has been sprayed	To adhere autologous skin grafts to surgically prepared wound beds resulting from burns; to adhere to tissue flaps during rhytidectomy in individuals ≥1 year of age: The aerosolized sealant should be applied to the wound in a painting motion from side to side to achieve a single thin application; the skin graft should be attached to the wound bed immediately after product has been sprayed	Syringe: 2 ml 4 ml 10 ml

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous skin and mucous membrane agents are summarized in Table 16.

Table 16. Comparative Clinical Trials with the Skin and Mucous Membrane Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Actinic Keratosis				
Wolf et al.[56] (2001) Diclofenac 3% gel applied BID vs placebo	DB, PC, RCT Patients ≥18 years of age with AK	N=118 90 days	Primary: Proportion of patients with no lesions as rated by TLNS and CLNS; proportion of patients rated as "completely improved", on the IGII and the PGI Secondary: Not reported	Primary: The proportion of patients with TLNS=0 was 50% of patients in the diclofenac group compared to 20% in the placebo group (P<0.001). The proportion of patients with CLNS=0 was 47% in the diclofenac group compared to 19% in the placebo group (P<0.001). The proportion of patients with IGII=4 was 47% in the diclofenac group compared to 195 in the placebo group (P<0.001) and a combined 79% of patients in the diclofenac group had achieved complete (IGII=4) or significant (IGII=3) lesion improvement compared to 45% in the placebo group. The proportion of patients with PGII=4 was 41% in the diclofenac group compared to 17% in the placebo group (P<0.001) and a combined 77% of patients in the diclofenac group achieved complete (PGII=4) or significant (PGII=3) lesion improvement compared to 33% in the placebo group. Secondary: Not reported
Ulrich et al.[57] (2010) Diclofenac 3% gel applied BID vs placebo	RCT Organ transplant patients with multiple AK	N=32 16 weeks	Primary: Clinical clearance; safety Secondary: Not reported	Primary: In the diclofenac 3% gel treatment group, a complete clearance of AK lesions was achieved in 41% of patients compared to 0% of patients in the placebo group (P<0.01). Adverse effects included mild erythema and mild to moderate swelling of the areas treated. No graft rejections or trends for a deterioration of graft function were detected. No meaningful trends were observed in laboratory results. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Van der Geer et al.[58] (2009) Diclofenac 3% gel applied BID for four weeks followed by 5-aminolevulinic acid-PDT two weeks later vs placebo applied BID for 4 weeks followed by 5-aminolevulinic acid-based PDT two weeks later	DB, PC, RCT Patients ≥18 years of age with AK on the dorsum of both hands	N=10 Treatment: 4 weeks Follow-up: 12 months	Primary: TLNS, total TTS, and GII Secondary: Pain during PDT; safety	Primary: In both groups, there was a significant decrease in the number of lesions compared to baseline at six weeks, six months and 12 months after PDT. Prior to PDT, more lesions had cleared in the placebo group than in the diclofenac group. At 12 months after PDT, patients had significantly fewer lesions on the hand treated with diclofenac compared to the placebo hand. At the six-week and six-month visit after PDT, TTS significantly decreased in both groups compared to baseline. Global improvement was scored by patients and by the investigator. No significant differences were found between the treatment groups. During follow-up, no deterioration was scored in either group. At six weeks and six months after PDT, the scores of the independent physician varied from some/moderate improvement to complete remission. These scores were similar for the diclofenac group and the placebo group. Secondary: In the diclofenac group, patients experienced more pain overall, with a mean pain score of 3.0 compared to 2.6 in the placebo group (P=0.2). One patient had a severe reaction after PDT on the hand pre-treated with diclofenac. The hand was swollen, red and erosive, but this resolved spontaneously within a week.
Nelson et al.[59] (2004) Diclofenac 3% gel applied BID	MC, OL Patients 48 to 100 years of age with a diagnosis of five or more AK lesions contained in 1 to 3 blocks (5 cm^2) on the forehead, central	N=76 Treatment: 90 days Follow-up: 30 days	Primary: IGII, TLNS, and CLNS Secondary: Not reported	Primary: Diclofenac gel demonstrated a decrease in the TLNS as early as 30 days after treatment initiation and the decrease was greatest at 90 and 120 days post-treatment. Baseline TLNS was 8.4 lesions, decreasing to 6.1 on day 30, 3.2 on day 60, 1.4 on day 90, and 0.8 on day 120. The percentage of patients with ≥75% lesion clearance was 78% at day 90 and 85% at day 120.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	face, or scalp)			The percentage of patients with 100% lesion clearance was 41% at day 90 and 58% at day 120. Diclofenac gel demonstrated a decrease in the CLNS of 78% from baseline at day 90 and 83% from baseline at day 120. The percentage of patients with ≥75% lesion clearance was 69% at day 90 and 72% at day 120. The percentage of patients with 100% lesion clearance was 32% at day 90 and 45% at day 120. The IGII indicated that AK lesions were significantly improved in 45% of patients and completely improved in 27% of patients at day 90. At day 120, 42% were considered significantly improved and 42% were considered completely improved. Secondary: Not reported
Nelson et al.[60] (2007) Diclofenac 3% gel applied for 90 days	MC, OL Patients with AK lesions of the upper and lower lip (both cutaneous and mucosal surfaces)	N=22 Treatment: 90 days Follow-up: 30 days	Primary: Target lesion clearance, cumulative lesion clearance, IGII, patient satisfaction, tolerability and degree of oozing, crusting, and erythema Secondary: Not reported	Primary: The mean percent decrease of target lesions was 67% at day 90 and 85% at day 120 (P<0.0001). The mean percent decrease of cumulative lesions was 68% at day 90 and 83% at day 120 (P≤0.0002). At day 90 of treatment, 37% of patients had achieved 100% AK lesion clearance based on the TLNS, improving to 42% at day 120. At day 90 of treatment, 32% of patients had 100% AK lesion clearance based on the CLNS, improving to 37% at day 120. At day 90 of treatment, 58% of the patients had 75% or more AK lesion clearance based on the TLNS, improving to 89% at day 120. At day 90 of treatment, 53% of the patients had 75% or more AK lesion clearance based on the CLNS, improving to 79% at day 120. At day 30 of treatment, 66% of the patients evaluated were rated a 4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(completely improved/cleared) or 3 (significantly improved) by the investigators. This efficacy continued to improve at day 60 (80%), day 90 (85%), and day 120 (100%; P≤0.0005). Patients were highly satisfied with diclofenac sodium 3% gel. There were two reported adverse events for the 22 enrolled patients. The mean results for erythema, oozing, and crusting measured at baseline through follow-up at day 120 showed a decrease in erythema and crusting over time with oozing reported for one patient at day 30. Secondary: Not reported
Kose et al.[61] (2008) Diclofenac 3% gel applied QD vs imiquimod 5% cream applied three times per week	OL, RCT Patients with AK	N=49 12 weeks	Primary: Complete response according to IGII and PGII Secondary: Not reported	Primary: According to the IGII results, a complete response was observed in 12% of the diclofenac group and 22% of the imiquimod group (P>0.05). According to the PGII scores, a complete response was observed in 28% of the diclofenac group and 23% of the imiquimod group (P>0.05). Both treatments were well tolerated, with most adverse events related to skin. Secondary: Not reported
Jorizzo et al.[62] (2002) Fluorouracil 0.5% cream applied QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with at least five AKs on the face or frontal scalp that are ≥4 mm in diameter	N=207 1 to 4 weeks	Primary: AK lesion reduction (physician global assessment of improvement ratings), absolute reductions from baseline in AK lesion counts and proportional	Primary: Fluorouracil 0.5% was significantly more effective than placebo for all primary efficacy comparisons (P<0.001). Absolute and percentage reductions in AK lesions from baseline were significantly greater in the fluorouracil group compared to the placebo groups at week one, two, and four (P<0.001). The proportion of patients with total lesion clearance was significantly greater in the fluorouracil group compared to the placebo group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			reductions Secondary: Not reported	The physician global assessment of improvement scores were significantly improved in the fluorouracil group compared to the placebo group at weeks one, two, and four (P<0.001). Secondary: Not reported
Jorizzo et al.[63] (2004) Fluorouracil 0.5% cream applied QD for 7 days vs placebo Patients with residual lesions after the 4-week follow-up period received cryosurgery.	DB, MC, PC, RCT Patients ≥18 years of age with five or more visible or palpable AK lesions on the face	N=144 12 months	Primary: Reduction in AK lesions at the four-week follow-up visit, proportion of patients with complete clearance of AK lesions at the four-week follow-up visit before cryosurgery, occurrence rate at the six-month follow-up visit, clearance rate the six-month follow-up visit Secondary: Not reported	Primary: At four weeks, patients in the fluorouracil group had significantly fewer lesions compared to the patients in the placebo group (4.3 and 9.1 respectively; P<0.001). The absolute and percentage reductions in AK lesions from baseline were significantly greater in the fluorouracil group compared to the placebo group (P<0.001). Complete clearance of AK lesions at the four-week follow-up was observed in 16.7% of patients in the fluorouracil group and 0% in the placebo group (P<0.001). Six months after initial treatment, 30% of patients who had received both fluorouracil and cryosurgery were clear of AK lesions compared to 7.7% in the placebo and cryosurgery group (P<0.001). The mean number and percentage reduction of AK lesions was significantly improved in the fluorouracil and cryosurgery group compared to the placebo and cryosurgery group (P=0.01), though the mean absolute change from baseline was not significant. There were 11 patients clear of AK lesions at the original four-week follow-up and of those, five remained clear at six months. Secondary: Not reported
Loven et al.[64] (2002) Fluorouracil 0.5%	CS, RCT, SB Patients ≥18 years of age with a	N=21 8 weeks	Primary: Reduction in number of AK lesions compared	Primary: There was a reduction in lesion count of 8.8 in the patients receiving the 0.5% cream and 6.1 in patients receiving the 5% cream (P=0.006 and P=0.054 respectively compared to baseline). The difference between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied QD vs fluorouracil 5% cream applied BID	diagnosis of AK with ≥6 AK lesions (minimum of three on each side of treatment area)		to baseline, total clearance of AK lesions at the end of the four-week post-treatment period, tolerability, patient preference questionnaire Secondary: Not reported	groups was also significant (P=0.044). The mean absolute change in baseline in the number of AK lesions by treatment side showed that the 0.5% cream had a mean decrease of 8.2 lesions on the left side of the face and 9.5 on the right side of the face compared to the 5% cream which had a mean decrease of 6.3 lesions on the left side of the face and 6.0 on the right side (significance of this finding not discussed). The percentage change in the number of AK lesions after treatment was 67% for the 0.5% cream and 47% for the 5% cream (P<0.001 and P<0.05 respectively) but no significant difference was observed between groups. The proportion of patients with total clearance of AK lesions was 43% for both treatment groups. Differences in the incidence of erosion, burning, pruritus, pain, edema, and other signs and symptoms were not significant between groups, however a lower cumulative proportion of patients reported these symptoms in the 0.5% group compared to the 5% group. The severity of facial irritation was rated as mild in 19% of patients treated with the 0.5% cream and 14.3% of patients in the 5% group, moderate in 33.3% in the 0.5% group and 28.6% in the 5% group, and severe in 47.6% of patients in the 0.5% group and 57.1% in the 5% group. On the patient preference questionnaire, 85% of patients preferred the 0.5% cream and 15% of patients preferred the 5% cream (P=0.003). Eight patients felt their skin looked better after treatment with the 0.5% cream and one patient felt their skin looked better after treatment with the 5% cream, five people felt that the 0.5% cream “did a better job” compared to two people who felt the 5% cream “did a better job”, and five patients preferred the physical properties of the 0.5% cream compared to 0 patients preferring the 5% cream. Significantly more patients expressed a willingness to re-treat with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.5% cream if necessary (P=0.031). Secondary: Not reported
Stough et al.[65] (2010) Fluorouracil 0.5% cream applied QD for 4 weeks (treatment cycle 1) At week 52, patients with residual lesions on previously treated areas (other than the face/anterior scalp) were treated with cryotherapy. Those with residual lesions on the face/scalp received fluorouracil for four weeks. At week 60, any remaining face/anterior scalp lesions were treated with cryotherapy (treatment cycle 2).	MC, OL Patients with multiple AKs on the face/anterior scalp and other body sites	N=277 18 months	Primary: Safety Secondary: Reduction and clearance rates of AK lesions; facial lesion recurrence rates, identification of the need for retreatment of facial lesions 12 months after initial treatment	Primary: One patient discontinued therapy due to a treatment-related adverse event in treatment cycle 1 due to moderate conjunctivitis during week two. No patients discontinued therapy due to an adverse event during or after treatment cycle 2. Almost all treatment-related adverse events involved either the skin and appendages or the eyes. Application site reactions of skin and appendages were rated as severe in 19.1% of patients. Eye irritation was rated as severe in 1.1% of patients during treatment cycle 1. Only one patient withdrew from the study due to a treatment-related adverse event (moderate conjunctivitis). During both posttreatment periods, no treatment-related adverse events were experienced by 2% or more of patients. Six (2.2%) patients experienced treatment-related adverse events involving the skin. No treatment-related adverse events involving eye irritation were reported posttreatment. Secondary: After week eight, the number of AK lesions was significantly reduced on the face/anterior scalp and all other treated body sites (P<0.0001). Clearance rates were 30.5% (hands), 39.8% (face/anterior scalp), and 79.1% (lips). After week 60, face/anterior scalp AKs were significantly reduced (P<0.0001) and the clearance rate was 33.3%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tanghetti et al.[66] (2007) Fluorouracil 5% cream applied BID for two to four weeks (5-FU) vs imiquimod 5% cream applied two times per week for 16 weeks	MC, RCT, SB Patients >21 years of age with at least four AK lesions on the face, forehead, or scalp	N=39 24 weeks	Primary: Change in AK count, complete clearance, physician's global assessment, patient perception of efficacy, physician's assessment of erythema, and patient perception of discomfort associated with the treatment Secondary: Not reported	Primary: At week 24, the total AK count was reduced by 94% from baseline with 5-FU compared to 66% with imiquimod (P<0.05). Complete clearance of AKs was attained in a significantly greater proportion of patients in the 5-FU group than the imiquimod group by week 24 (84 vs 24%; P<0.01). Mean scores for the physician's global assessment showed that 5-FU resulted in significantly greater efficacy than imiquimod from week four through week 24. Patient ratings were similar and revealed consistently greater efficacy with 5-FU than with imiquimod. Physician assessments of erythema showed that mean levels were moderate in the 5-FU group at week four and decreased post-treatment to less than mild from week eight onward. Mean levels of erythema in the imiquimod group remained at mild levels throughout the 16-week duration of treatment and did not decrease substantially until week 24. The patients' mean ratings of discomfort associated with treatment were less than "slightly painful" in both groups throughout the study. Secondary: Not reported
Jorizzo et al.[67] (2010) Imiquimod 3.75% cream applied QD for 2 two-week cycles vs	DB, RCT Patients with ≥5 AKs on the face following cryosurgery	N=247 26 weeks	Primary: Complete clearance rates; adverse events Secondary: Not reported	Primary: Medial total AK reductions were 86.5% in the imiquimod group compared to 50% in the placebo group (P<0.0001). The proportion of patients with complete clearance was 30.2% in the imiquimod group compared to 3.3% in the placebo group (P<0.0001). One patient discontinued therapy for a treatment-related adverse event in the imiquimod group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Secondary: Not reported
Swanson et al.[68] (2010) Imiquimod 2.5% cream applied QD for 2 two-week cycles vs imiquimod 3.75% cream applied QD for 2 two-week cycles vs placebo	MC, RCT (2 trials) Adults with 5 to 20 AK in an area >25 cm^2 on either the face or the balding scalp, but not both	N=479 Treatment: 2 two-week cycles Follow-up: 8 weeks	Primary: Complete clearance rate, partial clearance rates, percent change in AK number, IGIP score, safety Secondary: Not reported	Primary: Complete clearance rates, partial clearance rates, and percent reduction in AK lesions from baseline were all significant for imiquimod 2.5% and 3.75% compared to placebo. Efficacy for imiquimod 3.75% was numerically greater than that of imiquimod 2.5% for these outcomes, and statistically different at the visit for both partial clearance (P=0.047) and percent change in AK lesions from baseline (P=0.048). Complete clearance rates were 2.5% (95% CI, 0.3 to 8.7) and 10.1% (95% CI, 4.5 to 19) for placebo, 23.5% (95% CI, 14.8 to 34.2) and 38.0% (95% CI, 27.3 to 49.%) for imiquimod 2.5%, and 25.9% (95% CI, 16.8 to 36.9) and 45.6% (95% CI, 34.3 to 57.2) for imiquimod 3.75%, respectively (P<0.001 for all vs placebo). There was a greater increase in mean IGIP scores, and a greater proportion of patients who were considered significantly or much improved, for both imiquimod groups compared to placebo group, and for imiquimod 3.75% compared to 2.5%. There were 15 serious adverse events reported in 12 patients (two placebo, five imiquimod 2.5%, five imiquimod 3.75%). Only one serious adverse event, severe diarrhea in a patient in the imiquimod 3.75% group, was considered by the investigator to be probably related to study cream. Secondary: Not reported
Shaffelburg.[69] (2009) Imiquimod 5% cream applied two times per week vs	PC, RCT Adults with ≥10 AKs on the face	N=25 12 months	Primary: Clearance rates, adverse events Secondary: Not reported	Primary: At month 12, median lesion reductions was 89.9% with imiquimod compared to 74.5% with placebo (P=0.0023). No patient discontinued for an adverse event. Severe local skin reactions occurring in the most patients were erythema (17%) and flaking/scaling/dryness (13%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo All patients were treated with PDT with aminolevulinic acid 20% at baseline and at month 1.				Secondary: Not reported
Lebwohl et al.[70] (2004) Imiquimod 5% cream applied QD two times per week vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with four to eight AK lesions with a contiguous 25 cm^2 treatment area on the face or balding scalp, but not both	N=436 Treatment: 16 weeks Follow-up: 8 weeks	Primary: Complete clearance rate Secondary: Partial clearance rate	Primary: The complete clearance rate was significantly higher in the imiquimod group (45.1%) compared to the placebo group (3.2%; P<0.001). Secondary: The partial clearance rate was significantly better in the imiquimod group compared to the placebo group (59.1 vs 11.8%, respectively; P<0.001). At the eight-week post-treatment visit, the median percent reduction in the number if AK lesions was 83.3% for the imiquimod group compared to 0% for the placebo group (half of the patients in the imiquimod group had at least an 83.3% reduction in the number of AK lesions). During the treatment period 48% of patients in the imiquimod group and 33% of patients in the placebo group had an increase in AK lesion count at one or more of the treatment visits. This was positively correlated with complete clearance rates- patients in the imiquimod group who experienced complete clearance had a higher rate of AK lesion counts during the treatment period. Complete clearance rates increased as the severity of erythema, edema, erosion/ulceration, weeping/exudate, and scabbing/crusting increased (P<0.05).
Stockfleth et al.[71] (2002) Imiquimod 5%	DB, PC, RCT Patients 45 to 85 years of age with	N=36 Treatment: 12 weeks	Primary: Clearance rates at the end of treatment and at 14	Primary: In the imiquimod group, 84% of patients were recorded as having complete clearance of lesions (95% CI, 64 to 95; P<0.001compared to placebo group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied QD three times per week vs placebo	AK in a treatment area that did not exceed 20 cm^2	Follow-up: 1 year	weeks, recurrence of AK lesions in patients treated with imiquimod one-year posttreatment Secondary: Not reported	In the imiquimod group, 8% (two patients) were recorded as having partial clearance (one had a reduction in 50% of AK lesion size and the other had a 75% reduction). No change in size or number of lesions was recorded in the remaining two patients (P<0.001 compared to placebo group). No changes in the size or number of lesions in the placebo group were recorded (P<0.001 compared to imiquimod group). One year after treatment, the clinical recurrence rate in patients treated with imiquimod was 10%. Patients in the placebo group were not assessed at one year. Secondary: Not reported
Stockfleth et al.[72] (2004) Imiquimod 5% cream applied BID three times week vs placebo	DB, PC, RCT Patients 45 to 85 years of age with AK in a treatment area that did not exceed 20 cm^2	N=25 Treatment: 12 weeks Follow-up: 2 years	Primary: Recurrence of AK lesions in patients treated with imiquimod up to two years post-treatment Secondary: Not reported	Primary: At 18 months, 16% of patients developed new AK lesions or were lost to follow-up and at 24 months, 20% had developed new AK lesions or were lost to follow-up. None of these patients had developed SCC after treatment with imiquimod. Ten placebo-treated patients were observed for one year. In those patients, spontaneous remission of AK lesions was reported in one patient; all of the remaining nine developed new AKs and one developed SCC. Secondary: Not reported
Zeichner et al.[73] (2009) Imiquimod 5% cream applied QD once weekly for 24 weeks vs	DB, PC, RCT, SC Patients ≥18 years of age with ≥6 AKs on the face, head, and scalp	N=20 6 months	Primary: Efficacy using an IAS, adverse events Secondary: Not reported	Primary: At the posttreatment visit, 46.7% of patients had marked improvement or better with imiquimod compared to 6.7% of patients receiving placebo. All patients had some improvement with imiquimod, whereas six patients had no improvement and seven had slight worsening with placebo. The average change in IAS score was 12.20 for imiquimod compared to -0.27 for placebo (P=0.0002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Skin reactions were minimal or nonexistent in most patients. Secondary: Not reported
Lee at al.[74] (2005) Imiquimod 5% cream applied QD two or three times per week for 16 weeks vs placebo This study followed patients who had showed complete clearance of AK lesions at 8 weeks post-treatment in four phase III studies, and invited them back for a 1-time evaluation at 12-18 months post-original treatment.	OS Patients 45 to 86 years of age with AK who demonstrated complete clearance of AK lesions at eight weeks post-treatment in four phase III clinical trials of imiquimod vs placebo cream	N=146 Single visit (12 to 18 months post-original treatment)	Primary: AK recurrence rate Secondary: Not reported	Primary: The recurrence rate of AK lesions was lower in patients who had previously received imiquimod three times/week (24.7%) compared to those who had received it two times/week (42.6%). Patients with fair skin had a higher recurrence of AK lesions compared to patients with Fitzpatrick type III-V skin (in the three times/week group: 29 vs 14%, and in the two times/week group: 50 vs 33%). The recurrence rate of AK lesions in the placebo-treated patients was 46.7%. Statistical comparisons between groups were not reported. Secondary: Not reported
Korman et al.[75] (2005) Imiquimod 5% cream applied QD three times per week for 16 weeks	MA Patients ≥18 years of age with four to eight AK lesions with a contiguous 25 cm^2 treatment	N=492 Treatment: 16 weeks Follow-up: 8 weeks	Primary: Complete clearance rate Secondary: Partial clearance rate, median	Primary: Complete clearance was observed in 48.3% of patients in the imiquimod group and 7.2% of patients in the placebo group (P<0.001). Secondary: Partial clearance was observed in 64% of patients in the imiquimod group and in 13.6% of patients in the placebo group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	area on the face or balding scalp		percentage of reduction of baseline AK lesions at the eight-week post-treatment visit	The median percentage of reduction in AK-lesion count was 86.6% in the imiquimod group and 14.3% in the placebo group. Stated another way, half of the patients in the imiquimod group had at least an 86.6% reduction in the number of baseline AK lesions. There was a difference noted in complete and partial clearance rates between the two studies: complete clearance rates were 56.4 vs 40.8% and partial clearance rates were 71.8 vs 56.8%.
Krawtchenko et al.[76] (2007) Imiquimod 5% cream applied QD three times per week for 4 weeks vs fluorouracil (5-FU) 5% ointment applied BID for four weeks vs cryosurgery (one or two courses of therapy)	RCT Patients with a minimum of five typical, visible, and histologically proven AK lesions in one anatomical area of up to 50 cm^2 at head or neck	N=75 Treatment: 4 weeks Follow-up: 12 months	Primary: Complete clearance at the TOC, sustained clearance at 12 months, cosmetic outcome Secondary: Not reported	Primary: Complete clearance at the TOC was observed in 68% of the cryosurgery group, in 96% of the 5-FU group, and in 85% of the imiquimod group, respectively (P=0.03). Total clearance of AK at TOC was histologically confirmed in 32% of the cryotherapy group, 67% of the 5-FU group (P=0.03) and 73% of the imiquimod group (P=0.008). The 12 month sustained clearance rate of initially cleared individual lesions was 28% for cryosurgery, 54% for 5-FU and 73% for imiquimod (P<0.01). The 12 month sustained clearance of the total treatment field was 4, 33, and 73% of patients after cryosurgery, 5-FU, and imiquimod, respectively (P<0.01). Based on the investigator's assessments, 4% of patients in the 5-FU group and the cryosurgery group, but 81% of patients in the imiquimod group showed an excellent cosmetic outcome (P<0.002). Similar results were obtained from the patients' assessments. Secondary: Not reported
Sotiriou et al.[77] (2009) Imiquimod 5%	RCT Patients with non-hyperkeratotic grade	N=30 6 months	Primary: Clearance rate, patient preference, adverse events	Primary: After one month, the overall lesion complete response rate was 70.16% for PDT and 18.26% for imiquimod cream (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied QD three times per week for four weeks (course 1) vs 5-aminolevulinic acid PDT Patients who had not cleared all of their lesions in the imiquimod group participated in a second 4-week treatment cycle (course 2).	I (mild) and grade II (moderate) AKs on the dorsa of hands and forearms		Secondary: Not reported	At month six, the overall lesion complete response rate was 65.32% for PDT (95% CI, 56.9 to 73.7) compared to 55.65% for imiquimod (95% CI, 46.6 to 64.7; P>0.05). At month six, 80% of the lesions in the PDT group had an excellent cosmetic outcome compared to 75% of those treated with imiquimod. Good, fair and poor outcome was observed in 19.1 and 0% lesions treated with PDT and in 20.5 and 0% lesions treated with imiquimod, respectively (P=0.065). Results from patient questionnaire showed that patients preferred PDT regarding the procedure (69 vs 31%). Only 55% of the patients favored PDT in terms of efficacy compared to 45% who favored imiquimod. If they had to be treated again, 70% of patients would prefer PDT compared to 30% of patients who would prefer imiquimod cream. The most commonly reported adverse events were expected, were related to the type of therapeutic procedure and were mild to moderate and transient in nature. No patient discontinued the study due to adverse events. Secondary: Not reported
Lebwohl et al. (2012)[78] Ingenol mebutate 0.015% QD on the face or scalp three consecutive days vs placebo or	DB, MC, RCT Patients ≥18 years of age with four to eight clinically typical, visible, and discrete actinic keratoses within a 25 cm^2 contiguous field on the face or scalp or on the trunk or extremities	N=547 (face or scalp) N=458 (trunk or extremities) 12 months	Primary: Complete clearance of all clinically visible AK at day 57 Secondary: Partial clearance (reduction of ≥75% in number of clinically visible actinic keratoses) on day 57, percentage of	Primary: *Face and scalp* There was a significantly greater proportion of patients that experienced complete clearance in the ingenol mebutate group compared to placebo (42.2 vs 3.7%; P<0.001). *Trunk and extremities* There was a significantly greater proportion of patients that experienced complete clearance in the ingenol mebutate group compared to placebo (34.1 vs 4.7%; P<0.001). Secondary: *Face and scalp* A significantly greater percentage of patients in the ingenol mebutate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ingenol mebutate 0.05% QD on the trunk or extremities two consecutive days vs placebo			change from baseline in total number of actinic keratoses and safety	group compared to placebo had partial clearance (63.9 vs 7.4%; P<0.001). Patients in the ingenol mebutate group had a greater median reduction from baseline in the number of actinic keratoses (83 vs 0%; P value not reported). *Trunk and extremities* A significantly greater percentage of patients in the ingenol mebutate group compared to placebo had partial clearance (49.1 vs 6.9%; P<0.001). Patients in the ingenol mebutate group had a greater median reduction from baseline in the number of actinic keratoses (75 vs 0%; P value not reported). Patients treated with ingenol mebutate had greater local skin reaction scores compared to placebo. The most common adverse reactions were pruritus, irritation and pain.
Atopic Dermatitis				
Gollnick et al.[79] (2008) Pimecrolimus 1% cream applied BID at the first sign or symptom of a relapse vs placebo Patients were also allowed to use moderately potent corticosteroids to treat flares.	DB, MC, PC, PG, RCT Adults ≥18 years of age with mild to moderate AD who were clear/almost clear of disease	N=543 26 weeks	Primary: Number of days without topical corticosteroid use for disease worsening, flares requiring topical corticosteroid use, physician office visits Secondary: Not reported	Primary: The mean number of topical corticosteroid-free days was significantly higher in the pimecrolimus cream group than in the placebo cream group (152 vs 138.7 days, respectively; P<0.001). Treatment with pimecrolimus cream reduced the mean number of flares requiring topical corticosteroid use from 1.39 to 0.97 compared to placebo cream (P=0.0014). Patients on pimecrolimus cream made 30% fewer unscheduled visits to their physician's office than patients on placebo cream (156 vs 223, respectively). Secondary: Not reported
Sigurgeirsson et al.[80] (2008)	DB, MC, PC, RCT Children and	N=521 26 weeks	Primary: Number of days without topical	Primary: The mean number of topical corticosteroid-free days was significantly higher in the pimecrolimus cream group than in the control group (160.2

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pimecrolimus 1% cream applied BID at the first sign or symptom of recurring AD vs placebo Patients were allowed to use moderately potent corticosteroids to treat flares.	adolescents 2 to 17 years of age with a history of mild or moderate AD who were clear/almost clear of disease		corticosteroid use for disease worsening, flares requiring topical corticosteroid use, physician office visits Secondary: Not reported	vs 137.7 days, respectively; P<0.0001). Patients on pimecrolimus cream experienced 50% fewer flares requiring topical corticosteroids than patients on placebo cream (0.84 vs 1.68, respectively; P<0.0001). Patients on pimecrolimus cream had fewer unscheduled visits to their physician's office than patients on placebo cream (87 vs 246, respectively). Secondary: Not reported
Zuberbier et al.[81] (2007) Pimecrolimus 1% cream applied BID vs placebo Patients were allowed to use prednicarbate 0.25% cream if a flare occurred that was not controlled by study medication.	RCT Children and adolescents 2 to 17 years of age with a history of severe AD	N=184 24 weeks	Primary: Percentage of days patients used prednicarbate instead of study medication Secondary: Not reported	Primary: Patients on pimecrolimus required topical corticosteroids on a mean of 29% of study days compared to 35% of patients on placebo (P=0.1841). On the head and neck only, patients on pimecrolimus required topical corticosteroids on a mean of 10% of study days compared to 19% of patients on placebo (P=0.0009). In patients with acute severe disease (IGA > or=4), topical corticosteroids were used on 28% of the days in the pimecrolimus group compared to 45% in the placebo group (P= 0.0024). In patients with acute severe disease (IGA > or=4) on the head and neck, topical corticosteroids were used on 10% of study days with pimecrolimus vs 30% with placebo (P<0.0001). Secondary: Not reported
Zuberbier et al.[82] (2008)	DB, MC, RCT Children and	N=140 24 weeks	Primary: Percentage of days patients used	Primary: Patients in the pimecrolimus group needed prednicarbate treatment on the face on 11.7% of the study days compared to 20.7% of the study days in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pimecrolimus 1% cream applied BID vs placebo Patients were allowed to use prednicarbate 0.25% cream if a flare occurred that was not controlled by study medication.	adolescents 2 to 17 years of age with facial AD and mild to moderate disease after treatment of the initial flare with prednicarbate 0.25% cream		prednicarbate instead of study medication Secondary: Not reported	the placebo group (P=0.0024). Fifty percent of patients in the pimecrolimus group had no flare on the face during the treatment period compared to 37.5% of patients in the placebo group (P=0.012). The median time to first flare in pimecrolimus-treated patients was twice as long as in patients receiving placebo (138 vs 68 days, respectively; P=0.01). Primary: Percentage of days patients used prednicarbate instead of study medication Secondary: Not reported
Murrell et al.[83] (2007) Pimecrolimus 1% cream applied BID vs placebo	DB, PC, RCT Patients 12 years of age or older with mild to moderate head and neck AD who were intolerant of, or dependent on, topical corticosteroids	N=200 12 weeks (6-week RCT followed by 6-week OL phase)	Primary: Facial investigator's global assessment score at six weeks Secondary: Head and neck EASI, pruritus score, eyelid dermatitis, facial skin atrophy and telangiectasia	Primary: A significantly higher percentage of patients treated with pimecrolimus was cleared or almost cleared of facial AD compared to placebo (47 vs 16%, respectively). Secondary: A statistically significant difference was also seen on head and neck EASI and pruritus score. Significantly more pimecrolimus-treated patients than placebo-treated patients achieved clearance of eyelid dermatitis (45 vs 19%, respectively). Among the 77 patients with skin atrophy at baseline, treatment with pimecrolimus was associated with a reversal in skin thinning. Of the 112 patients with telangiectasia at baseline, no statistically significant difference was seen between treatment groups. Adverse events occurred with similar frequency in both groups.
Kapp et al.[84] (2002)	DB, MC, PC, PG, RCT	N=251 12 months	Primary: Incidence of flares of AD at six	Primary: There was a significantly lower number of flares in the pimecrolimus group compared to the placebo group (67.6% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pimecrolimus 1% cream applied BID at the first sign of a flare until complete clearance of signs and symptoms vs placebo Patients were also allowed to use moderately potent corticosteroids to treat flares.	Infants 3 to 23 months of age with a clinical diagnosis of AD		months Secondary: Investigator's IGA score, (EAS), and caregiver's assessments of pruritus and overall level of disease control (pruritus was assessed by the caregiver for 24 hours prior to study visits and ranked on a scale of 0 [none] to 3 [severe], and were asked to assess the level of control over the preceding seven days on a 4-point scale. The IGA score, pruritus assessment, and caregiver assessments were dichotomized into treatment success [score of 0 or 1] or treatment failure [all other scores]).	pimecrolimus group had no flare at six months vs 30.4% in the placebo group; P<0.001). At 12 months, 56.9% of patients in the pimecrolimus group had no flares compared to 28.3% of patients in the placebo group. Baseline severity of AD did not affect the trend towards a lower incidence of flares in the pimecrolimus group. Patients in the pimecrolimus group had a significantly longer flare-free period compared to patients in the placebo group (P<0.001) and the mean number of flares was lower in the pimecrolimus group compared to the control group (P<0.001). In the pimecrolimus group, 63.7% of patients did not require a corticosteroid during the study period, compared to 34.8% in the placebo group and the proportion of study days on a corticosteroid was 3.2% in the pimecrolimus group compared to 6.2% in the placebo group. Secondary: An IGA score of 0 or 1 (clear or almost clear) was achieved in 44.6% of patients in the pimecrolimus group compared to 8.7% in the placebo group (P<0.001). The maximum benefit of therapy was achieved by day 22 in the pimecrolimus group compared to three months in the placebo group and the magnitude of effect was greater in the pimecrolimus group (54.9% had achieved an IGA score of 0 or 1 by day 22 compared to 39.1% in the placebo group (P=0.034). At month six, a significantly greater proportion of patients in the pimecrolimus group had clear or nearly clear skin compared to those in the placebo group (52.9 vs 37.0%; P=0.03). At month 12, a higher number of patients in the pimecrolimus group had clear or nearly clear skin compared to the placebo group, though this difference was not statistically significant (53.9 vs 47.8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				EASI mean total scores were significantly lower for patients in the pimecrolimus group compared to the placebo group at day 43 (P<0.0001) but were not significantly different at month six, nine, or 12 (P>0.076). Pruritus scores were significantly lower for patients in the pimecrolimus group compared to the placebo group at day 43, month six and month nine (P<0.016) but were not significantly different at month 12 (P=0.074). A significantly higher number of patients in the pimecrolimus group had a caregiver assessment of 0 or 1 (complete or good disease control) compared to the placebo group at day 43 and month six (P<0.016), but the differences were not significant at month nine or 12 (P>0.058).
Staab et al.[85] (2005) Pimecrolimus 1% cream applied BID vs placebo	DB, MC, PC, PG, RCT Patients 3 to 23 months of age diagnosed with atopic eczema affecting some part of face and affecting ≥5% of BSA, and having a baseline IGA score of mild severity or greater	N=196 4 weeks	Primary: Parents' quality of as measured by the questionnaire for PQoL-AD, pruritus and sleep loss, using the SCOR-AD, severity of disease, using IGA, and degree of disease control as measured by the EASI Secondary: Not reported	Primary: Significant improvements were seen in all domains of the PQoL-AD in favor of pimecrolimus (P<0.05). The most significant differences were seen in the domains of "psychosomatic well-being", "emotional coping", and "acceptance of disease". There was a significant pruritus treatment effect observed in favor of pimecrolimus by day two (P=0.018) and a significant improvement in sleep observed by day three (P=0.002). By day 29, the mean percentage change in the SCOR-AD index was -55.2% for pimecrolimus and 1.13% for the placebo group (P=0.002). Treatment success (IGA=0 [clear] or IGA=1 [almost clear]) was observed in 53.5% of patients in the pimecrolimus group at day 29 compared to 10.6% of patients in the placebo group (P<0.001). The mean EASI decreased by 71.5% in the pimecrolimus group compared to 19.4% in the placebo group by the end of the four week treatment phase (P<0.001). The reduction in EASI was observed as early as day four in the pimecrolimus group and it decreased by 38.5% compared to a decrease of 17.6% in the placebo group on day four (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Kaufman et al.[86] (2006) Pimecrolimus 1% cream applied BID for 7 days vs placebo	DB, MC, PC, PG, RCT Patients 18 to 81 years of age with mild to moderate AD affecting ≥5% of total BSA	N=198 7 days of treatment with optional 5 week extension	Primary: Time taken to achieve pruritus improvement of ≥1 point on a 4-point pruritus severity scale compared to baseline Secondary: Percentage of patients achieving pruritus improvement of ≥1 point compared to baseline within 48 and/or 72 hours, percentage of patients with a pruritus response within four, five, six, and seven days of treatment, the percentage of patients with a pruritus severity score of 0 (absent) or 1 (mild) for treatment days two, three, four, five, six, and seven regardless of baseline scores, and the percentage of patients with an	Primary: There was a significant improvement in pruritus (≥1 point) in the pimecrolimus group compared to the placebo group over the seven day treatment period (P=0.001). The median time to pruritus improvement (≥1 point) was two days in the pimecrolimus group compared to four days in the placebo group. Secondary: Improvements in pruritus scores (≥1 point) were seen by day two (within 48 hours) in 56% if pimecrolimus patients compared to 34% of patients in the placebo group (P=0.003). By day three (within 72 hours), 72% of pimecrolimus patients reported improvements in pruritus severity compared to 45% of placebo patients (P<0.001). In the pimecrolimus group, 81% of patients sustained their pruritus relief on days four to seven compared to 63% in the placebo group who showed improvement by day seven (P<0.001). For days two to seven: 42% of pimecrolimus patients recorded “mild” or “absent” pruritus scores compared to 27% in the placebo group by day two (P=0.04), 55% of pimecrolimus patients recorded “mild” or “absent” pruritus scores compared to 31% in the placebo group by day three (P=0.002), and 63% of pimecrolimus patients recorded “mild” or “absent” pruritus scores compared to 36% in the placebo group by day seven (P<0.001). Significant improvements in IGA score (≥1 point reduction) were seen in 53% of the pimecrolimus patients compared to 20% of the placebo patients by day 7 (P<0.001). During the open label extension period (146 patients), pruritus and IGA score improvements were maintained or improved in 92% of patients previously treated with placebo and 76% of patients previously treated with pimecrolimus.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			IGA score improvement of ≥1 point at study completion compared to baseline	During the extension, 83% of patients overall improved or maintained their condition, and 45% scored their pruritus as "mild" and 25% scored their pruritus as "absent" at the end of the extension.
Hoeger et al.[87] (2009) Pimecrolimus 1% cream BID vs placebo Completion of the DB phase occurred on day 43 or at the time a patient achieved a facial IGA of 0. During the OL phase patients were treated intermittently with pimecrolimus BID; treatment was discontinued when clearance occurred and was resumed upon recurrence of first signs and symptoms of AD. Use of other	DB, MC, OL, PC, RCT Patients 2 to 11 years of age with mild to moderate facial AD who were dependent on, or intolerant of topical corticosteroids	N=200 12 weeks (6 weeks DB followed by 6 weeks OL)	Primary: Efficacy (assessed by facial IGA score) Secondary: Head and neck EASI, overall EASI, pruritus severity score, time to clearance of facial AD, the amount of study drug used, safety and tolerability	Primary: A significantly greater proportion of patients treated with pimecrolimus became clear/almost clear of facial AD lesions at day 43 compared to patients in the placebo group (74.5 vs 51.0%, respectively; P<0.001). Statistically significant differences between groups were apparent at day 22, with 57.1% of pimecrolimus-treated patients experiencing clearance or almost clearance of their facial AD compared to 36.0% of placebo-treated patients (P=0.004). Improvements in facial IGA continued into the OL phase for the pimecrolimus group (87.6% at day 64 and 90.3% at day 85). A substantial improvement was also seen in patients who switched from placebo to pimecrolimus in the OL phase, of whom 79.5% at day 64 and 88.6% at day 85 achieved facial IGA scores of 0/1. Secondary: A significantly greater proportion of pimecrolimus-treated patients at day eight were EASI responders (defined as patients achieving ≥60% improvement in head and neck EASI compared to baseline) compared to placebo (37.8 vs 18.0%, respectively; P<0.003), rising to 77.6 vs 55.0%, respectively, at day 43 (P<0.001). Improvement continued into the OL phase for the pimecrolimus group and for those who switched to pimecrolimus. Overall EASI scores showed a similar trend to those for the head and neck, with significantly more overall EASI responders in the pimecrolimus group than the placebo group at day 22 (51.0 vs 27.0%, respectively; P<0.001) and at day 43 (71.4 vs 38.0%, respectively; P<0.001). At day eight, 89.8 and 60.0% of pimecrolimus- and placebo-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medications that could potentially have an effect on AD (topical or systemic corticosteroids, phototherapy, topical antibiotics or oral immunosuppressants) was not permitted.				patients had no or mild pruritus of the head and neck (P<0.001), increasing to 93.9 vs 68.0%, respectively, at day 43 (P<0.001). This improvement continued into the OL phase in the pimecrolimus group, and in those who switched to pimecrolimus. Facial AD cleared twice as rapidly in patients treated with pimecrolimus compared to placebo (median time to clearance [facial IGA 0/1]: 22 vs 43 days, respectively; P value not reported). A higher proportion of pimecrolimus-treated patients was cleared of eyelid dermatitis at six weeks compared to placebo-treated patients (41.8 vs 31.0%, respectively; P=0.140). This improvement continued into the OL phase, and a marked improvement was seen in those patients who switched to pimecrolimus. Drug usage, by weight, for the head and neck was similar in the pimecrolimus and placebo groups in both the DB and OL phases. The mean±SD of total usage during the DB phase in the pimecrolimus and placebo groups were 24.2±19.5 g vs 26.9±21.9 g (P value not reported). In the OL phase drug usage was 19.0±15.5 g vs 21.6±18.4 g (P value not reported). Drug usage for the rest of the body was slightly lower in the pimecrolimus group than in the placebo group (DB phase, 45.5±28.7 vs 50.7±39.0 g; OL phase, 35.6±25.4 vs 39.0±28.5 g; P values not reported). Most treatment-emergent adverse events were mild to moderate in both phases of the study. Forty out of 99 (40.4%) pimecrolimus-treated patients and 34/101 (33.7%) placebo-treated patients experienced at least one adverse event during the DB phase. During the DB phase the most commonly reported adverse events were nasopharyngitis, application site irritation and pyrexia. Fewer adverse events were reported during the OL phase with the frequency of application site reactions being comparable between the two groups.
Papp et al.[88] (2005) Pimecrolimus 1% cream applied BID	ES, OL Infants 3 to 23 months of age with a clinical diagnosis	N=91 12 months	Primary: Proportion of patients with no flares, treatment success rates	Primary: The median number of days of pimecrolimus use during the 12 months of the present study was 99.0, and 27.5% of these patients required corticosteroids during this time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
at the first sign of flare until complete clearance of signs and symptoms Patients were also allowed the use of moderately potent corticosteroids to help treat flares.	of AD		(proportion of patients with clear or almost clear skin as indicated by an IGA of 0 or 1), EASI, percentage of total BSA affected by AD, course of disease (proportion of disease-free days without the use of any medication), adverse effects Secondary: Not reported	Seventy-six patients used pimecrolimus for two years (original study by Kapp et al, and present study combined) and there was a progressive reduction in the mean proportion of pimecrolimus treatment days from 73.7% during the first three months of the second year to 42.3% during the last three months of the second year. The proportion of patients in this study who did not use topical corticosteroids during the first year was 71.1% and this increased to 72.4% during the second year. Overall, 57.9% of patients in the pimecrolimus group did not use corticosteroids at all during the two years. The percentage of patients experiencing no flares during the second year was 76.9% and 8.8% had only a single flare. In patients on pimecrolimus for two years, the proportion experiencing no flares increased from 77.6% during the first year to 85.5% during the second year. The proportion of patients who were clear or almost clear of signs of AD increased from 36.3% at the beginning of the second year to 71.4% at the end of the second year. The mean EASI score decreased from 5.8 to 2.9 and the mean percentage of total BSA affected by AD decreased from 11.3% to 6.6%. At the beginning of the first, DB year, 75% of patients treated with pimecrolimus for two years had moderate or severe disease. At the end of the second year, the percentage of patients with minimal residual activity or were clear of signs of AD was 69.7%. Only 13.2% had an IGA of >2. In this same group of patients, an improvement in EASI scores was already evident at 3 months and persisted for the remaining 21months. The mean percentage of total BSA affected by AD decreased from 28.4% at the beginning of the first year to 7.3% at the end of the second year. The proportion of disease-free days increased from 30% during the first six months of the second year to 50.9% during the last two months. The majority of adverse effects reported were conditions commonly seen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in childhood such as nasopharyngitis, pyrexia, cough, diarrhea, ear infection, bronchitis, rhinitis, vomiting, and gastroenteritis. There were no reports of application site reactions. Secondary: Not reported
Meurer et al.[89] (2010) Pimecrolimus 1% cream applied BID and fluticasone 0.05% cream applied BID vs fluticasone 0.05% cream applied BID (TCS)	DB, MC, PC, RCT Patients 2 to 17 years of age with severe AD	N=376 Treatment: 4 weeks Observation: 12 weeks	Primary: Incidence of predefined adverse events associated with the topical use of corticosteroids Secondary: Incidence of all other adverse events, time to relapse of AD, time to AD treatment success, QOL	Primary: With the exception of erythematous rash, seen more often in the combination group, there were no differences in the frequency of adverse events of clinical interest (e.g., folliculitis, infected eczema, or herpes simplex infection) between the combination and monotherapy groups. Secondary: The overall incidence of adverse events was comparable between the combination and TCS monotherapy groups. The most frequently reported adverse events in both treatment groups were infections and infestations in 25 to 30% of patients. The overall proportion of patients with severe adverse events was 2.6% in the combination group and 1.6% in the TCS monotherapy group. The proportion of patients with adverse events related to the study drug was higher in the combination group (6.3%) compared to the TCS monotherapy group (4.4%). There was no significant difference in the time to relapse of AD in the observational period between the combination and TCS monotherapy treatment groups (P=0.754). There was no significant difference between the treatment groups with respect to treatment success for whole body IGA or facial IGA (P=0.790 and P=0.085, respectively). There was no significant difference between the two treatment arms for change in overall EASI from baseline during the treatment period (P=0.827).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference between the combination group and TCS monotherapy group with respect to pruritus treatment success (P=0.528). The mean percentage decrease in PQoL-AD total score from baseline was higher in the TCS monotherapy group (54.4%) compared to the combination group (35.7%).
Kempers et al.[90] (2004) Pimecrolimus 1% cream applied BID until clearing or for 6 weeks vs tacrolimus 0.03% ointment applied BID until clearing or for 6 weeks	MC, PG, RCT, SB Patients 2 to 17 years of age with moderate AD	N=141 6 weeks	Primary: Incidence of local application-site reactions Secondary: Formulation attributes, safety, and efficacy (measured by IGA and patient assessment)	Primary: The incidence of application-site reactions decreased with time in both groups, but this was more pronounced in the pimecrolimus group. Application-site reactions were experienced by 24% of patients in the pimecrolimus group and 26% in the tacrolimus group. Erythema/irritation was reported in 8% of the pimecrolimus patients compared to 19% in the tacrolimus patients (P=0.039). Itching was reported in 8% of the pimecrolimus patients compared to 20% in the tacrolimus patients though this difference was not statistically significant (P=0.073). Warmth/stinging/burning was reported in 20% of the pimecrolimus patients compared to 17% in the tacrolimus patients though this difference was not statistically significant (P=0.931). The duration of application-site reactions tended to be shorter in the pimecrolimus group compared to the tacrolimus group. None of the patients in the pimecrolimus group who experienced erythema/irritation reported that it lasted longer than 30 minutes, compared to 85% of patients in the tacrolimus group who reported that this application-site reactions lasted between 30 minutes and 12 hours (P<0.001). None of the patients in the pimecrolimus group who experienced warmth/burning/stinging reported that it lasted longer than 30 minutes, compared to 67% of patients in the tacrolimus group who reported that this application-site reactions lasted between 30 minutes and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				12 hours (P<0.001). The difference between the two treatment groups in the duration of itching was not significant (P=0.559). Secondary: A significantly higher proportion of patients/caregivers in the tacrolimus group reported that their skin felt oily compared to the pimecrolimus group (P<0.001). There was no significant difference in the proportion of patients who reported that their skin felt dry during treatment (P=0.308). At day 43, a significantly higher proportion of patients reported that pimecrolimus was suitable for use on sensitive facial skin, had a non-sticky feel, and was easy to apply and rub in compared to tacrolimus (P<0.020). There was no significant difference in the spreadability of either product (P=0.06). The overall incidence of adverse effects was similar between the treatment groups: 86% of patients in the pimecrolimus group reported adverse effects compared to 845 in the tacrolimus group. There was no significant difference in IGA scores of clear/almost clear between treatment groups at any visit, though both increased compared to baseline values (P>0.05). On day 22, significantly more patients in the tacrolimus group reported absent or mild pruritus compared to the pimecrolimus group (P=0.042), though differences on all other days were not significant. On day 43, there were no significant differences between treatment groups in the proportion of patients achieving IGA or pruritus scores of 0 or 1 (P=0.493).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				IGA response rates were slightly higher in the tacrolimus group compared to the pimecrolimus group from day eight to 43, though these differences were not statistically significant (except for day 22 as mentioned above). More than 60% of patients in both groups reported absent or mild pruritus. The change from baseline in BSA affected by AD was similar in both treatment groups, though pimecrolimus tended to have a greater effect on the head and neck compared to tacrolimus which tended to have a greater effect on the legs.
Doss et al.[91] (2010) Tacrolimus 0.03% ointment applied BID vs fluticasone 0.005% ointment applied BID	DB, MC, RCT Patients 2 to 15 years of age with moderate to severe AD who had responded inadequately to topical corticosteroids	N=239 6 weeks	Primary: Response rate at week three Secondary: Changes in the mEASI score, global assessment of clinical response by investigators and patients, pruritus, sleep quality	Primary: In the PP analysis, response rates were 86.3% with tacrolimus and 91.5% with fluticasone (95% CI, -11.8 to 1.2). Tacrolimus was found to be non-inferior to fluticasone. In the ITT analysis, response rates were 84.3% with tacrolimus and 89.5% with fluticasone (P=0.0012). Secondary: The overall mean percentage change in total mEASI score was -79.5% in the tacrolimus group and -82.3% in the fluticasone group. Moderate or better improvement on the physicians' global assessment occurred in 93.6 and 92.4% of patients in the tacrolimus and fluticasone groups, respectively (ITT; P=0.05). Patients/parents considered global condition to have improved or greatly improved in 86.9% of patients receiving tacrolimus and 88.6% of those receiving fluticasone (ITT; P=0.047, PP; P=NS). Patients' assessment of pruritus improved in those receiving tacrolimus, with median change at day 21 of -84.0% compared to -91.5% in those receiving fluticasone (P=0.008). There was no significant difference in quality of sleep between the treatment groups (median change: tacrolimus, -91.5%; fluticasone, 92.6%). The incidence of adverse events was similar among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Application site burning occurred more frequently with tacrolimus.
Doss et al.[92] (2009) Tacrolimus 0.1% ointment applied to facial lesions BID vs fluticasone 0.005% ointment applied to facial lesions BID	DB, MC, RCT Patients ≥16 years of age with moderate to severe AD of the face	N=468 3 weeks	Primary: Change in the mLEASI score Secondary: Facial erythema and pruritus, global clinical response	Primary: After three weeks, the response rate was 93.3% with tacrolimus and 87.8% with fluticasone as assessed by mLEASI (ITT; P=0.026, PP; P=0.046). Secondary: After three weeks, median changes in facial pruritus scores were -89.3% with tacrolimus compared to -88.3% with fluticasone (P=NS). Facial erythema improved in both treatment groups (P=NS). The physicians' global assessment of clinical response for the facial region was significantly different between the two groups. A total of 88% of patients in the tacrolimus group and 79% of patients in the fluticasone group showed marked or excellent improvement, or clearance of lesions (P=0.043). The patients' global assessment of clinical response for the facial region was significantly different between the two treatment groups. A total of 64% of patients in the tacrolimus group and 55% of patients in the fluticasone group considering their condition to have 'greatly improved' (P=0.014).
Reitamo et al.[93] (2005) Tacrolimus 0.1% ointment applied BID until clear and then for seven additional days vs hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) and	DB, MC, RCT Patients ≥18 years of age with moderate to severe AD	N=972 6 months	Primary: Response rate at month three (improvement in mEASI) Secondary: Response rate at other time points, mEASI, EASI, physician's global evaluation of clinical response, patient's assessment of global response,	Primary: At month three, 72.6% of patients in the tacrolimus group responded to treatment compared to 52.3% of patients in the corticosteroid group (P<0.001). Secondary: The tacrolimus group had a higher response rate at all other time points throughout the six months compared to the corticosteroid group (P<0.001). A significant improvement in mEASI was observed as early as day eight in both treatment groups and increased up to the six-month point. At month six, the median percentage change in mEASI was -87.7% in the tacrolimus group and -82.5% in the corticosteroid group (P<0.008). The improvement in EASI and affected BSA followed the same trend. For

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydrocortisone acetate 1% ointment applied BID (head and neck)			physician's assessment of individual signs, affected BSA, patient's assessment of itch and quality of sleep, and the number of days on treatment as a percentage of days in the study	EASI, the median percentage change was -85.0% in the tacrolimus group and -81.5% in the corticosteroid group (P=0.01). For the BSA, the median percentage change was -88.2% for the tacrolimus group and -80.3% in the corticosteroid group (P=0.001). Physicians' global assessments of clinical response was higher in the tacrolimus group compared to the corticosteroid group (P<0.001). There was a greater reduction in individual signs of AD in the tacrolimus group compared to the corticosteroid group and more patients in the tacrolimus group experienced clearance or excellent improvement (at month six, 61.3% of tacrolimus patients and 46.4% of corticosteroid patients had clearance or excellent improvement, P<0.001). Patients' assessments were significantly higher in the tacrolimus group compared to the corticosteroid group. At six months, 86.6% of patients in the tacrolimus group rated their AD as much better or better compared to 71.8% of patients in the corticosteroid group (P<0.001). Itch and quality of sleep improved significantly in both treatment groups. Patients in the tacrolimus group remained in the study longer compared to the corticosteroid group and had a lower number of treatment days as a percentage of days in the study.
Poole et al.[94] (2010) Tacrolimus 0.1% ointment applied BID until clear and then for seven additional days vs hydrocortisone butyrate 0.1%	DB, MC, RCT Patients ≥18 years of age with moderate to severe AD	N=972 6 months	Primary: QOL (SF-36) assessed using a physical component summary and a mental component summary Secondary: Not reported	Primary: For the physical component summary, patients receiving tacrolimus gained 3.3 points on average compared to 2.3 points in the corticosteroid group (P=0.033). For the mental component summary, patients receiving tacrolimus improved by an average 6.0 points compared to 3.4 points in the corticosteroid group (P<0.001). For the eight SF-36 domains, all except 'Physical Functioning' (P=0.106) showed significant differences in favor of tacrolimus. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied BID (trunk and extremities) and hydrocortisone acetate 1% ointment applied BID (head and neck)				Not reported
Mandelin et al.[95] (2010) Tacrolimus 0.1% ointment applied BID vs hydrocortisone acetate 1% ointment applied BID (head and neck) and hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) Flares were treated BID until 7 days after clearance, and treatment resumed in the event of a recurrence or new flare.	DB, RCT, SC Patients ≥18 years of age with moderate to severe AD	N=80 1 year	Primary: Response rate as measured by affected BSA, improvement in EASI and mEASI, adverse events Secondary: Not reported	Primary: After three months, the proportion of patients with > 60% improvement in mEASI was similar for both groups (tacrolimus, 77.5%; hydrocortisone, 72.5%). After six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by affected BSA: 5.4% (95% CI, 1.5 to 28.4) and 15.5% (95% CI, 5.6 to 48.8), respectively (P<0.05). After six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by the EASI score: 3.2 (95% CI, 1.4 to 9.1) and 7.1 (95% CI, 3.0 to 17.9), respectively (P<0.05). After 12 months, 57.5% of patients receiving tacrolimus were rated by their physician as having a response of "cleared or excellent" for the global evaluation of clinical response compared to 42.5% of patients receiving the corticosteroid regimen (P=0.26). When the head and neck region was considered separately, 60.0% of the patients receiving tacrolimus and 30.0% of the patients receiving the corticosteroid regimen were rated as "cleared or excellent" by the physician (P=0.01). Adverse events occurred in 40 patients (100%) in the tacrolimus group and in 34 patients (85.0%) in the corticosteroid group (P=0.03), which was primarily due to the higher incidence of application-site skin burning sensation with tacrolimus. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Kubota et al.[96] (2009) Phase 1 Tacrolimus 0.03% ointment applied in the morning and a strong- or weak-potency corticosteroid ointment in the evening applied for 2 weeks Phase 2 Tacrolimus 0.03% ointment applied BID on weekdays and a strong- or weak-potency corticosteroid ointment applied on weekends for 2 weeks Phase 3 Tacrolimus 0.03% ointment applied QD for 2 weeks, then emollient applied for 6 weeks (with use of tacrolimus for flares)	OL Pediatric patients with AD	N=28 12 weeks	Primary: EASI score, IGA, severity of pruritus, sleep disturbance, and CDLQI or IDQOL questionnaires Secondary: Not reported	Primary: After the sequential therapy, mean EASI scores significantly decreased from 12.87 at baseline to 1.43 at six weeks, and continuous improvement was observed throughout the following six-week period (1.39 at 12 weeks). The patient assessment of pruritus score decreased during the initial two weeks, from 2.35 at baseline to 1.03, and this improvement was maintained throughout the study (1.00 at 12 weeks). Sleep disturbance score decreased from 1.00 at baseline to 0.03 at six weeks and to 0.04 at 12 weeks. Investigators' Global Assessment at six weeks showed 3% clear, 48% excellent, 39% marked, and 10% moderate improvement, and 7, 46, 42%, and 4% at 12 weeks, respectively. On the CDLQI survey, the mean QOL score significantly improved, from 5.14 at baseline to 2.33 at six weeks and to 2.63 at 12 weeks. On the IDQOL survey, the mean QOL score also significantly improved, from 6.40 at baseline to 2.20 at six weeks and 2.75 at 12 weeks. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fleischer et al.[96] (2007) Tacrolimus 0.1% ointment applied BID vs pimecrolimus 1% cream applied BID	MC, RCT, SB Patients ≥18 years of age with moderate to very severe AD	N=281 6 weeks	Primary: Response rate as measured by the EASI, treatment success rate Secondary: Not reported	Primary: Tacrolimus-treated patients had significantly greater reduction in the EASI score compared to pimecrolimus-treated patients (57 vs 39%, respectively; P=0.0002). Treatment success was significantly greater among the tacrolimus-treated patients compared to pimecrolimus-treated patients (40 vs 22%, respectively; P=0.001). Improvement in percentage of total BSA affected was significantly greater among the tacrolimus-treated patients compared to pimecrolimus-treated patients (49 vs 34%, respectively; P=0.01). Both treatment groups had similar improvements in patient assessment of itch. Significantly more pimecrolimus-treated patients than tacrolimus-treated patients withdrew from the study due to lack of efficacy (10 vs 1, respectively; P=0.005). There were no significant differences in the incidences of adverse events between the two treatment groups. Secondary: Not reported
Abramovits et al.[97] (2008) Tacrolimus 0.1% ointment applied BID vs pimecrolimus 1% cream applied BID	MC, RCT, SB Patients ≥16 years of age with moderate AD	N=188 6 weeks	Primary: Response rate as measured by the EASI, Investigators' global AD assessment Secondary: Not reported	Primary: Tacrolimus ointment-treated patients had significantly greater reduction in EASI score compared to pimecrolimus cream-treated patients (59 vs 43%, respectively; P=0.01). Significantly more tacrolimus ointment-treated patients than pimecrolimus cream-treated patients improved by 1 or more grades on the investigators' global AD assessment (P<0.02). A total of five pimecrolimus cream-treated patients discontinued the study early due to lack of efficacy compared to no tacrolimus ointment-treated patients (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events occurred at a similar frequency for both treatment groups. Secondary: Not reported
Paller et al.[99] (2005) Tacrolimus 0.03% or 0.1% ointment applied BID for up to 6 weeks or until 7 days after clearance vs pimecrolimus 1% cream applied BID for up to 6 weeks or until 7 days after clearance	Pooled analysis (3 trials) Patients ≥2 years of age with mild to severe AD	N=1,065 6 weeks	Primary: Change in EASI score at week six Secondary: IGADA where success means clear or almost clear, percent of BSA affected, patient's assessment of itch, and safety	Primary: The change in baseline in EASI score at week six was significantly greater in the tacrolimus groups compared to the pimecrolimus groups in adults (54.1 and 34.9%, respectively; P<0.0001), children with moderate to severe disease (67.2 and 56.4%, respectively; P=0.04), and in the combined analysis (52.8 and 39.1%, respectively; P<0.0001). In the study evaluating pediatric patients with mild AD, there was a significant difference in EASI score favoring tacrolimus at week one (P=0.04), and a trend toward advantage with tacrolimus at week six, but this difference was not significant (P=0.07). In all patients with moderate disease, the percentage reduction in EASI score at week six was significantly higher in the tacrolimus group compared to the pimecrolimus group (P=0.003). In patients with head and neck involvement, the percentage reduction in EASI score at week six was greater in the tacrolimus group compared to the pimecrolimus group (57 and 42%, respectively; P=0.01). Secondary: IGADA scores were significantly better at six weeks for tacrolimus compared to pimecrolimus in the adult patient group, in the children with moderate to very severe disease, and in the combined analysis (all P<0.01) but this difference was not significant in the pediatric patients with mild disease. At six weeks, there was a significantly greater reduction with tacrolimus compared to pimecrolimus in percentage of BSA affected for the adult patients, for the pediatric patients with moderate to very severe disease, and in the combined analysis (all P<0.001), and this difference was observed as early as week three (P<0.01). In pediatric patients with mild

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				disease, a significant difference in favor of tacrolimus was observed at week one (P=0.02) but this difference was not significant at week six (P=0.15). At week six in all three studies, the reduction in itch score was significantly greater in all the tacrolimus groups compared to the pimecrolimus groups (P<0.01) and significant differences in favor of tacrolimus were observed as early as week one in both pediatric studies (P<0.05). The most common adverse effects in all studies were local application site reactions including burning and stinging. In both pediatric studies, there were no significant differences observed in adverse effects between tacrolimus and pimecrolimus groups. In the adult study, application site burning occurred more frequently in the tacrolimus group compared to the pimecrolimus group (P=0.02) early in treatment, but by week one there were no significant differences observed between the groups. In the pediatric study of patients with mild AD, significantly more patients withdrew from the study due to an adverse effect in the pimecrolimus group compared to the tacrolimus group (P=0.002).
Kirsner et al.[100] (2010) Tacrolimus 0.03% or 0.1% ointment applied BID for up to 6 weeks or until 7 days after clearance vs pimecrolimus 1%	MA (subgroup analysis of pooled data from Paller et al.) Patients ≥2 years of age with mild to severe AD who were treated with corticosteroids within the 30 days prior to enrollment	N=347 6 weeks	Primary: Change in EASI score at week six Secondary: IGADA where success means clear or almost clear, percent of BSA affected, patient's assessment of itch, and safety	Primary: At week six, the mean percentage improvement in EASI score was significantly greater for patients treated with tacrolimus compared to patients treated with pimecrolimus (53.2 vs 33.7%, respectively; P=0.0002). Secondary: At week six, significantly more patients treated with tacrolimus achieved treatment success ("Clear" or "Almost Clear" by IGADA score) than patients treated with pimecrolimus (P=0.0007). Significantly more of the patients (with mild, moderate or severe/very severe AD at baseline) treated with tacrolimus than with pimecrolimus improved by one or more grades on the IGADA (P=0.0006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied BID for up to 6 weeks or until 7 days after clearance				Relative to baseline, the improvement in the percent of BSA affected was significantly greater with tacrolimus than with pimecrolimus at week six (P=0.002). Itch was significantly improved among patients treated with tacrolimus compared to those treated with pimecrolimus (P=0.002). Adverse events were similar with both treatments (24.0% for tacrolimus vs 25.6% for pimecrolimus). The most common adverse events were application-site burning (9.9% with tacrolimus vs 14.2% with pimecrolimus; P=0.3) and application-site itching (7.0% with tacrolimus vs 10.2% with pimecrolimus; P=0.3).
Yin et al et al.[101] (2011) Tacrolimus 0.03% ointment or 0.1% ointment BID for six weeks or until seven days after clearance vs pimecrolimus 1% cream BID for six weeks or until seven days after clearance	MA Patients adult and pediatric patients with mild to severe AD	N=1,834 6 weeks or until seven days after clearance	Primary: IGADA at week one, three and six or end of study (success means clear or almost clear) for pediatric and adult patients based on severity of AD Secondary: Safety endpoints (overall incidences of all adverse events) and withdrawals due adverse events and lack of efficacy	Primary: IGADA scores were significantly better at six weeks for tacrolimus 0.1% compared to pimecrolimus 1% in the adult patient group at week three (RR, 0.55; 95% CI, 0.42 to 0.73) and week six/end of study (RR, 0.58; 95% CI, 0.46 to 0.72). In the children with moderate to very severe disease, IGADA scores were significantly better at six weeks/end of study (RR, 0.55; 95% CI, 0.34 to 0.88). The combined analysis of efficacy show that tacrolimus was more effective than pimecrolimus at week three and at week six/end of study (three weeks RR, 0.67; 95% CI, 0.56 to 0.80; six weeks RR, 0.65; 95% CI, 0.57 to 0.75). There was no significant difference in IGADA scores for pediatric patients with mild disease taking 0.03% tacrolimus or 1% pimecrolimus. Secondary: In adults, incidence of adverse events (most often reported as application site reactions) occurred more frequently in the tacrolimus 0.1% group compared to the pimecrolimus group (RR, 1.30; 95% CI, 1.02 to 1.66). In pediatric patients with mild-moderate AD, there were no significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				differences observed in adverse effects between the tacrolimus 0.3% and pimecrolimus. In pediatric patients with moderate-very severe AD, there were no significant differences observed in adverse effects between the tacrolimus 0.1% and pimecrolimus. Fewer pediatric patients with mild AD treated with 0.03% tacrolimus withdrew due to lack of efficacy than 1% pimecrolimus (RR, 0.05; 95% CI, 0.00 to 0.84). There was no difference in withdrawals between 0.03% tacrolimus and 1% pimecrolimus in pediatric patients with moderate AD. There was no difference in withdrawals between 0.1% tacrolimus and1% pimecrolimus in the treatment of adult patients or moderate to very severe pediatric patients. Combined analyses of withdrawal showed that fewer tacrolimus-treated patients withdrew because of a lack of efficacy (RR, 0.32; 95% CI, 0.19 to 0.53) or adverse event (RR, 0.43; 95% CI, 0.24 to 0.75), compared to pimecrolimus-treated patients.
Bieber et al.[102] (2007) Tacrolimus 0.03% ointment BID to all affected BSA vs methyl-prednisolone aceponate (MPA) 0.1% ointment in the evening (vehicle ointment	CS, DB, MC, RCT Patients 2 to 15 years of age with a history of moderate to severe AD for at least 1 year experiencing acute flare of AD according to IGA (≥4) with at least 5% of total BSA involvement	N=265 3 weeks	Primary: Treatment success (defined as a score of clear or almost clear in the static IGA score) Secondary: The percentage change in EASI and patient's assessment of itch and sleep, children's DLQI, patient's	Primary: In both groups, treatment was successful in the majority of patients by the end of treatment: MPA, 66.6%; tacrolimus, 66.9%. The difference between treatment groups was not statistically significant (P=0.9314). At day 14 the success rate was 50.3% for MPA vs 41.1% for tacrolimus. The number of patients cleared at the end of treatment was 37.2% for MPA and 29.4% for tacrolimus. All patients in the MPA groups and 97.1% in the tacrolimus group reported an improved IGA score at the end of treatment (P values not reported). Secondary: Substantial improvement in EASI was noted at days four and seven for both treatment groups. However, there was a greater mean percentage change from baseline for EASI with MPA compared to tacrolimus during the study. At the end of treatment the mean percentage change from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
was applied in the morning)			assessment of global response, affected BSA and medication costs	baseline for EASI was 89.7% in the MPA group compared to 85.3% in the tacrolimus group. The difference between the two groups was significant after seven days of treatment (P=0.0352) and after 14 days of treatment (P=0.0214) but not at day 21 (P=0.0667). The percentage of affected BSA decreased from approximately 29.0% at baseline for both treatment groups to 6.8% in the MPA group compared to 7.7% in the tacrolimus group at the end of the study. The mean intensity of itching declined substantially from baseline to end of treatment and was particularly pronounced in the MPA group. The change in assessment of itch was statistically significant for MPA by day four (day four; P=0.026; day seven; P=0.0006; day 14; P=0.0007; day 21; P=0.0004). The improvement in quality of sleep with MPA was significantly better than tacrolimus at day 14 (P=0.0409) and at the end of treatment (P=0.0094). Medication cost comparison between MPA and tacrolimus were significant for MPA (P=0.0001). Six patients in the tacrolimus group and none from the MPA group experienced adverse reactions including pruritus, erythema, skin burning and hot flushes that were attributed to treatment. A total of four patients (all in the tacrolimus group) discontinued the study due to adverse events. No patients in the MPA group and two patients in the tacrolimus group reported a worsening of the disease compared to baseline.
Ashcroft et al.[103] (2005) Tacrolimus or pimecrolimus vs topical	MA Patients with AD	N=6,897 1 week to 12 months	Primary: For pimecrolimus: proportion of patients rated by the investigator as clear or almost clear For tacrolimus: proportion of	Primary: <u>For pimecrolimus:</u> In five trials evaluating pimecrolimus vs placebo, pimecrolimus was significantly more effective than placebo at three weeks (P<0.0001), and three of these found that pimecrolimus retained this efficacy at six weeks (P<0.0001). Another trial found no significant difference at six months between pimecrolimus and placebo. In three PC trials, there were significantly fewer flares at six months in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
corticosteroids or placebo			patients achieving at least 90% improvement from baseline Secondary: Patients' global assessments of feeling better or much better, proportion of patients with flares of AD, improvements in QOL, tolerability assessed by overall rates of withdrawal, withdrawal due to adverse effects, proportion of patients with burning of the skin and skin infections	pimecrolimus group compared to the placebo group, and remained more effective at preventing flares at 12 months. One trial evaluated pimecrolimus and a potent corticosteroid and found that betamethasone valerate 0.1% was significantly more effective than pimecrolimus after three weeks treatment when evaluating the proportion of patients who were clear or almost clear (P=0.0008). One study evaluated pimecrolimus vs a potent corticosteroid on the trunk and a mild corticosteroid on the face and found that the combination of corticosteroids was significantly more effective than pimecrolimus (when evaluating the proportion of patients moderately clear or better) at one week, three weeks, and six months but found no difference at 12 months. One direct comparison of pimecrolimus 1% cream and tacrolimus 0.03% ointment found no difference in the proportion of patients (children) who were clear or almost clear at six weeks (P=0.15). One study evaluating pimecrolimus QID compared to pimecrolimus two times daily found no difference in the proportion of patients clear or almost clear at the end of three weeks. <u>For tacrolimus:</u> One trial compared tacrolimus 0.03%, tacrolimus 0.1%, and placebo and found that the 0.03% strength was significantly more effective compared to placebo when evaluating the proportion of patients clear or achieving excellent improvement (P=0.006), but that the 0.1% strength did not differ from placebo (P=0.13) at three weeks. When evaluating patients' assessments of improvement as better or much better, both strengths proved significantly better than placebo. Three other trials reported the same outcomes as described above after 12 weeks and found both strengths to be significantly more effective than placebo (P<0.0001). Two trials compared tacrolimus 0.03% and 0.1% vs hydrocortisone 1% and found that tacrolimus was significantly more effective than hydrocortisone when evaluating the proportion of patients clear or achieving excellent improvement at three weeks (P<0.0001). One trial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared tacrolimus 0.1% and alclometasone 0.1% and found that tacrolimus was significantly more effective than alclometasone for treating facial dermatitis. One trial compared tacrolimus 0.03 and 0.1% and hydrocortisone butyrate 0.1% (a potent corticosteroid) and found that the 0.03% tacrolimus was significantly less effective than the hydrocortisone butyrate judged by the proportion of patients clear or achieving excellent improvement at three weeks (P=0.008); but no significant difference was seen between the 0.1% strength of tacrolimus and the hydrocortisone butyrate (P=0.65). Two trials compared tacrolimus 0.1% with betamethasone valerate 0.1% or hydrocortisone butyrate 0.1% and found that the tacrolimus was as effective as the corticosteroids in the proportion of patients achieving at least marked improvement. One trial compared tacrolimus 0.1% with a regimen of hydrocortisone butyrate 0.1% on the trunk and extremities and hydrocortisone acetate 1% on the head and neck. It found that tacrolimus was significantly more effective than the combined corticosteroid regimen when evaluating the proportion of patients clear or achieving excellent improvement at 12 weeks (P<0.0001). Six trials compared tacrolimus 0.1% and 0.03%. Three trials found no difference in proportion of patients clear or achieving excellent response at three weeks between the two strengths (P=0.44) and the remaining three found tacrolimus 0.1% to be significantly more effective than the 0.03% strength (P=0.04) at 12 weeks. Secondary: Significantly more patients withdrew from treatment in the placebo groups than with either pimecrolimus or tacrolimus (P<0.05). Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus group compared to the placebo group but was significantly higher in the tacrolimus group compared to the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus or tacrolimus groups compared to topical corticosteroids, nor did rates when comparing tacrolimus 0.03 to 0.1%. Skin irritation and skin burning did not differ significantly between pimecrolimus groups and placebo (P=0.257), but the rate was significantly higher with pimecrolimus compared to betamethasone valerate 0.1% or a combined regimen of triamcinolone acetonide 0.1% and hydrocortisone acetate 1%. Both strengths of tacrolimus were more likely to cause skin burning compared to placebo (P=0.010) and were more likely to cause skin burning compared to mild or potent corticosteroids. QOL was difficult to measure and different outcome measures were used in the studies. In two studies, parents judged QOL to be improved in patients taking pimecrolimus compared to placebo, and three trials showed increases in QOL in patients taking tacrolimus 0.03and 0.1% compared to placebo. Tacrolimus 0.1% was found to have a significantly greater improvement on QOL in adults compared to the 0.03% strength, but no significant differences were found in infants and children. No QOL assessments were found comparing pimecrolimus and tacrolimus to topical corticosteroids.
El-Batawy et al.[104] (2009) Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	MA Patients with AD	N=7,378 (19 trials) Variable duration	Primary: Efficacy Secondary: Not reported	Primary: Pimecrolimus and tacrolimus were significantly more effective than placebo. Compared to topical corticosteroids, tacrolimus 0.1% and 0.03% ointment was as effective as moderate potency topical corticosteroids, and more effective than a combined steroid regimen. Tacrolimus was more effective than mild potency topical corticosteroids. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chen et al.[105] (2010) Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	MA Pediatric patients with AD	N=6,288 (20 trials) Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: More patients using tacrolimus had a good response than those in control groups including placebo, 1% hydrocortisone acetate and 1% pimecrolimus. The corresponding OR were 4.56 (95% CI, 2.80 to 7.44), 3.92 (95% CI, 2.96 to 5.20) and 1.58 (95% CI, 1.18 to 2.12). The effect difference between 0.03% and 0.1% tacrolimus ointments was not statistically significant (OR, 0.90; 95% CI, 0.55 to 1.48). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to the placebo. The major adverse events were burning and pruritus. Secondary: Not reported
Hui et al.[106] (2009) Tacrolimus or pimecrolimus vs no exposure to topical calcineurin inhibitors	RETRO Patients >6 months of age with AD	N=953,064 Variable duration	Primary: Risk of cancer Secondary: Not reported	Primary: The age- and sex-adjusted HR for all cancers were 0.93 (95% CI, 0.81 to 1.07; P=0.306) for tacrolimus-exposed vs -unexposed patients and 1.15 (95% CI, 0.99 to 1.31; P=0.054) for pimecrolimus-exposed vs -unexposed patients. T-cell lymphoma was the only cancer associated with a significantly increased risk among patients exposed to tacrolimus (HR, 5.04; 95% CI, 2.39 to 10.63; P<0.001) or pimecrolimus (HR, 3.76; 95% CI, 1.71 to 8.28; P=0.01). Secondary: Not reported
Basal Cell Carcinoma				
Gross et al.[107] (2007) Fluorouracil 5% cream applied BID	OL Adults with ≥1 biopsy proven superficial BCC on the trunk or limbs	N=29 15 weeks	Primary: Clinical evidence of cure, pain, erythema, scarring, patient satisfaction Secondary: Not reported	Primary: Among the 31 lesions treated, 90% were histologically cured by the fluorouracil treatment. The mean time to clinical cure was 10.5 weeks. Fluorouracil cream was generally well tolerated with no patient discontinuing prematurely due to adverse events and no serious adverse events occurring. The most common treatment-related adverse events were erythema and erosion.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The patient assessment of pain demonstrated that mean levels were close to none throughout the study and the majority of lesions (68%) were not associated with pain at any time point. The peak level of erythema was none in one (3%) lesion, mild in five (16%) lesions, moderate in 22 (71%) lesions, and severe in three (10%) lesions. The last erythema scores reported for each lesion revealed that seven (23%) had no erythema, 19 (61%) had mild erythema, and five (16%) had moderate erythema. The last scarring scores reported for each lesion showed that 26 (84%) had no scarring and 5 (16%) were rated as having mild scarring. Patients were very satisfied with the study treatment at all time points. Secondary: Not reported
Romagosa et al.[108] (2000) Fluorouracil 5% cream (Efudex®) applied BID for 4 weeks vs fluorouracil 5% cream in a phosphatidyl choline carrier applied BID for 4 weeks	DB, RCT Patients with a histologically confirmed moderate thickness BCC	N=13 Treatment: 4 weeks Follow-up 12 weeks	Primary: Cure rate Secondary: Not reported	Primary: The cure rate in the phosphatidyl choline group was 90% and the cure rate in the regular fluorouracil group was 57% (P=NS). Secondary: Not reported
Schulze et al.[109] (2005) Imiquimod 5%	DB, MC, PC, RCT Patients ≥18 years of age with a	N=166 Treatment: 6 weeks	Primary: Composite clearance rate	Primary: Composite clearance rates were 77% for the imiquimod group compared to 6% for the placebo group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied QD for 6 weeks vs placebo	histologically confirmed primary sBCC located on the trunk, limbs, neck, or head	Follow-up: 12 weeks	Secondary: Histological clearance rate	Secondary: Histological clearance rates were 80% in the imiquimod group compared to 6% for the placebo group (P<0.001). The prevalence of sBCC in post-treatment excision histology in the imiquimod group was 16%.
Giesse et al.[110] (2004) Imiquimod 5% cream applied QD 5 times per week vs imiquimod 5% cream applied QD 7 times per week vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a histologically confirmed sBCC on the limbs, trunk, neck, or head	N=724 Treatment: 6 weeks Follow-up: 12 weeks	Primary: Composite clearance rate, adverse events Secondary: Not reported	Primary: The composite clearance rates for the five times per week and seven times per week imiquimod groups were 75% (95% CI, 68 to 81) and 73% (95% CI, 66 to 79), respectively. Clearance rates based on histological data only for the five times per week and seven times per week groups were 82% (95% CI, 76 to 87) and 79% (95% CI, 73 to 85), respectively. Composite and histological clearance rates for the placebo groups were 2 to 3% (P<0.001). The percentage of patients who experienced ≥1 adverse event during the treatment phase in the five times per week, seven times per week, and placebo groups were 58, 64, and 36%, respectively. The percentage of patients who experienced ≥1 adverse event during the post-treatment period in the five times per week and seven times per week groups was 33 and 31%, respectively. Influenza symptoms, myalgia, malaise, fatigue, and fever were reported in <3% in any treatment group. Adverse effects seen in ≥3% in any treatment group include application site reactions, headache, upper respiratory tract infection, sinusitis, back pain, and pain. The incidence of headache was statistically higher in the five times per week group compared to its corresponding placebo group (P=0.027). Application site reactions possibly or probably related to treatment occurred in 29% of patients in the imiquimod five times per week group, and in 43% of the seven times per week group, compared to 2.8% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				6.6% of patients in the respective placebo groups. Less than 10% of patients experienced a severe adverse effect. Local skin reactions were more intense in the active treatment groups compared to the placebo groups. Local skin reactions were most intense at three weeks and fell back to at or below baseline by week 12. Local skin reactions had significantly higher severity ratings in the imiquimod groups compared to their respective placebo groups (P<0.001).Erythema was the most commonly observed local skin reactions. Erythema, vesicles, edema, erosion, and scabbing/crusting were all significantly more severe in the imiquimod seven times per week group compared to the five times per week group (P<0.05). There was a significant correlation observed between the intensity of the local skin reactions and clearance rates in both imiquimod groups (P<0.05). Secondary: Not reported
Marks et al.[111] (2004) Imiquimod 5% cream applied QD 5 times per week vs imiquimod 5% cream applied QD 7 times per week	OS Patients with a histologically confirmed sBCC on their trunk, limbs, or neck	N=67 (208 tumors) 18 weeks	Primary: Presence of residual tumor upon clinical and histological evaluation 12 weeks after treatment, tolerability of treatment Secondary: Not reported	Primary: Histological clearance occurred in 161 tumors (77%). In the five times per week group, 100% of patients had clearance of at least one tumor compared to 93% in the seven times per week regimen. Tumors cleared in 47% of patients in the five times per week regimen and in 58% of patients in the seven times per week regimen. In the five times per week regimen, 89% of patients had 50% or more of their tumors clear compared to 84% in the seven times per week regimen. Local skin reactions were common, but well tolerated and there was a correlation to the intensity of local inflammatory reactions and the histological clearance of tumors. Lower histological clearance was noted on the lower extremities accompanied by a lower incidence of local inflammatory reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Gollnick et al.[112] (2005) Imiquimod 5% cream applied QD 5 times per week on consecutive days for 6 weeks	OL, OS Patients 21 to 89 years of age with a histologically confirmed sBCC on the limbs, trunk, neck, or head	N=182 Treatment: 6 weeks Follow-up: 24 months	Primary: Non-recurrence rate Secondary: Not reported	Primary: The initial clearance rate for the ITT population was 89.6% at the 12-week post-treatment visit. Fourteen patients who were clinically clear of their treated tumor at the 12-week visit had clinical evidence of recurrence at the 24-month follow-up. Of these patients, histological data was available for 13 patients, of whom two had no histological evidence of recurrence. The estimated proportion of patients who were clinically clear of their treated tumor after a single six-week treatment at five times per week declined from 87.3% at month three to 79.4% at month 24. Secondary: Not reported
Gollnick et al.[113] (2008) Imiquimod 5% cream applied QD 5 times per week on consecutive days for 6 weeks	OL, OS Patients 21 to 89 years of age with a histologically confirmed sBCCon the limbs, trunk, neck, or head	N=182 Treatment: 6 weeks Follow-up: 5 years	Primary: Non-recurrence rate Secondary: Not reported	Primary: The initial clearance rate for the ITT population was 89.6% at the 12-week post-treatment visit. During the five-year follow-up period, 18 clinical recurrences occurred at the target tumor site, eight and 10 of which occurred during the first six and 12 months of follow-up, respectively. The five-year Kaplan-Meier and life-table estimates for sustained clinical clearance of those patients initially cleared were 84.5 and 86.9%, respectively, and 90.3% considering histology. The estimate of overall treatment success for all treated patients at the end of follow-up was 77.9%. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Quirk et al.[114] (2010) Imiquimod 5% cream applied QD 7 times per week for 6 weeks	MC, OL Patients ≥18 years of age with a histologically confirmed sBCCon the limbs, trunk, neck, or head	N=169 Treatment: 6 weeks Follow-up: 60 months	Primary: Initial clearance, tumor recurrence, adverse events Secondary: Not reported	Primary: The initial clearance rate at the 12-week posttreatment visit was 94.1%. Of 157 patients who entered the long-term follow-up period, 20 had a clinical recurrence of their target sBCC, occurring within the first 24 months for 14 patients. The overall estimate of treatment success was 80.4% at 60 months (95% CI, 74.4 to 86.4). Local skin reactions and application site reactions occurred predominantly during the treatment period and resolved posttreatment. Secondary: Not reported
Peris et al.[115] (2005) Imiquimod 5% cream applied QD 3 times per week for 12 weeks	OL, OS Patients 45 to 83 years of age with a superficial or a nodular BCC with multiple or recurrent lesions where surgery is not an option or if treatment other than surgery was requested	N=49 (94 tumors) Treatment: 12 weeks Follow-up: 12 months	Primary: Clinical remission at the end of treatment and recurrences during the post-treatment observational period Secondary: Adverse effects	Primary: Overall, complete response was seen in 85.1% of the lesions. Partial remission was seen in 11.7% of lesions. None of the patients experienced a total lack of response, or had worsening of the lesions. A complete response was observed in 93.3% of superficial BCCs in 26 patients. Of these, 37.1% regressed after six weeks of treatment, 42.9% after two more weeks of treatment, and 20% after the full 12 weeks of treatment. A PR was observed in 5.3% of superficial BCCs in four patients. A complete response was observed in 52.6% of nodular BCCs in 10 patients after the full 12 weeks of treatment. A PR was seen in the remaining 36.8% of lesions. Two of the seven patients with PR were treated for an additional four weeks without further improvement. Recurrence was observed in 2.9% of successfully treated sBCCs six to eight months after treatment discontinuation. No recurrence was observed in the remaining 68 sBCCs and in 10 successfully treated nodular BCCs after 12 to 34 months of follow-up. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Local adverse effects were observed in 67.3% of patients, and no patients experienced systemic adverse effects. Erythema was observed in 63.3% of patients, erosion in 53.1%, ulceration in 24.5%, vesicle formation in 14.3%, edema in 6.1%, pruritus in 67.3%, and burning in 24.5%. Hyperpigmentation and hypopigmentation were each observed in one and 15 patients respectively six months after treatment discontinuation. All skin reactions were rated as mild to moderate by the patients, with the exception of one patient who experienced a severe local reaction on the nose.
Garcia-Martin et al.[116] (2010) Imiquimod 5% cream applied QD 5 times per week for 6 weeks	OL Adults with a nodular BCC on the eyelid	N=15 24 to 28 months	Primary: Complete clinical clearance, adverse events Secondary: Not reported	Primary: All tumors showed histopathological remission within three months of starting imiquimod, and sustained clinical remission was documented in each patient after 24 to 28 months' follow-up. Adverse effects during treatment with imiquimod were almost exclusively local in nature (conjunctival irritation and discomfort with blinking). Overall tolerability was rated as excellent (n=1), good (n=7), or bad (n=7). Secondary: Not reported
Cutaneous T-Cell Lymphoma				
Breneman et al.[117] (2002) Bexarotene gel, 0.1%, 0.5%, and 1.0%, applied in incremental dose adjustments from 0.1% gel every day to 1.0% gel 4 times daily or the maximal tolerated	MC, OL Adults with early-stage (TNM stages IA-IIA) CTCL	N=67 Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: Patients achieved an overall response rate of 63% and a CCR rate of 21%. Median projected time to onset of response was 20.1 weeks (range, 4.0 to 86.0 weeks), and the estimated median response duration from the start of therapy was 99 weeks. Patients with no previous therapy for mycosis fungoides responded at a higher rate (75%) than those who previously underwent topical therapies (67%). Adverse events were generally mild to moderate in severity and were confined to treatment sites. Treatment-limiting toxic effects were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose				associated with skin irritation and increased with gel exposure. Secondary: Not reported
Heald et al.[118] (2003) Bexarotene 1% gel applied QD, BID, TID, QID, escalated as tolerated	MC, OL Patients ≥18 years of age with CTCL staged as IA, IB, or IIA according to the TNM staging system for TNM, and refractory or intolerant to, or have reached the 6-month or greater response plateau on at least 2 prior therapies	N=50 16 weeks with an option to continue treatment	Primary: PGA, or CA Secondary: Overall extent of cutaneous disease (percentage involvement of total BSA), index lesion erythema, plaque elevation, scaling, pruritus, hypo- or hyperpigmentation, surface area response to treatment, time to response, duration of response, and time to disease progression, responses to the patient QOL questionnaire	Primary: CCR or PR was observed in 44% of patients according to the PGA and in 46% of patients according to the CA. Responses were observed in 64% of patients with Stage IA disease and 50% of patients with Stage IB disease. Patients with Stages IIA disease did not respond to therapy. Secondary: The percentage of BSA involvement decreased from a baseline value of 9.0 to 6.6% at week 16 and 4.5% at week 44. Index lesion erythema, plaque elevation, scaling, pruritus, hypopigmentation or hyperpigmentation all improved during the study (no specific percentages given). There was a decrease in the aggregate of index lesions by 9.7% at week 24 and 70% at week 40. The earliest time to response was recorded at 28 days and the latest was recorded at 504 days. The time to relapse (duration of response) was recorded at 214.5 days in 26% of responding patients. The time to disease progression ranged from one to 87 days. When asked to compare general CTCL status at baseline and at week 16, 75% of patients reported that they were moderately or much improved, and 705 of patients at week 16 were moderately or very satisfied with treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kaposi's Sarcoma				
Walmsley et al.[119] (1999) Alitretinoin 0.1% gel applied TID for 2 weeks, then QID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a positive diagnosis of KS	N=268 12 weeks	Primary: Patient's cutaneous KS tumor response rate as evaluated by the group of six index lesions, responses were categorized as a CCR, PRA, PRH, PD, or SD Secondary: Not reported	Primary: CCR was observed in a significantly higher percentage of patients treated with alitretinoin 0.1% gel (35%) compared to placebo (18%; P=0.002). This statistically significant difference was maintained when the results were adjusted for baseline CD4+ counts and the number of raised lesions at baseline (P=0.00185). The incidence of PD as a best response was lower in the alitretinoin group compared to the placebo group. Reponses were analyzed based on age, race, aggregate area of index lesions, and Karnofsky performance scores and the response rate in the alitretinoin group remained significantly higher compared to the placebo (P=0.002, P=0.002, P=0.0015, and P=0.003, respectively). One hundred and eighty four patients received open label alitretinoin treatment following the 12 week blinded phase and 49% of these patients met the criteria for response and of these patients, two achieved complete response. Time to first response was significantly faster in the alitretinoin group compared to the placebo group (P=0.0001). Overall response rates (CCR plus PR) was significantly higher in the alitretinoin group (28%) compared to the placebo group (13%; P=0.001). Treatment with placebo was associated with less lesion pain compared to treatment with alitretinoin (P=0.007). Secondary: Not reported
Bodsworth et al.[120] (2001) Alitretinoin 0.1% gel applied BID	DB, MC, PC, RCT Patients >18 years of age with documented HIV	N=134 12 weeks	Primary: Objective assessment of cutaneous KS tumor response	Primary: The overall response rate (CCR plus PR) was 37% for the alitretinoin gel group vs 7% for the placebo gel group (P=0.00003). The only patient to achieve a CCR was in the alitretinoin-treated group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	infection and biopsy proven cutaneous KS		rate using ACTG response criteria designated as CCR, PR, SD, or PD Secondary: Individual indicator lesion response, physician's subjective assessment, patient's subjective assessment	Incidence of PD was lower for the alitretinoin gel group than for the placebo gel group (19 vs 35%, respectively; P=0.047). Positive responses to alitretinoin gel were observed for patients who were considered refractory to prior KS treatment. Response rates for these patients during the DB protocol were two of four (50%) for the alitretinoin group and zero of nine (0%) for the placebo group. Secondary: When evaluating the response of individual lesions, 34% responded in the alitretinoin treatment group compared to 11% of indicator lesions in the placebo control group (P≤0.00001). Both physicians and patients reported overall response rates of 40% for the alitretinoin gel group and 10% for the placebo gel group (P=0.00004).
Postherpetic Neuralgia				
Backonja et al.[121] (2008) Capsaicin 8% patch applied for 60 minutes as a single application vs capsaicin 0.04% patch applied for 60 minutes as a single application (control group) Patients were pretreated with a topical anesthetic cream for 60	DB, MC, RCT Patients 18 to 90 years of age with PHN, an average baseline NPRS score of 3 to 9, and ≥6 months had elapsed since shingles-vesicle crusting	N=402 12 weeks	Primary: Percentage change in NPRS scores from baseline to weeks two through eight Secondary: Percentage change in NPRS scores from baseline to weeks two to 12; percentage of patients considered improved on the PGIC and CGIC; changes in the BPI, SF-MPQ and SF-32v2 questionnaires	Primary: Patients who were treated with capsaicin 8% reported a -29.6% change in pain in the eight-week study compared to a -19.9% change in the control group (P=0.001). Secondary: A greater percentage reduction in NPRS scores was reported during the 12-week study by patients in the capsaicin 8% group than by patients in the control group (P=0.002). In both treatment groups, the mean percentage change in NPRS pain scores was smaller in patients who took other neuropathic pain medications than in those who did not take neuropathic pain medications. More patients in the capsaicin 8% group regarded themselves to have improved (slightly, much, or very much) compared to patients in the control group at weeks eight and 12. The results of the other assessments (≥50% reductions, BPI, SF-MPQ, and SF-36v2) showed greater improvements with capsaicin 8% than with the control patch. There were no differences in the proportion of patients with changes in concomitant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
minutes before patch application. The area was cleansed with a cleansing gel to remove residual capsaicin after patch removal.				neuropathic pain medication use between groups. The percentage of patients with at least one adverse event was 99% in the capsaicin 8% group and 88% in the control group. The greater incidence of treatment-emergent adverse events in the capsaicin 8% group was primarily due to expected local capsaicin-related reactions at the application site (e.g., pain and erythema), most of which were transient and mild to moderate in severity.
Irving et al.[122] (2011) Capsaicin 8% patch applied for 60 minutes as a single application vs capsaicin 0.04% patch applied for 60 minutes as a single application (control group)	DB, MC, RCT Patients 18 to 90 years of age with PHN, an average baseline NPRS score of 3 to 9, and ≥6 months had elapsed since shingles-vesicle crusting	N=418 12 weeks	Primary: Percentage change in NPRS score from baseline to weeks two to eight; adverse events Secondary: Not reported	Primary: Patients receiving capsaicin 8% patch had a significantly greater mean reduction from baseline in pain during weeks two to eight compared to the control group (32.0 vs 24.4%, respectively; P=0.011). A ≥30% reduction in mean NPRS scores was achieved in 46% of patients receiving capsaicin 8% patch compared to 34% of patients in the control group (P=0.02). Pain was significantly lower with capsaicin 8% compared to the control group by week two, and greater pain reduction was maintained throughout the remaining 12-week study period. Most adverse events were application site specific (erythema and pain) and were mild to moderate in severity. Secondary: Not reported
Webster et al.[123] (2010) Capsaicin 8% patch applied for 30, 60, or 90 minutes as a single application vs	DB, MC, RCT Patients ≥18 years of age with PHN an average baseline NPRS score of 3 to 9, and ≥6 months had elapsed since shingles-vesicle crusting	N=299 12 weeks	Primary: Percentage change in ‘‘average pain for the past 24 hours’’ NPRS scores from baseline to weeks two through eight Secondary:	Primary: The mean reduction in “average pain for the past 24 hours” from baseline to weeks two to eight was 26.5% with capsaicin 8% compared to 17.3% in the control group (P=0.0286). Patients treated for 90, 60, or 30 minutes reported similar mean reductions in pain of 27.8, 25.6, and 26.2%, respectively. However, only the 90-minute dose group was significantly different from control (P=0.0438). Secondary: During weeks two to 12, the mean reduction in “average pain for the past

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
capsaicin 0.04% patch applied for 60 minutes as a single application (control group) Patients were pretreated with a topical anesthetic cream for 60 minutes before patch application. The area was cleansed with a cleansing gel to remove residual capsaicin after patch removal.			Percentage change in NPRS scores from baseline to weeks two to 12; percentage of patients considered improved on the PGIC and CGIC; changes in the BPI questionnaire; changes in the SFMPQ questionnaire	24 hours" was 25.0% with capsaicin 8% compared to 14.7% in the control group (P=0.0120). Patients treated for 90, 60, or 30 minutes reported similar mean reductions in pain of 26.1, 24.4, and 24.4%, respectively. The 90-minute as well as the 60-minute dose groups were significantly different from control (P=0.0240 and P=0.0491, respectively). PGIC results demonstrated that more patients in the total capsaicin 8% group reported improvement (slightly, much or very much) at week four (56%), week eight (55%), and week 12 (55%) compared to the pooled control group (42, 45, and 41% for weeks four, eight, and 12, respectively). CGIC results demonstrated that more patients in the total capsaicin 8% group reported improvement (slightly, much, or very much) at week four (59%), week eight (55%), and week 12 (52%) compared to the pooled control group (42, 45 and 42% for weeks four, eight and 12, respectively). There were significant differences in the 90-minute capsaicin 8% group, compared to the control group, in CGIC at weeks four (P=0.0168) and eight (P=0.0154). No other treatment groups showed significant differences from control in PGIC or CGIC. The total capsaicin 8% group and the 60-minute capsaicin 8% group reported significant (P<0.05) improvements from screening to week eight compared to the pooled control group in each BPI category except the ''pain has interfered'' categories. Patients treated with capsaicin 8% for 30 minutes reported significant improvements from screening to week eight compared to the control group in each BPI category except ''pain at its least'' and ''pain has interfered.'' In the 90-minute capsaicin 8% group, the only significant improvement from screening to week eight compared to the pooled control group was in ''pain has interfered with mood in the last 24 hours.''
Webster et al.[124] (2010) Capsaicin 8% patch applied for 60 minutes as a single application	DB, MC, RCT Patients ≥18 years of age with PHN, an average baseline NPRS score of 3 to 9, and ≥3 months had elapsed since	N=155 12 weeks	Primary: Percentage change in ''average pain for the past 24 hours'' NPRS scores from baseline to weeks two through eight	Primary: Patients treated with capsaicin 8% reported a mean 36.5% reduction in pain during weeks two to eight compared to 29.9% in the control group (P=0.296). Secondary: Forty-nine percent of patients treated with capsaicin 8% were considered to have responded to treatment (≥30% mean decrease from baseline in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs capsaicin 0.04% patch applied for 60 minutes as a single application (control group) Patients were pretreated with a topical anesthetic cream for 60 minutes before patch application. The area was cleansed with a cleansing gel to remove residual capsaicin after patch removal.	shingles-vesicle crusting		Secondary: Percentage change in NPRS scores from baseline to weeks two to 12; percentage of patients considered improved on the PGIC and CGIC; changes in the BPI questionnaire; changes in the SFMPQ questionnaire	pain) during weeks two to eight compared to 45% of patients in the control group (P=0.574). The proportion of patients who achieved a ≥50% decrease in pain scores from baseline to weeks two to eight was similar between the treatment groups (36%). There was no significant difference in the percentage of patients who considered themselves to have much, or very much improved among the treatment groups at weeks eight and 12 (P=NS). The results of the CGIC were comparable to the results of the PGIC. There was no significant difference in improvement among the treatment groups as assessed by study investigators at week four (46 vs 37%), week eight (51 vs 40%) and week 12 (46 vs 32%). Other patient-rated questionnaires (BPI and SFMPQ) showed no significant differences between the capsaicin 8% and control group.
Backonja et al.[126] (2010) <u>RCT</u> Capsaicin 8% patch applied for 60 minutes as a single application vs capsaicin 0.04% patch applied for 60 minutes as a single application (control group)	DB, OL, RCT Patients ≥18 years of age with PHN, an average baseline NPRS score of 3 to 9, and ≥6 months had elapsed since shingles-vesicle crusting	N=38 RCT 4 weeks OL 40 weeks	Primary: Change from baseline in the mean morning and evening NPRS scores during days eight to 28, change in weekly mean of morning and evening average NPRS scores, change in BPI from screening to termination Secondary:	Primary: <u>RCT</u> Patients treated with capsaicin 8% had a mean 32.7% decrease from baseline in mean morning and evening NPRS scores during days eight to 28, compared to a 4.4% decrease for the control group (P=0.003). BPI results demonstrated significant differences between the capsaicin 8% and control groups, for “pain at its worst in the last 24 hours” (mean change from baseline -1.7 vs 0.3 for capsaicin 8% and control groups, respectively; P=0.014) and “average pain” (-1.3 vs 0.4; P=0.032, respectively). For the remaining items, no difference was observed between the capsaicin 8% and control groups. Responses to each SAT question were not different between the treatment groups. <u>OL</u> The mean change from baseline in mean morning and evening NPRS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<u>OL</u> Capsaicin 8% patch applied for 60 minutes (up to 3 additional treatments were allowed) Patients were pretreated with a topical anesthetic cream for 60 minutes before patch application.			Not reported	scores during weeks two to 12 after the initial DB treatment was -33.8% for capsaicin 8.0 vs 4.9% for control. Fifty-three percent of capsaicin 8% patients had a ≥33% decrease from baseline in mean morning and evening NPRS scores during weeks two to four, 56% during weeks five to eight, and 78% during weeks nine to 12. None of the control patients had a ≥33% decrease in NPRS score at any time point. The mean percentage change in NPRS scores from baseline was -31.4% after the first OL treatment; -30.0% after the second OL treatment; and -34.1% after the third OL treatment. Secondary: Not reported
Simpson et al.[126] (2010) Capsaicin 8% patch applied for 60 or 90 minutes (up to 3 additional treatments were allowed) Patients were pretreated with a topical anesthetic cream for 60 minutes before patch application.	OL Patients 18 to 90 years of age with PHN or HIV-DSP who had previously completed a 12-week study	N=106 48 weeks	Primary: Safety and efficacy Secondary: Not reported	Primary: During the 48 week study, 96% of patients reported one or more treatment-emergent adverse events. The most frequently reported treatment-emergent adverse events were transient, mild-to-moderate application site erythema, pain, edema, and papules. Small, transient pain-related increases in blood pressure during and immediately after 8% capsaicin application were observed. There was no evidence of an increased incidence of adverse events, dermal irritation, intolerability, or impaired neurological function with repeated treatments. PHN patients had a mean percent decrease from baseline in NPRS score during weeks 12 and 48 of 19.4 and 35.6%, respectively. HIV-DSP patients had a mean percent decrease from baseline in NPRS score during weeks 12 and 48 of 0.3 and 12.4%, respectively. The BPI subject-rated questionnaire demonstrated improvements in all five categories for PHN subjects and three of the five categories for HIV-DSP subjects at week 12. At week 48 or termination, both PHN and HIV-DSP patients reported improvement in all five categories.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At week 12, 65% of PHN patients and 74% of HIV-DSP patients reported being improved (very much, much, or slightly) on the PGIC questionnaire and 33% of both PHN and HIV-DSP patients rated themselves as much improved (much or very much). The proportion of patients reporting improvement increased at week 48 (75% of PHN patients and 80% of HIV-DSP patients feeling improved, with 44 and 54%, respectively, feeling much or very much improved). Secondary: Not reported
Psoriasis				
Tosti et al.[127] (2009) Acitretin 0.2 to 0.3 mg/kg/day	OL Patients 28 to 67 years of age with moderate to severe nail psoriasis	N=36 6 months	Primary: Clinical evaluation, and NAPSI before therapy, during therapy, and 6 months after treatment Secondary: Not reported	Primary: The mean percentage reduction of the NAPSI score and modified NAPSI score were 41 and 50%, respectively. Clinical evaluation at six months showed complete or almost complete clearing of the nail lesions in nine patients (25%), moderate improvement in nine (25%), mild improvement in 12 (33%), and no improvement in six (11%). Patients' perception of treatment efficacy was high in 11 patients, moderate in 10, low in three, and absent in eight cases. Secondary: Not reported
Rim et al.[128] (2003) Acitretin 10 to 20 mg/day titrated up to a maximum dose of 40mg/day vs	RCT Patients with chronic plaque type psoriasis with over 5% involvement of total BSA	N=60 4 to 52 weeks	Primary: Efficacy using the PASI Secondary: Not reported	Primary: After 12 weeks, 40% of patients in the calcipotriol plus acitretin group achieved complete clearance and 15% of patients in the acitretin monotherapy group achieved complete clearance (P<0.05). No significant differences were observed with regards to the degree of reduction of PASI scores after 12 weeks in both groups, however patients in the calcipotriol plus acitretin group showed faster remission at an early stage of therapy. After 52 weeks, 60% of patients in the calcipotriol plus acitretin group and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acitretin 10 to 20 mg/day titrated up to a maximum dose of 40 mg/day and calcipotriol ointment 50 µg/g applied BID up to a maximum of 60 mg/week				40% of patients in the acitretin monotherapy group achieved complete clearance (P<0.05). The duration of treatment and total dose of retinoid required to achieve clearance were slightly lower in the calcipotriol+acitretin combination group; however, this was not statistically significant. With the exception of liver enzyme elevation, adverse effects were not significantly different between the two treatment groups. Secondary: Not reported
van de Kerkhof et al.[129] (1998) Acitretin 20 mg QD (maximum of 70 mg/day or 1 mg/kg/day) vs acitretin 20 mg QD (maximum of 70 mg/day or 1mg/kg/day) and calcipotriol ointment (50 µg/g) applied BID (maximum of 120 mg/week)	DB, MC, PC, RCT Patients ≥18 years of age with a clinical diagnosis of severe/extensive psoriasis vulgaris which was not deemed responsive to topical treatment alone	N=135 12 weeks	Primary: Investigator assessment of the extent and severity of the patient's psoriasis, using the PASI scoring system; patient assessment of overall response to treatment considering both the extent and the severity of the psoriasis Secondary: Not reported	Primary: In the calcipotriol group, the mean change in PASI from baseline to the end of the DB treatment was -13.2 (P<0.001). In the placebo group, the mean change in PASI from baseline to the end of the DB treatment was -8.8 (P<0.001). Comparing the two treatment groups at the end of the treatment, there was a statistically significant difference, favoring calcipotriol treatment (P=0.007). Comparing the mean whole-body scores for redness, thickness and scaliness at the end of the DB treatment, there was a statistically significant difference between the two treatment groups, favoring calcipotriol treatment (P=0.0001, P=0.002 and P=0.03, respectively). The patients' overall assessments revealed that comparing the two treatment groups at the end of the treatment, there was a trend which appeared to favor calcipotriol therapy (P=0.05). Secondary: Not reported
Mittal et al.[130] (2009)	DB, RCT Patients 18 to 65	N=41 12 weeks	Primary: Change in PASI score; adverse	Primary: The percent reduction in the PASI score from baseline to 12 weeks of treatment was 64.2% (95% CI, 49.2 to 79.3) in the acitretin and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Acitretin 25 mg QD vs acitretin 25 mg QD and pioglitazone 15 mg QD	years of age with moderate to severe chronic plaque-type psoriasis		events Secondary: Not reported	pioglitazone group compared to 51.7% (95% CI, 38.7 to 64.7) in the acitretin plus placebo group (P=0.04). Overall, the lesions cleared or almost cleared in seven patients (37%) in the acitretin plus pioglitazone group compared to two patients (9%) in the acitretin plus placebo group (P=0.06). At 12 weeks, PASI75 was achieved in eight patients (42%) in the acitretin plus pioglitazone group compared to five patients (23%) in the acitretin plus placebo group (P=0.31). PASI75 was attained earlier (by week eight in two patients (11%) in the acitretin plus pioglitazone group compared to one patient (4%) in the acitretin plus placebo group (P=0.59). Most of the adverse events observed were mild and tolerable. Common adverse events involved mucocutaneous and musculoskeletal complaints. There were no abnormalities in laboratory parameters, including serum lipid levels, liver function test results, and fasting blood glucose levels, in either group. Secondary: Not reported
Veronikis et al.[131] (1999) Calcipotriene applied BID vs coal tar 1% emulsion applied BID	CS, SB Patients 18 to 75 years of age with plaque-type psoriasis	N=20 12 to 125 days	Primary: Erythema, scaling, and plaque thickness Secondary: Not reported	Primary: The scores for erythema, scaling, and plaque thickness significantly decreased in both the calcipotriene group and the coal tar group (P<0.05), though there were no significant differences observed between treatment groups. Secondary: Not reported
Alora-Palli et al.[132] (2010) Calcipotriene 0.005% cream	RCT Patients ≥18 years of age with moderate, chronic	N=60 Treatment: 12 weeks	Primary: Change in PASI Secondary: Change in PGA	Primary: After 12 weeks, mean PASI scores improved by 58% in the LCD group and by 37% in the calcipotriene group (P<0.05). Significantly more patients in the LCD group achieved PASI 50 than in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
applied BID vs liquor carbonis distillate (LCD) 15% solution (equivalent to 2.3% coal tar) applied BID	plaque psoriasis	Follow-up: 6 weeks	scale score, Pruritus Scale score, DLQI, and patient-reported psoriasis symptoms score Secondary: Not reported	the calcipotriene group (P<0.05). Secondary: The LCD group had more patients (14/27) with absent or minimal psoriasis on the PGA scale than the calcipotriene group (6/28) by the end of treatment (P<0.05). Patients' DLQI scores, Pruritus Scale scores, and patient's scores for flaking/scaling, itch, redness/irritation, burning sensation, roughness/texture, and overall discomfort improved with both treatments (P<0.05 vs baseline). Improvement in redness/irritation was more pronounced in the LCD group (52%) than in the calcipotriene group (29%; P<0.05). Significantly fewer patients in the LCD group than in the calcipotriene group lost their PASI 50 response at week 18 after six weeks without treatment (P<0.05) or had PGA scores at week 18 worsen to pre-treatment severity (P<0.01). Between week 12 and week 18, PASI scores and PGA scores worsened after stopping calcipotriene therapy (P<0.05), but not after stopping LCD therapy. Patients' Pruritus Scale scores worsened after stopping calcipotriene therapy (P=0.006) but not after stopping LCD therapy (P=0.28). This difference was significant between treatment groups (P=0.003). Patients' DLQI scores improved after stopping LCD therapy (P=0.03), but worsened directionally after stopping calcipotriene therapy (P=0.13). This difference was significant between treatment groups (P=0.009). Patients scores for scaling/flaking, redness/irritation, itch, and roughness/texture worsened after stopping calcipotriene therapy (P<0.05), but not after stopping LCD therapy. More LCD- than calcipotriene-treated patients considered their psoriasis to be stabilized or improved after 6 weeks without treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients' assessments of convenience, tolerability and overall opinion of LCD solution and calcipotriene cream were comparable and favorable for both products. Secondary: Not reported
Feldman et al.[133] (2012) Calcipotriene 0.005% foam BID vs vehicle foam (Two studies reported of identical design).	DB, MC, PG, RCT Patients ≥12 years of age with plaque psoriasis involving 2 to 20% of BSA	N=529 8 weeks	Primary: Treatment success defined as change from baseline at week eight of at least two grades and an ISGA score of 0 or 1 Secondary: Change from baseline in ISGA score, ISGA score of 0 or 1, target lesion score of 0 or 1 for erythema and at least a 2-grade improvement from baseline, target lesion score of 0 or 1 for scaling and at least a 2-grade improvement from baseline, a target lesion score of 0 for plaque psoriasis, and adverse effects	Primary: In Study 1, 14% of the calcipotriene group achieved treatment success compared to 7% in the vehicle group (P=0.058). In Study 2, there was a significantly greater proportion of patients that achieved treatment success in the calcipotriene group compared to placebo (P=0.016). Secondary: In Study 1, there was no significant difference in the proportion of patients with mild severity (ISGA scores of 2) who achieved treatment success between the two groups (3 vs 9%; P=0.167). For patients with moderate disease severity (ISGA score of 3), the treatment success rate was significantly higher in the calcipotriene group compared to vehicle (19 vs 6%; P=0.009). In Study 2, there was no significant difference in the proportion of patients with mild severity (ISGA scores of 2) who achieved treatment success between the two groups (14% vs 13%; P=0.859). For patients with moderate disease severity (ISGA score of 3), the treatment success rate was significantly higher in the calcipotriene group compared to vehicle (32 vs 17%; P=0.015). For Study 1, the secondary endpoints for IGSA score of 0 or 1, target lesion score for erythema, scaling, and psoriasis were not considered significant because the primary endpoint failed to reach significance. For Study 2, the proportion of patients with target lesion score of 0 or 1 and grade-2 improvement in the calcipotriene group compared to vehicle was significantly greater for erythema (P=0.034), scaling (P=0.004), but not plaque thickness (P=0.052). A similar proportion of patients in the calcipotriene group experienced

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse effects compared to the vehicle group (16 vs 18%).
Feldman et al.[134] (2013) Calcipotriene 0.005% foam BID vs vehicle foam	DB, MC, PG, RCT Patients ≥12 years of age with plaque psoriasis involving 3 to 10% of total BSA (excluding scalp and face), with an ISGA of 3 at baseline, target lesion of >2 cm^2 on the trunk or extremities with a score of 2 or 3 for erythema, scaling and plaque thickness and plaque psoriasis on ≥10% of the total scalp surface area with an ISGA score of 3 at baseline	N=363 8 weeks	Primary: Proportion of patients with ISGA score of 0 or 1 for scalp involvement at week eight Secondary: Proportion of patients with ISGA score of 0 or 1 for body involvement at week eight; target lesion score of 0 or 1 for erythema, sling and plaque thickness; and an improvement of ≥2 grades; primary and secondary endpoints at weeks two and four	Primary: A significantly greater proportion of patients in the calcipotriene group had an ISGA score of 0 or 1 for scalp involvement compared to vehicle (40.9 vs 24.2%; P<0.001). Secondary: At week eight, there was no significant difference in the proportion of patients with an ISGA score of 0 or 1 for total body involvement between the groups (P=0.544). At week eight, there was no significant difference in the proportion of patients that achieved an ISGA score of 0 or 1 and an improvement of ≥2 grades for target lesion erythema (P=0.112), scaling (P=0.059) or plaque thickness (P=0.116). At weeks two and four, there were a significantly greater proportions of patients in the calcipotriene group that achieved an ISGA score of 0 or 1 for scalp psoriasis compared to vehicle (P=0.41 and P<0.001, respectively), scaling (P=0.02 and P=0.015, respectively). At week four, there was a significantly greater proportion of patients in the calcipotriene group that achieved an ISGA score of 0 or 1 and an improvement of ≥2 grades for target lesion erythema (P<0.001) and plaque thickness (P=0.036), but not at week two (P=0.895 and P=0.268, respectively). The mean percent reduction in the percent of scalp affected by psoriasis was significantly greater in the calcipotriene patients compared to vehicle at week four (P=0.017) and eight (P=0.002), but not at week two (P=0.159). There was a higher incidence of treatment related adverse events with calcipotriene compared to vehicle (17 vs 7%). The most common adverse event was application site reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sharma et al.[135] (2003) Calcipotriol 0.005% ointment applied BID vs coal tar 5% ointment applied QHS	RCT, SB Patients 16 to 60 years of age with nearly bilaterally symmetrical lesions of stable plaque psoriasis	N=36 12 weeks	Primary: Improvements in the ESI of psoriatic lesions, relapse rates, and self-assessment by patient of efficacy and acceptability Secondary: Not reported	Primary: At four weeks, there was a significant improvement (>50% reduction in ESI score) in 60% of patients on the calcipotriol side compared to 23.3% of patients on the coal tar side (P<0.01). At eight weeks, there was a significant improvement (>505 reduction in ESI score) in 73.3% of patients on the calcipotriol side compared to 33.3% of patients on the coal tar side (P<0.01). At eight weeks, there was a marked improvement (>75% reduction in ESI score) in 26.6% of patients on the calcipotriol side compared to 0% of patients on the coal tar side. At 12 weeks, there was a marked improvement (>75% reduction in ESI score) in 53.3% of patients on the calcipotriol side compared to 33.3% of patients on the coal tar side (P<0.01). At 12 weeks, there was a significant improvement observed in 86.7% of patients for both calcipotriol and coal tar. The median time for attaining a >50% reduction in ESI score for calcipotriol was 6.1±1.9 weeks and 9.6±1.8 weeks for coal tar (P<0.01). During the eight week follow-up period, relapse was observed in 10% of patients on the calcipotriol side compared to 16.7% of patients on the coal tar side, though this difference was not significant (P>0.05). There was no significant difference between the physician and patient assessments of degree of improvement at any time during the study. There was a preference for calcipotriol ointment for visual presentability, lack of staining, and cosmetic elegance compared to coal tar. Secondary: Not reported
Thaci et al.[136] (2001)	OS, PRO Patients 30 to 62	N=3,396 8 weeks	Primary: Investigator assessment of	Primary: There was a significant decrease in mean PSSI after eight weeks of therapy in the group treated only with calcipotriol solution from 16.0 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calcipotriol 50 µg/mL solution applied BID as monotherapy or in combination with other treatments	years of age with scalp psoriasis		psoriasis severity based on the PSSI at each visit, investigators' global assessments of changes in psoriasis, tolerance, and cosmetic acceptance of the treatment, and investigator and patient comparison of this therapy to previous therapies Secondary: Not reported	4.9 and in the patients treated with calcipotriol solution in combination with other agents from 20.7 to 6.2 (P<0.001). There was an additional therapeutic effect noted in patients treated with calcipotriol solution in combination with selective ultraviolet phototherapy and topical corticosteroids (P<0.001 and P<0.01 respectively). Investigators rated the improvements to be very good or good in 79.8% of patients. Among patients, 75.7% rated the improvements to be very good or good, 91.7% rated the treatment to be very well or well tolerated, and 95.8% rated the cosmetic acceptance to be very good or good. Investigators rated calcipotriol solution to be more effective than past treatments in 45.1% of patients. Safety was rated as improved by 32.4% of patients compared to past treatments. Application of the product was rated easier by 36.8% of patients. Calcipotriol was rated cosmetically more acceptable than previous treatments by 45.1% of patients. There were no major differences between investigator and patient global assessments. Secondary: Not reported
Reygagne et al.[137] (2005) Calcipotriol 0.005% solution applied BID	MC, PG, RCT, SB Patients ≥12 years of age with moderate to severe scalp psoriasis	N=151 4 weeks	Primary: GSS and theTSS Secondary: Pruritus, surface area of scalp affected by	Primary: Clobetasol propionate was shown to be significantly more efficacious compared to calcipotriol in TSS measures (P<0.001 at week two and P=0.028 at week four) and GSS measures (P<0.001 at week two and P=0.016 at week four). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clobetasol 0.05% shampoo applied QD			psoriasis	Erythema, plaque thickening, adherent desquamation, and pruritus improved in both treatments groups but a greater improvement was observed in the clobetasol group. The percentage of scalp surface area affected showed significant difference in favor of clobetasol (P=0.02).
Tosti et al.[137] (1998) Calcipotriol 50 µg/g ointment applied BID vs betamethasone 64 mg/g ointment and salicylic acid 0.03 g/g ointment applied BID	DB, RCT Patients ≥18 years of age with a diagnosis of nail bed psoriasis with severe subungual hyperkeratosis	N=58 3 months with an optional additional 2 months of treatment for responders	Primary: Nail thickness expressed in millimeters using a micrometer caliper, patient assessment of acceptability of treatment Secondary: Not reported	Primary: For fingernail psoriasis, subungual hyperkeratosis was reduced by 26.5% in the calcipotriol group and by 30.4% in the betamethasone and salicylic acid group after three months and the difference between groups was not significant. Eight patients in the calcipotriol group and 10 patients in the betamethasone and salicylic acid group were considered responders (>50% reduction in subungual hyperkeratosis in at least one nail). At five months, responders showed a 49.2% reduction in hyperkeratosis in the calcipotriol group and 51.7% reduction in the betamethasone and salicylic acid group (P<0.001). For toenail psoriasis, hyperkeratosis was reduced by 20.1% in the calcipotriol group and 22.9% in the betamethasone plus salicylic acid group at three months (P<0.001 from baseline), but the differences between groups were not significant. Seven patients in the calcipotriol group were considered responders and 12 in the betamethasone and salicylic acid group (>50% reduction in subungual hyperkeratosis in at least one nail). At five months, there was a further reduction in hyperkeratosis in the calcipotriol group (40.7%) and in the betamethasone and salicylic acid group (51.9%) from baseline (P<0.0001 for both groups, between-group differences not reported). Differences in patient assessment of the acceptability of their treatment at three and five months were not significant between groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Crosti et al.[139] (1997) Calcipotriol 50 µg/g ointment applied BID vs betamethasone dipropionate ointment and salicylic acid ointment applied BID	RCT Patients ≥18 years of age with mild stable psoriasis	N=160 Treatment: 6 weeks Follow-up 1 month	Primary: Improvement in PASI scores, investigator assessments of efficacy Secondary: Not reported	Primary: At the end of the study period, trunk lesions had disappeared in 21.3% of calcipotriol patients and 16.3% of betamethasone and salicylic acid patients, lesions on the arms had disappeared in 21.3% of calcipotriol patients and 15.0% of betamethasone and salicylic acid patients, and lesions on the legs had disappeared in 13.8% of calcipotriol patients and 10.0% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.05), but not significant between groups. Erythema of the trunk disappeared in 21.3% of calcipotriol patients and 17.5% of betamethasone and salicylic acid patients, erythema of the arms disappeared in 25.0% of calcipotriol patients and 16.3% of betamethasone and salicylic acid patients, and erythema of the legs disappeared in 20.0% of calcipotriol patients and 12.5% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. Skin infiltration on the trunk disappeared in 30.0% of calcipotriol and betamethasone and salicylic acid patients, skin infiltration on the arms disappeared in 55.0% of calcipotriol patients and 56.2% of betamethasone and salicylic acid patients, and infiltration on the legs disappeared in 42.5% of calcipotriol patients and 36.3% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. Exfoliation on the trunk disappeared in 48.8% of calcipotriol patients and 41.3% of betamethasone and salicylic acid patients, scales on the arms disappeared in 61.3% of calcipotriol patients and 55.0% of betamethasone and salicylic acid patients, and scales on the legs disappeared in 23.8% of calcipotriol patients and 37.5% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. By 6 weeks of treatment, PASI scored decreased 66.8% in the calcipotriol patients and 60.8% of betamethasone and salicylic acid patients compared to baseline (P<0.001). Significance for the between-group differences was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				not reported. Investigators assessed 79% of patients in the calcipotriol group and 89.4% of patients in the betamethasone and salicylic acid group as improved or healed. Treatment acceptability was assessed as "good" or "excellent" by 83.8% of patients in the calcipotriol group and 76.3% of the betamethasone and salicylic acid group. Significance for the between-group differences was not reported. Secondary: Not reported
Parslew et al.[140] (2005) Calcipotriene and betamethasone dipropionate applied QD vs placebo	MA Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,534 (4 trials) Up to 4 weeks of treatment	Primary: Percent change in PASI Secondary: PASI after one week of treatment (assessed in three of the four studies), IGA	Primary: The mean PASI at baseline was 10.2 in patients <60 and 9.7 in patients ≥60. The mean reduction in PASI was 67.8% in patients <60 and 72.6% in patients ≥60. Secondary: More than half of the treatment response was seen after the first week of treatment with a 39% reduction in PASI in patients <60 and a 40.75 reduction in patients ≥60. In the two studies assessing IGA of Disease Severity, 52.1% of patients <60 and 52.8% of those ≥60 had controlled disease after up to four weeks of treatment. A total of 59% of patients <60 and 64.4% of those ≥60 judged themselves as having attained treatment success. A similar portion of patients <60 and ≥60 experienced lesional or perilesional adverse reactions during the study.
Tyring et al.[141] (2010) Calcipotriene 50 µg/g and	DB, RCT Patients ≥18 years of age with scalp psoriasis who were	N=177 8 weeks	Primary: Proportion of patients with cleared or minimal disease	Primary: In the calcipotriene and betamethasone group, 71.9% of patients had cleared or minimal disease at week eight by the IGA compared to 40.5% in the placebo group (OR, 3.30; 95% CI, 1.62 to 6.72; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betamethasone dipropionate 0.5 mg/g scalp formulation applied QD vs placebo	Hispanic or Latino and/or Black or African American		Secondary: Investigator's assessment of clinical signs of scalp psoriasis; patient's global assessment of severity of scalp psoriasis	Secondary: For total sign score ≤1, thickness of scalp psoriasis absent and patient's global assessment of cleared/very mild), calcipotriene and betamethasone was significantly more effective than placebo (P=0.004, P=0.002 and P=0.004, respectively). For absence of redness and scaliness of scalp psoriasis, the response rate was greater with calcipotriene and betamethasone than placebo (P=0.010 and P=0.017, respectively). There were 7.0% of patients in the calcipotriene and betamethasone group with 11 adverse events, compared to 7.9% of patients with four adverse events in the placebo group (OR, 0.88; 95% CI, 0.23 to 3.44; P=1.00).
Menter et al.[142] (2013) Calcipotriene 50 µg/g and betamethasone dipropionate 0.5 mg/g suspension vs betamethasone dipropionate 0.5 mg/g suspension vs calcipotriene 50 µg/g suspension vs vehicle suspension	DB, MC, RCT Patients ≥18 years of age with mild to moderate psoriasis for ≥6 months involving ≥10% of the arms, legs or trunk and amenable to treatment with ≤100 g of medication per week	N=1,152 8 weeks	Primary: Proportion of patients achieving controlled disease (IGA score of clear or almost clear and ≥2 point change from baseline) at weeks four and eight Secondary: Change from baseline in PASI at weeks four and eight	Primary: At week four, there was a significantly greater proportion of patients achieving controlled disease in the calcipotriene and betamethasone group (13.3%) compared to calcipotriene groups (5.2%; P=0.019) and vehicle (2.1%; P=0.001). There was no significant difference in achievement of controlled disease between the calcipotriene and betamethasone and betamethasone groups (12.5%; P=0.82). At week eight, the calcipotriene and betamethasone group had a significantly greater proportion of patients achieving controlled disease (29%) compared to the betamethasone (21.5%), calcipotriene (14.6%) and vehicle groups (6.3%; P≤0.008 for all comparisons). Secondary: At week four, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (46.4%) compared to the betamethasone (42.7%), calcipotriene (32.2%) and vehicle groups (17.4%; P≤0.038 for all comparisons). At week eight, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (55.8%) compared to the betamethasone (48.6%), calcipotriene (43.6%) and vehicle groups (20.9%; P<0.001) for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Singh et al.[143] (2000) Calcipotriene 0.005% ointment applied BID on weeks 2 and 4 and augmented betamethasone 0.05% cream applied QD on weeks 1 and 3 vs augmented betamethasone 0.05% cream applied QD for 4 weeks	PG, RCT, SB Patients 20 to 50 years of age with stable plaque psoriasis	N=52 4 weeks	Primary: Proportion of patients having at least 90% reduction in baseline PASI scores at the end of the four week study period Secondary: PASI scores on a weekly basis, reduction in PASI scores after two to four weeks, patients with marked improvement or almost clear at the end of treatment	Primary: In the betamethasone group, 18.5% of patients had a 90% or greater reduction in baseline PASI scores after four weeks of therapy compared to 68% of patients in the calcipotriene and betamethasone group (P<0.001). Secondary: PASI scores were significantly lower in the calcipotriene and betamethasone group compared to the betamethasone group at different points of time except on days 0 and seven. The percentage reduction in PASI scores after two and four weeks of treatment was significantly higher in the calcipotriene and betamethasone group compared to the betamethasone group. The proportion of patients with marked improvement or who were almost completely cleared at the end of treatment was significantly higher in the calcipotriene and betamethasone group compared to the betamethasone group in both investigator and patient assessments.
Douglas et al.[144] (2002) Calcipotriene and betamethasone ointment applied BID (CB) vs betamethasone ointment applied BID (B) vs	DB, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,106 4 weeks of treatment and an additional 4 weeks of OL treatment with calcipotriene	Primary: Mean percent change in PASI from baseline after four weeks Secondary: Speed of response as assessed from percent change in PASI after one week, mean percentage decrease in the thickness of psoriatic lesion	Primary: There was a significant reduction in mean percent change in PASI from baseline to week four in the CB group compared to the B group and the C group (74.4, 61.3, and 55.3% respectively; P<0.001). Secondary: There was a significant reduction in mean percent change in PASI after week one in the CB group compared to the B group and the C group (47.4, 39.8, and 31% respectively; P<0.001). There was a significant reduction in the mean percent change in thickness of the psoriatic lesion from baseline to week four in the CB group compared to the B group and the C group (79.4, 61.7, and 63% respectively; P<0.001). There was no significant difference in the percent of patients reporting

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriene ointment applied BID (C)			from baseline after four weeks	adverse effects in any of the treatment groups.
Kaufman et al.[145] (2002) Calcipotriene and betamethasone ointment applied QD (CB) vs betamethasone ointment applied QD (B) vs calcipotriene ointment applied QD (C) vs vehicle ointment QD (V)	DB, PC, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body regions	N=1,603 4 weeks	Primary: PASI score, IGA score, PGA score assessing patients with treatment success (defined as marked improvement or clearance of disease) Secondary: Not reported	Primary: There was a significant decrease in PASI score in the CB group compared to the B, C, and V groups (-71.3, -57.2, -46.1, and -22.7% respectively; P<0.001). There was a significantly larger number of patients assessed as having controlled disease according to the IGA score in the CB group compared to the B, C, and V groups (276, 176, 107, and 16 respectively; P<0.001). There was a significantly larger number of patients assessed as having treatment success according to the PGA scores after four weeks in the CB group compared to the B, C, and V groups (316, 216, 137, and 15 respectively; P<0.001). Secondary: Not reported
Papp et al.[146] (2003) Calcipotriene and betamethasone ointment applied BID (CB) vs	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body areas	N=1,028 4 weeks	Primary: Mean percent reduction in PASI from baseline to the end of treatment Secondary: Speed of response assessed as the	Primary: There was a significant percent reduction in PASI at the end of treatment in the CB group compared to the B, C, V groups (73.2, 48.8, 63.1, and 28.8% respectively; P<0.001). Secondary: There was a significant reduction in the mean percent change in PASI from baseline to after one week of treatment in the CB group compared to the B, C, and V groups (48.1, 28.4, 41.4, and 21.5% respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betamethasone ointment applied BID (B) vs calcipotriene ointment applied BID (C) vs vehicle ointment BID (V)			mean percent change in PASI from baseline after one week of treatment	
Guenther et al.[147] (2002) Calcipotriene and betamethasone ointment applied QD vs calcipotriene and betamethasone ointment applied BID vs calcipotriene ointment applied BID vs	DB, MC, PC, PG, PRO, RCT Patients 18 to 86 years of age with a diagnosis of psoriasis vulgaris involving at least 10% of one or more body regions	N=828 4 weeks	Primary: Percentage change in PASI from baseline to week four Secondary: Percentage change in thickness score of a target psoriatic lesion from baseline to each treatment visit, speed of response assessed by change in PASI from baseline to week two, investigator's overall assessment of treatment efficacy, adverse effects	Primary: The difference in PASI from baseline to week four in the combination treatment groups of once and BID was not significant (5.4%; P=0.052). The once-daily combined-medication group had a significantly reduced PASI compared to the calcipotriol group (68.6 vs 58.8%; P<0.001) and the placebo group (68.6 vs 26.6%; P<0.001). The twice-daily combined-medication group had a significantly reduced PASI compared to the calcipotriene group and the placebo group (P<0.001). Secondary: No significant difference was observed between the QD combined-medication group and the calcipotriene group or the once vs BID combined-medication groups in lesion thickness. There was a significant difference in lesion thickness in the once and BID combination-medication groups compared to the placebo group at the end of treatment (P<0.001). After one week of treatment, the change in PASI was greater in the combined-medication groups (45.5% for QD and 47.6% for BID)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				compared to the calcipotriene group (33.6%) and the placebo group (20%); (P<0.001). There was no significant difference observed in the speed of response between the QD and BID combination groups (P=0.30). For the investigators' and patients' assessment of efficacy, there was a higher percentage of responders (those achieving marked improvement or clearing) in the QD and BID combination groups (QD: 63.3% investigators, 65.3% patients, BID: 73.5% investigators, 70.1% patients) compared to the calcipotriene group (50.7% investigators, 51.5% patients), and the placebo group (9.2% investigators, 12.6% patients; P<0.033). According to investigators' assessments, 14% of patients receiving the QD and 20.1% of patients receiving the BID combination products achieved clearance compared to 9.7% in the calcipotriene group and 0% in the placebo group. A significantly lower proportion of patients experienced adverse effects in both combination groups compared to the calcipotriene group (P<0.01). The percentage of patients with lesional or perilesional adverse reactions was less in the combination groups and the placebo group compared to the calcipotriene group (9.9% QD combination group, 10.6% BID combination group, 19.8% calcipotriene group, 12.5% placebo group).
van de Kerkhof[148] (2004) Calcipotriene and betamethasone ointment applied QD vs calcipotriene and betamethasone	DB, MC, PC, RCT Patients 18 to 86 years of age with a diagnosis of psoriasis vulgaris involving at least 10% of one or more body regions	N=828 4 weeks	Primary: Changes in the PDI, EuroQOL 5D, VAS, and the EuroQOL 5D-VAS score from baseline to the end of the study (each of these tools measure overall QOL) Secondary:	Primary: Results of the PDI scores indicate that patients' QOL improved significantly in both combination groups and the calcipotriene group compared to baseline (P<0.001). No significant effect was seen in the placebo group (P>0.1). No statistical difference was found in QOL based on PDI score between the combination groups and the calcipotriene group (P>0.1), though a significant difference was noted in favor of the combination groups when compared to the placebo group (P<0.001). At baseline, pain/discomfort and anxiety/depression were the most

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied BID vs calcipotriene ointment applied BID vs placebo			Not reported	significant problems reported by psoriasis patients. Parameters for pain/discomfort and anxiety/depression improved to a greater extent in the combination groups than in the calcipotriene and placebo groups. The VAS scores from baseline to the end of the study showed a significant improvement in QOL in both combination groups and the calcipotriene group (P<0.001), and no significant difference was seen in the placebo group from baseline (P>0.1). There was a significant improvement observed in the EuroQOL 5D-VAS score between both combination groups compared to the placebo group (P<0.001), as well as the QD combination group compared to the calcipotriene group (P<0.05). PASI reduction in both combination groups was significantly greater compared to the calcipotriene group and the placebo group after one week (P<0.001). Secondary: Not reported
Kragbale et al.[149] (2004) Calcipotriene and betamethasone ointment applied QD for 8 weeks followed by calcipotriene ointment applied QD for 4 weeks (Group 1) vs	DB, PG, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis	N=971 12 weeks	Primary: Mean percent change in PASI from baseline to week eight, proportion of patients with absent or very mild disease according to the IGA at the end of eight weeks Secondary: Mean percent change in PASI	Primary: There was a significant reduction in the mean percent change in PASI from baseline to week eight in group 1 compared to groups 2 and 3 (73.3, 68.2, and 64.1% respectively; P<0.001). There was a significantly greater percentage of patients with absent or very mild disease in group 1 compared to groups 2 and 3 (55.3, 47.7, and 40.7% respectively; P<0.001). Secondary: There were no significant differences between the three groups with respect to reduction in PASI scores at week 12. At week 12, significantly more patients in group 2 were assessed as having absent or very mild disease compared to group 3 (P=0.026).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriene and betamethasone ointment applied QD for 4 weeks followed by calcipotriene ointment applied QD on weekdays and calcipotriene and betamethasone ointment applied QD on weekends for 8 weeks (Group 2) vs calcipotriene ointment applied BID for 12 weeks (Group 3)			from baseline to each visit and at 12 weeks, proportion of patients with absent/very mild disease according to IGA severity at each visit and at 12 weeks	
van de Kerkhof et al.[150] (2005) Calcipotriene and betamethasone ointment applied QD	MA Patients ≥18 years of age with a diagnosis of psoriasis vulgaris involving at least 10% of one or more body areas	N=1,534 Up to 4 weeks	Primary: Percent change in PASI from baseline Secondary: Rate of disease response assessed by the mean reduction in PASI (after week one), patients who achieved treatment success (marked improvement or clearance), and	Primary: Among patients with severe disease at baseline, there was a 71.6% mean reduction in PASI at week four, 68.9% in patients with moderate disease, and 67.2% in patients with mild disease. Secondary: Among patients with severe disease at baseline, there was a 41.2% mean reduction in PASI after week one, 39.3% in patients with moderate disease, and 38.5% in patients with mild disease. Among patients with severe disease at baseline, 44.4% of patients achieved treatment success after four weeks according to IGA, 60.7% in patients with moderate disease, and 63.8% in patients with mild disease. Among patients with severe disease at baseline, 54.2% of patients achieved treatment success after four weeks according to patient's

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients with controlled disease (absent or very mild disease) according to IGA and PASI	assessments, 60.9% in patients with moderate disease, and 61.2% in patients with mild disease. According to PASI-defined baseline disease severity, 38.7% of patients had controlled disease after four weeks, 52.9% in patients with moderate disease, and 66.1% in patients with mild disease. According to IGA-defined baseline disease severity, 44.1% of patients had controlled disease after four weeks, 53.0% in patients with moderate disease, and 69.3% in patients with mild disease.
Menter et al.[151] (2009) Clobetasol 0.05% spray applied BID for four weeks vs calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment applied daily for four weeks	MC, RCT Patients 18 to 80 years of age with stable plaque psoriasis involving 3 to 20% of the BSA	N=122 8 weeks	Primary: Efficacy as assessed by ODS, investigator global assessment, PQOL-12 Secondary: Not reported	Primary: After two weeks, 41% of patients receiving clobetasol had treatment success (clear or almost clear) compared to 27% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, 75% of patients receiving clobetasol were clear or almost clear compared to 45% of patients receiving calcipotriene and betamethasone dipropionate (P=0.003). After eight weeks, 14% of patients receiving clobetasol were clear or almost clear compared to 8% of calcipotriene and betamethasone dipropionate patients. After four weeks, there was no significant difference in treatment success (clear or mild as assessed using the investigator global assessment scale) among the treatment groups (73% for clobetasol vs 65% for calcipotriene and betamethasone dipropionate). After two weeks, 52% of patients receiving clobetasol were clear or mild compared to 33% of patients receiving calcipotriene and betamethasone dipropionate (P=0.054). After eight weeks, 41% of patients receiving clobetasol were clear or mild compared to 24% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, PQOL-12 scores decreased by 36.1 points with clobetasol and by 30.8 points with calcipotriene and betamethasone dipropionate. After two weeks, PQOL-12 scores decreased by 24.4 points with clobetasol and by 21.4 points with calcipotriene and betamethasone dipropionate. After eight weeks, PQOL-12 scores decreased by 15.9 points with clobetasol and by 10.1 points with calcipotriene and betamethasone dipropionate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patient satisfaction surveys indicate that more patients were satisfied with clobetasol than with calcipotriene and betamethasone dipropionate. Compliance was similar in both treatment groups (100% for clobetasol and 97% for calcipotriene and betamethasone dipropionate). Erythema, scaling and dryness were similar in both treatment groups. More patients experienced stinging/burning with clobetasol. Secondary: Not reported
Luger et al.[152] (2008) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g	DB, MC, RCT Patients with moderate to severe scalp psoriasis	N=869 52 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: Disease was satisfactorily controlled in 92.3% of visits in the calcipotriol-betamethasone group vs 80.0% in the calcipotriol group (P<0.001). Adverse drug reactions were less frequent in the calcipotriol-betamethasone group compared to the calcipotriol group (17.2 vs 29.5%; P<0.001). Incidences of adverse events possibly associated with long-term corticosteroid use were low in both the calcipotriol-betamethasone (2.6%) and the calcipotriol (3.0%) groups. Secondary: Not reported
Saraceno et al.[153] (2007) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g applied QD for 4 weeks, followed by calcipotriol 50	MC, RCT Patients >18 years of age with mild to moderate plaque psoriasis	N=150 12 weeks	Primary: Changes in the PASI after four weeks of treatment Secondary: Maintenance of the PASI score with calcipotriol as a sequential therapy	Primary: A significant improvement of PASI score was demonstrated in patients receiving QD treatment with calcipotriol and betamethasone dipropionate compared to BID treatment with calcipotriol at week two (P<0.001). These results were confirmed and maintained at week four (P<0.001). Secondary: Treatment with calcipotriol from week five to week 12 was associated with a further clinical improvement and treatment with calcipotriol and betamethasone dipropionate was associated with maintenance of the results. At week 12, no significant differences of PASI score were seen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/g cream applied BID for 8 weeks vs calcipotriol 50 µg/g cream applied BID for 12 weeks			in the following eight weeks; safety of the study drugs; patients' QOL, as assessed by the Skindex-29	between the two groups. The QOL assessment showed a marked improvement in terms of Skindex-29 in both groups at weeks two and four as compared to baseline. Similarly to the clinical improvement, the QOL results were significantly superior in the calcipotriol and betamethasone dipropionate group compared to the calcipotriol group (P<0.001). Treatments were well tolerated. Common side effects included erythema, burning, exacerbation of psoriasis, vesicles, lesional or perilesional irritation, itching.
van de Kerkhof et al.[154] (2009) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g	DB, MC, PG, RCT Patients with scalp psoriasis involving >10% of the scalp	N=1417 8 weeks	Primary: Proportion of patients with 'absence of disease' or 'very mild disease' according to investigators' assessments Secondary: Patient ratings of scalp psoriasis and adverse events	Primary: The proportion of patients with 'absence of disease' or 'very mild disease' at week eight was significantly higher in the calcipotriol and betamethasone group (68.4%) than the betamethasone dipropionate (61.0%; P=0.0079) or calcipotriol (43.4%; P<0.0001) groups. Secondary: The proportion of patients rating their scalp psoriasis as 'clear' or 'almost clear' was significantly higher in the calcipotriol and betamethasone group (69.6%) than for betamethasone dipropionate (59.9%; P=0.0006) or calcipotriol (44.7%; P<0.0001). The incidence of lesional/perilesional adverse events was lower in the calcipotriol and betamethasone and betamethasone dipropionate groups than the calcipotriol group.
Jemec et al.[155] (2008) Calcipotriol 50 µg/g and betamethasone	DB, MC, RCT Patients with scalp psoriasis	N=1505 8 weeks	Primary: Patients with ''absence of disease'' or ''very mild disease'' according to IGA	Primary: The proportion of patients who achieved ''absent'' or ''very mild'' disease at week eight was significantly greater in the calcipotriol and betamethasone group (71.2%) compared to the betamethasone dipropionate group (64.0%; P=0.011), the calcipotriene group (36.8%; P<0.0001), and the placebo group (22.8%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dipropionate 0.5 mg/g applied QD vs betamethasone dipropionate 0.5 mg/g applied QD vs calcipotriol 50 µg/g applied QD vs placebo			of disease severity at week eight Secondary: Total Sign Score at week eight, proportion of patients who were ‘‘almost clear’’ or ‘cleared’’ by patients’ assessment	Secondary: At week eight, the percentage change in Total Sign Score was significantly larger for the calcipotriol and betamethasone group (-70.8%) than for calcipotriene (-49.0%; P<0.0001) and for placebo (-35.6%; P<0.001). The difference vs betamethasone dipropionate, (-67.7%) was not statistically significant (P=0.12). The proportion of patients who rated their scalp psoriasis as ‘‘cleared’’ or ‘‘almost clear’’ at week eight was 68.6% for the calcipotriol and betamethasone group, 62.5% for betamethasone dipropionate, 38.3% for calcipotriene, and 20.7% for the placebo alone. The calcipotriol-betamethasone group was significantly more effective than calcipotriene (P<0.0001) and the placebo alone (P<0.0001). The difference vs betamethasone dipropionate was not statistically significant (P=0.2).
White et al.[156] (2006) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by calcipotriol cream 50 µg/g for 8 weeks (cream group) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5	RCT, SB (4 weeks), DB (8 weeks) Patients ≥18 years of age with a clinical diagnosis of psoriasis vulgaris affecting at least 10% of the arms and/or 10% of the trunk and/or 10% of the legs	N=1136 12 weeks	Primary: Assessment of the PASI, investigators’ global assessment of disease severity on a six-point scale (disease absent, very mild, mild, moderate, severe, or very severe), and adverse events Secondary: Not reported	Primary: The mean percentage change in the PASI from baseline to the end of the trial was -44.5% in the calcipotriene cream group, -58.4% in the alternating group, and -33.1% in the vehicle group. The mean difference between the calcipotriene cream and vehicle groups was -11.7% (P<0.001), and the mean difference between the alternating and vehicle groups was -24.7% (P<0.001). For the investigators' global assessment of disease severity at the end of the trial, the differences between the calcipotriene cream and vehicle groups, and between the alternating and vehicle groups demonstrated greater efficacy in the non-vehicle groups (P<0.001). The patients’ global assessment of disease severity demonstrated similar results (P<0.001). There were no statistically significant differences in the incidence of adverse drug reactions in the calcipotriene cream group relative to the vehicle group (P=0.21), or in the alternating group relative to the vehicle group (P=0.61). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/g ointment for 4 weeks followed by calcipotriol cream 50 µg/g on weekdays and calcipotriol and betamethasone on weekends for 8 weeks (alternating group) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by vehicle cream for 8 weeks (vehicle group)				Not reported
Kragballe et al.[157] (2006) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g for 52 weeks vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5	DB, RCT Patients ≥18 years of age with a clinical diagnosis of psoriasis vulgaris of the trunk and/or limbs	N=634 52 weeks	Primary: Adverse events Secondary: Not reported	Primary: Adverse drug reactions occurred in 21.7% of patients in the calcipotriol and betamethasone group, 29.6% in the alternating group and 37.9% in the calcipotriol group (P<0.001). The OR for an adverse drug reaction in the calcipotriol and betamethasone group relative to the calcipotriol group was 0.46 (95% CI, 0.3 to 0.7; P<0.001). The OR for the alternating group relative to the calcipotriol group was 0.69 (95% CI, 0.46 to 1.04; P=0.073), and for the calcipotriol and betamethasone group relative to the alternating group 0.66 (95% CI, 0.42 to 1.03; P=0.066). Adverse drug reaction of concern associated with long-term topical corticosteroid use occurred in 4.8% of patients in the calcipotriol and betamethasone group, 2.8% of patients in the alternating group and 2.9%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/g for 4 weeks followed by calcipotriol 50 µg/g for 4 weeks (alternating for 52 weeks) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g for 4 weeks followed by calcipotriol 50 µg/g for 48 weeks				of patients in the calcipotriol group. Those adverse drug reaction with the highest incidence were skin atrophy and folliculitis. Secondary: Not reported
De Jong et al.[159] (2003) Calcipotriol 50 µg/g ointment applied BID and MTX vs MTX Phase I: Cessation of MTX and treatment initiation of blinded topical treatment with either calcipotriol or placebo for total	DB, MC, PC, PG, RCT Patients ≥18 years of age with chronic plaque psoriasis who had been treated with MTX with or without topical treatment during the last 6 months and whose psoriasis had been stable for at least 3 months	N=98 54 weeks	Phase I: Relapse-free interval [relapse measured by the MPSS] Phase II: MTX-sparing effect of calcipotriol (measured by the dose of MTX needed) Phase III: Maintenance of the target MPSS on topical treatment plus the MTX dose used at the end of	Phases I and III: There was a statistically significant difference in favor of calcipotriol in MPSS scores (P=0.031). The median time to relapse was 113 days in the calcipotriol group compared to 35 days in the placebo group (P<0.001). There was no psoriasis relapse in 41.2% of patients in the calcipotriol group compared to 17.4%of patients in the placebo group. Phase II: The group treated with calcipotriol required a significantly reduced dose of MTX compared to the placebo group (3.3 compared to 6.3 mg/week [P<0.001]). At the end of phase II, the calcipotriol group required less MTX, 6.5 mg/week, than the placebo group, who required 9.9 mg/week of MTX (P=0.002). Investigator assessments of efficacy in the intent-to-treat population

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of 30 weeks or until relapse occurs. Phase II: MTX titration phase with open MTX treatment and continuation of blinded topical therapy for 18 weeks or until target MPSS reached. Phase III: Follow-up phase for patients reaching the target MPSS for a maximum of 6 weeks.			phase II (measured by the occurrence of relapse)	showed a non-significant trend in favor of calcipotriol (P=0.068).
Torras et al.[159] (2004) Calcipotriol 50 µg/g cream applied BID and PUVA 3 times per week vs PUVA 3 times per week	MC, PC, PG, RCT Patients ≥18 years of age with skin type II or III and a diagnosis of extensive psoriasis vulgaris covering 20 to 50% of BSA, and who were scheduled to receive PUVA therapy on the trunk and the limbs Phase I:	N=120 12 weeks	Primary: PASI scores, overall patient assessment of skin lesions, and the total UVA dosage needed Secondary: Not reported	Primary: Statistically significant decreases in PASI scores were observed form week two to week 10 with the decrease being greater in the calcipotriol group (P<0.0063). At the end of treatment, the PASI score was significantly lower in the calcipotriol group compared to the placebo group (-87.5 vs -49.6; P<0.001). In the calcipotriol group, 87.9% of patients achieved reductions of at least 75% in PASI scores and 69% achieved reductions of 90% in PASI scores compared to 47.3% and 36.4% respectively in the placebo group (P<0.001 between groups). The median duration of treatment needed to achieve these decreases was significantly shorter in the calcipotriol group compared to the placebo group (42 and 56 days vs 77 and 79 days,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Two week washout period during which patients received an emollient only, or a shorter wash out if patients had received no previous treatment and did not need the full 2 weeks Phase II: Patients received either calcipotriol 50 µg/g or placebo BID for at least 10 weeks Phase III: Within 1 week of randomization, patients received PUVA therapy 3 times per week in addition to topical therapy (methopsoralen was administered 2 hours prior to UVA treatment)			respectively; P<0.004). At the end of Phase III, overall patient assessment of lesions was rated moderately improved or totally cleared in 79.3% of patients in the calcipotriol group compared to 60% of patients in the placebo group (P<0.01). The total UVA dose needed in the calcipotriol group was significantly lower compared to the placebo group (P=0.016). The average number of irradiations needed was significantly lower in the calcipotriol group compared to the placebo group (P<0.01). The mean cumulative PUVA dose needed to achieve at least 90% reduction in PASI score was lower in the calcipotriol group compared to the placebo group (P=0.03). Secondary: Not reported
Lebwohl et al.[160] (2007) Calcitriol 3 µg/g ointment applied BID	DB, RCT Patients with mild to moderate chronic plaque psoriasis	N=839 8 weeks	Primary: GSS; safety Secondary: Not reported	Primary: Calcitriol 3 µg/g ointment was significantly more effective than placebo, with onset of therapeutic effect seen as early as week two and sustained at all subsequent visits. Calcitriol 3 µg/g ointment demonstrated good systemic and local safety profile comparable to its placebo with no effect on calcium homeostasis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: Not reported
Lebwohl et al.[161] (2009) Calcitriol 3 µg/g ointment applied BID	MC, OL Patients ≥12 years of age with mild to moderate chronic plaque psoriasis	N=324 26 to 52 weeks	Primary: Safety Secondary: Global assessment of improvement	Primary: Adverse events were reported for 40% of patients. The most common adverse events were abnormal laboratory test results, which included elevated blood calcitriol levels (7%), pathological blood PTH and calcitriol levels (0.3%), and elevated blood PTH levels (0.3%). Adverse events thought to be related to study treatment were noted for 45 patients (13.9%). Eight patients (2.5%) had adverse events leading to study discontinuation, and adverse events for four of these patients (1.2%) were considered related to treatment. These events included irritant dermatitis, pruritus, kidney pain, and urine abnormality (one patient each). Six patients experienced severe adverse events; none were related to calcitriol treatment. Secondary: At least marked improvement was reported by 131 of 249 patients (52.6%) at week 26 and 83 of 130 patients (63.8%) at week 52. Approximately 21% (52/249) of patients rated themselves as clear or almost clear at week 26 and 30% (39/130) at week 52. Mean percentage BSA decreased over time from 16.1% at baseline to 10.7% at end point.
Langner et al.[162] (1996) Calcitriol 3 µg/g ointment applied BID	MC, OL Patients ≥18 years of age with chronic plaque-type psoriasis	N=253 78 weeks	Primary: Overall improvement of the treated lesions; PASI score Secondary: Not reported	Primary: Ninety-six (40.1%) patients showed definite or considerable improvement at end-point compared to baseline, and clearance of psoriasis was reported in 39 (16.3%) patients. Forty-six patients who showed clearing or considerable improvement of psoriasis were withdrawn from the study due to this outcome. Eleven (23%) of these patients relapsed within three months and subsequently re-entered the study. From the remaining group of 36 patients, a relapse after 3 months was reported in six patients. The number of patients with severe or very severe psoriasis fell from 120

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(47.4%) at baseline to 54 (21.4%) at end-point. The number with none or slight psoriasis increased from 19 (7.5%) to 98 (38.8%). Pruritus showed a significant improvement over the course of the study. At baseline, 4.3% of the patients complained of severe, distressing pruritus, which had fallen to 1.2% at the three- and 12-month assessments. At the start of the study, only 17% of patients had no specific complaint of pruritus, but this had improved to 48.4% at the three-month assessment and 38.7% at end-point. The PASI score showed a marked improvement after three months treatment (53.2% reduction in score), which was maintained over the whole course of the study. Secondary: Not reported
Bourke et al.[163] (1997) Calcitriol 3 µg/g ointment vs calcipotriol 50 µg/g ointment	DB, RCT Patients with moderately extensive chronic plaque psoriasis	N=24 8 week	Primary: Change in the PASI scores Secondary: Not reported	Primary: Mean PASI in patients receiving calcitriol decreased from 13.0 to 8.8 (P<0.05). Mean PASI in patients receiving calcipotriol decreased from 14.9 to 4.7 (P<0.005). The reduction in PASI was significantly greater in the calcipotriol-treated group than in the calcitriol group (P<0.05). Secondary: Not reported
Zhu et al.[164] (2007) Calcitriol 3 µg/g ointment applied BID vs	RCT, SB Patients 18 to 65 years of age with mild to moderate chronic plaque-type psoriasis involving up to 35% of the BSA	N=250 12 weeks	Primary: Global assessment of improvement assessed by the investigator Secondary: Global assessment of improvement	Primary: At week 12, the mean global improvement score rated by the investigator was 2.27 for calcitriol and 2.22 for calcipotriol (P=NS). Secondary: At week 12, the mean global improvement score rated by the patient was 2.12 for calcitriol and 2.09 for calcipotriol. There was no significant different in the percentage of patients with at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriol 50 µg/g ointment applied BID			assessed by the patient; safety	least marked improvement with calcitriol (95.7%) compared to calcipotriol (85%; P=NS). The three clinical signs of the disease, plaque elevation, erythema and scaling, were significantly reduced in all treatment groups. Mean DSS decreased from 8.14 at baseline to 1.87 over the 12-week treatment with calcipotriol and from 8.10 to 2.54 with calcitriol (P<0.01). The cutaneous safety score as assessed by the investigator was higher with calcipotriol than with calcitriol (mean scores 0.3 vs 0.1), showing a better local tolerance of calcitriol. A total of 11 (8.9%) patients had a score of 2 or 3, corresponding to 'moderate' or 'severe' local reaction with calcipotriol, whereas only one (0.8%) patient had a 'moderate' reaction with calcitriol (P=0.0035).
Ortonne et al.[165] (2003) Calcitriol 3 µg/g ointment applied BID vs calcipotriol 50 µg/g ointment applied BID	RCT, SB Patients 18 to 70 years of age with mild to moderate chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas	N=75 6 weeks	Primary: Perilesional erythema and edema; Global assessment of improvement Secondary: Not reported	Primary: Perilesional erythema (P<0.001), perilesional edema (P<0.02) and stinging/burning (P<0.001) were all less severe with calcitriol than with calcipotriol. The IGA of local safety showed that calcitriol was better tolerated than calcipotriol. More patients considered calcitriol better or much better tolerated than calcipotriol (49.3 vs 10.7%, respectively; P<0.0001). Global assessment of improvement from baseline by the investigators was significantly greater for the calcitriol-treated lesions (P<0.02). A total of 44% of patients considered efficacy to be greater on the calcitriol-treated side than on the calcipotriol-treated side, whereas 29% of patients reported the opposite. The patient's global preference showed a significant difference in favor of calcitriol (P <0.02), with 57% of the patients rating calcitriol as being better or much better than calcipotriol. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Camarasa et al.[166] (2003) Calcitriol 3 µg/g ointment applied BID vs betamethasone dipropionate 0.05% ointment applied BID	DB, MC, RCT Adults with chronic plaque-type psoriasis of at least moderate severity	N=258 Treatment: 6 weeks Follow-up: 8 weeks	Primary: Global improvement of treated psoriatic lesions; PASI; relapse Secondary: Not reported	Primary: After six weeks, both calcitriol and betamethasone were found to be efficacious. Similar proportions of patients (79% in the calcitriol group and 82% in the betamethasone group) showed definite or considerable improvement in their psoriasis, or total clearance of lesions by treatment endpoint. The mean of the global improvement scores at endpoint were similar (2.31 for calcitriol and 2.55 betamethasone; P<0.05). Both treatment groups showed a clinically relevant decrease in the mean GSS which, at endpoint, was 1.58 for the calcitriol group and 1.36 for the betamethasone group (P<0.05). Each treatment also resulted in a marked improvement in the PASI from baseline to endpoint, with the absolute reduction in the mean PASI at endpoint being comparable between the groups (P>0.05). Relapse warranting new treatment within eight weeks of the study endpoint was required in 52% of patients who had been receiving calcitriol, at a mean of 25.3 days post-treatment. In the betamethasone group, relapse was required for 75% of patients at a mean of 23.4 days post-treatment. The proportion of responders remaining in remission at eight weeks post-treatment (48 and 25% for the calcitriol and betamethasone groups, respectively; P<0.01). The two study ointments were similar in terms of cosmetic acceptability. The overall opinion of the ointments by the majority of patients was generally 'good' or 'acceptable' (91 and 92%, for the calcitriol and betamethasone groups, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Liao et al.[167] (2007) Calcitriol 3 µg/g ointment applied BID vs tacrolimus 0.3 mg/g ointment applied BID	DB, RCT, SC Patients 18 to 70 years of age with chronic plaque psoriasis affecting face or genitofemoral regions	N=50 6 weeks	Primary: Mean reduction of the TAS Secondary: Percent of patients with complete or almost complete clearance based on the PGA score	Primary: The mean TAS significantly decreased by 51.4% for calcitriol, and 63.8% for tacrolimus. Tacrolimus was significantly more effective than calcitriol at week four and at the end of the six-week treatment period (P<0.05). Secondary: During the treatment period, there was no significant difference in the mean global improvement scores for tacrolimus or calcitriol (3.48 vs 2.67; P=0.066). At the end of the study, more patients achieved complete or almost complete clearance in the tacrolimus group compared to the calcitriol group (60 vs 33%; P<0.05).
Lahfa et al.[168] (2003) Calcitriol 3 µg/g ointment applied QPM and clobetasol 0.05% cream applied QAM vs calcipotriol 50 µg/g ointment applied QPM and clobetasol 0.05% cream applied QAM When the patient's skin had cleared or improved, the steroid was discontinued and	MC, RCT, SB Patients with mild to moderate chronic plaque-type psoriasis	N=125 12 weeks	Primary: Investigator's assessment of global improvement Secondary: Patients' assessments of global improvement, PASI, proportion of the BSA affected by psoriasis	Primary: No significant differences between the two regimen groups in the IGA of improvement were detected at any of the study time points (all, P>0.05). The global assessment by investigators at endpoint revealed a successful clinical response (marked improvement, almost clear or clear) for 79% of patients receiving calcitriol compared to 88% of patients receiving calcipotriol. Secondary: At study endpoint, there was complete clearing of psoriasis lesions in 26% of patients in the calcitriol group and in 25% of patients in the calcipotriol group. In each of the treatment groups, the beneficial effect of treatment on the severity of psoriasis was detected by a marked decrease in PASI. No significant differences between the two regimen groups were detected at any of the study time points.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
monotherapy with calcitriol or calcipotriol started.				
Rigopoulos et al.[169] (2007) Tazarotene 0.1 % cream applied QHS for 12 weeks vs clobetasol 0.05% cream applied QHS for 12 weeks	DB, RCT Patients with psoriasis including nail involvement	N=23 24 weeks	Primary: Assessment of pitting, onycholysis, subungual hyperkeratosis and salmon patches using the NAPSI Secondary: Not reported	Primary: There was no significant difference in pitting, onycholysis, subungual hyperkeratosis, or salmon patches between tazarotene and clobetasol after 12 weeks of treatment. Post hoc analysis at the end of the follow-up period (24 weeks) demonstrated clinical improvement for hyperkeratosis with tazarotene compared to clobetasol (P<0.001). All adverse events reported were mild, with the symptoms ameliorating after a few days. All patients in both groups declared satisfaction with the results at the end of the treatment period. Secondary: Not reported
Angelo et al.[170] (2007) Tazarotene 0.1% cream applied on one side of the body for 12 weeks vs clobetasol 0.05% cream applied on the other side of the body for 12 weeks	RCT, SB Patients with psoriasis and bilateral symmetrical lesions	N=36 16 weeks	Primary: Assessment of erythema, scaling and induration on a 4-point scale; investigators' overall assessment of psoriasis including extent and severity; treatment success Secondary: Not reported	Primary: During the 12-week treatment period, both tazarotene cream and clobetasol cream were associated with reduction in erythema scores from the baseline except at week two where tazarotene showed no improvement. Clobetasol cream was better than tazarotene cream in reducing the erythema throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene at weeks two, four, six and eight. During the 12-week treatment period, both tazarotene and clobetasol creams were associated with reduction in induration scores from baseline. Tazarotene was better than clobetasol in reducing the induration at weeks two, four, 10 and 12. The difference was statistically significant at week two. Both were equally effective at weeks six and eight. During the 12-week treatment period both tazarotene and clobetasol creams were associated with reduction in desquamation scores from baseline except at week two where tazarotene showed no reduction. Clobetasol cream was better than tazarotene cream in reducing the scaling

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene over the entire 12-week treatment period. The overall improvement at weeks two, four six, eight, 10 and 12 for tazarotene was ~20, ~33, ~43, ~53, ~55 and ~58% respectively and for clobetasol was ~33, ~55, ~73, ~78,~95 and ~95% respectively. Statistically significant differences favored clobetasol cream over tazarotene cream over the entire 12-week treatment period. Clobetasol produced higher success rates than tazarotene over the 12-week treatment period. Statistically significant differences favored clobetasol over tazarotene at weeks two and four. Treatment success rate was 100% at week six with clobetasol and was 73% with tazarotene. At week 12, it was 100% with clobetasol and 88% with tazarotene. Secondary: Not reported
Kumar et al.[171] (2010) Tazarotene 0.1% gel applied QHS vs crude coal tar 5% (CCT) ointment applied QHS	RCT Patients with chronic stable plaque psoriasis	N=27 Treatment: 12 weeks Follow-up: 8 weeks	Primary: Severity of psoriatic lesions and response to treatment evaluated by ESI Secondary: Not reported	Primary: In the per-protocol analysis, the mean percentage reduction in ESI score at the end of the treatment period was 74.15 and 77.37% with tazarotene and CCT, respectively (P>0.05). With regard to clinical response, marked, moderate, mild and no response was seen in 0, 3.7, 73.3 and 14.8% of patients, respectively, for both treatments at the end of four weeks of treatment. At the end of eight weeks, the corresponding grades of improvement were 3.7, 70.3, 29.9 and 0% for the tazarotene-treated side, and 3.7, 66.6, 29.6 and 0% for the CCT-treated side. At the end of the 12 weeks of treatment, all 27 patients had moderate to marked improvement on both sides. With tazarotene, marked improvement was seen in 40.7% of lesions, and moderate improvement in 59.2%. With CCT, marked improvement was seen in 59.2% and moderate improvement in 40.7%. Side effects were seen in 48.14% of patients treated with tazarotene: mild irritation (four patients), erythema (four), burning sensation (six), itching (one) and dryness and fissuring (two). No side effects were seen in any of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the patients treated with 5% CCT. Secondary: Not reported
Tzung et al.[172] (2005) Tazarotene 0.1% gel applied QHS and petrolatum applied QAM vs calcipotriene 0.005% ointment applied BID	CS, IB, RETRO Patients 12 to 80 years of age with a diagnosis of psoriasis and a total of 50 target lesion pairs	N=19 Treatment: 12 weeks Follow-up 4 weeks	Primary: Severity scores for scaling, plaque elevation, erythema, overall lesion severity, and patient self-reported efficacy Secondary: Not reported	Primary: At the end of the 12-week treatment period, the tazarotene plus petrolatum was as effective as calcipotriol in the reduction of scaling, plaque elevation, erythema, and overall lesion severity. Erythema worsened in the tazarotene plus petrolatum side in week one and reduction of erythema on this side was first observed in week two. The difference in erythema between sides was not significant after eight weeks. Lesion severity scores worsened on both sides during the post-treatment phase, though the tazarotene plus petrolatum side maintained the therapeutic effect significantly better in terms of scaling, plaque elevation, erythema, and overall severity at week 16 ($P<0.001$, $P<0.001$, $P=0.01$, and $P=0.007$ respectively). Patient-assessed success rates were 74% on the tazarotene plus petrolatum side and 85% on the calcipotriol side, though this difference was not significant ($P>0.46$). Secondary: Not reported
Schiener et al.[173] (2000) Tazarotene 0.05% gel applied QD and total body narrowband UVB irradiation QD 4 times per week vs	CS, IB Patients with psoriasis	N=10 ≥4 weeks	Primary: PASI Secondary: Not reported	Primary: PASI scores decreased on both treatment sides and there was no significant difference between treatment regimens. Complete clearance of the skin was observed after a median of 19 treatment sessions for both treatment regimens. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriene 0.005% ointment applied QD plus total body narrowband UVB irradiation QD 4 times per week				
Guenther et al.[174] (2000) Tazarotene 0.1% gel applied QHS and mometasone 0.1% cream applied QAM vs calcipotriene 0.005% applied BID	IB, MC, PG Patients with chronic, stable plaque psoriasis affecting 5 to 20% of total BSA	N=120 Treatment: 8 weeks Follow-up: 12 weeks	Primary: Physician-rated measures of efficacy including global improvement, plaque elevation, scaling, erythema, and percentage of BSA involvement; patient-rated assessments including efficacy of study treatment compared to previous therapies, comfort of treated skin, outlook for long-term control, and overall impression of treatment Secondary: Not reported	Primary: Physician-rated assessments: After two weeks of treatment, the percentage of patients achieving marked improvement (≥75% global improvement) was significantly higher in the tazarotene and corticosteroid group compared to the calcipotriene group (45 and 25% respectively; P<0.05). There was no significant difference in the percentage of patients achieving complete or almost complete clearance between the two treatment groups at any time. For trunk lesions, the mean percentage of reduction in plaque elevation was not significant between groups during the treatment phase, but was significantly higher in the tazarotene plus corticosteroid group at the end of treatment and week four of the post-treatment phase (P<0.05) For upper or lower limb lesions, no significant between-group differences in plaque elevations were observed at any point. For trunk lesions, the mean percentage of reduction in scaling was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at week four of the post-treatment phase (P<0.05). For upper or lower limb lesions, no significant between-group differences in scaling were observed at any point. For trunk lesions, the mean percentage of reduction in erythema was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at the end of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment (P<0.05). For upper or lower limb lesions, no significant between-group differences in erythema were observed at any point. For trunk lesions, the mean percentage of reduction in BSA involvement was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group after two and four weeks of treatment (P<0.01), though no significant differences were observed between groups in the post-treatment phase. For upper limb lesions, the tazarotene plus corticosteroid group had a significantly higher percentage of reduction in percentage of BSA involvement after two and four weeks of treatment compared to the calcipotriene group (P<0.05 at two weeks and P<0.01 at four weeks). No significant differences were observed during the post-treatment phase between groups. For lower limb lesions, significance was only achieved for patients admitted to the post-treatment phase and only at the end-of-treatment visit (P<0.001). <u>Patient-rated assessments:</u> A significantly greater percentage of patients rated their therapy more effective or much more effective than previously-tried therapies in the tazarotene plus corticosteroid group compared to the calcipotriene group (P<0.05). At the end of treatment, 16% of patients in the tazarotene plus corticosteroid group and 9% of patients in the calcipotriene group rated the comfort of their therapy as somewhat comfortable, 42 and 51% rated it as comfortable, and 27 and 25% rated it as very comfortable, respectively (the significance of these findings are not discussed). No significant between-group differences were observed in the percentage of patients who rated their outlook for long-term control as very promising or extremely promising at the end of the 12 week post-treatment phase. Overall impression of treatment favored the tazarotene plus corticosteroid

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				regimen compared to the calcipotriene regimen, however the percentages of patients who rated their impression of therapy as favorable or highly favorable did not differ between groups, except at the 12-week post-treatment visit (P<0.05). Secondary: Not reported
Bowman et al.[175] (2002) Tazarotene 0.05% gel and calcipotriene 0.005% ointment applied QAM and calcipotriene ointment applied QHS vs clobetasol 0.05% ointment applied BID	CS, OL, PRO Patients ≥18 years of age with psoriasis vulgaris that was chronically stable for at least 1 month prior to screening with at least 1 bilateral mirror image plaque on the trunk, arms, or legs	N=15 Treatment: 2 weeks Follow-up 4 weeks	Primary: Severity scores for erythema, scaling, and plaque elevation Secondary: Not reported	Primary: At the end of the two week treatment period, both the tazarotene plus calcipotriene side and the clobetasol side showed marked reductions in scaling, plaque elevation, and overall lesional severity (P<0.0001). There were no significant differences in the tazarotene plus calcipotriene side compared to the clobetasol side in the reduction in scaling (P=0.93), plaque elevation (P=0.76), and overall lesional severity scores (P=0.29). Erythema improved significantly more in the clobetasol-treated lesions during the treatment period (P<0.01) but there was no significant difference between the sides during the post-treatment period (P=0.20). Lesional severity scores worsened on both sides during the post-treatment phase. Plaque elevation returned more rapidly on the tazarotene plus calcipotriene side (P<0.01), but scaling, erythema, and overall lesional severity were not significantly different between the two treatments (P>0.05). No treatment-related adverse effects were reported on the clobetasol side. Adverse effects in the tazarotene plus calcipotriene side were mild and did not result in alteration of the treatment schedule for any patient. Secondary: Not reported
Skin Graft Adherence				
Griswold et al.[176] (2008) Fibrin sealant	MC, RCT, SB Burn patients with wounds measuring	N=138 28 days	Primary: Wound closure at day 28	Primary: The proportion of test sites with complete wound closure at day 28 was 70.3% with the fibrin sealant compared to 65.8% in stapled sites as determined by planimetry.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Artiss®) vs staples	≤40% of total body surface requiring wound excision and skin grafting		Secondary: Hematoma/seroma on day one, engraftment on day five, wound closure on day 14, investigator-assessed outcomes, patient-assessed outcomes	The proportion of test sites with complete wound closure at day 28 as assessed by blinded review of photographs was 43.3% with the fibrin sealant and 37.0% with staples. The fibrin sealant was non-inferior to the staples for complete wound closure by day 28. Secondary: Hematoma/seroma on day one occurred at significantly fewer fibrin-treated sites (29.7%) compared to stapled sites (62.3%; P<0.0001). Engraftment on day five was 100% in 62.3% of the fibrin-treated sites and 55.1% of the stapled sites (P=0.0890). Complete wound closure by day 14 occurred in 48.8% of the fibrin-treated sites and 42.6% of the stapled sites (P=0.2299). Fibrin sealant scored significantly better than staples for all investigator-assessed outcomes, including quality of graft adherence (P<0.0001), preference for method of fixation (P<0.0001), satisfaction with graft fixation (P<0.0001), and overall quality of healing (P<0.0001). Fibrin sealant scored significantly better than staples for all patient-assessed outcomes, including anxiety about pain (P<0.0001) and treatment preference (P<0.0001).
Warts				
Arican et al.[177] (2004) Imiquimod 5% cream applied 3 times per week for 12 weeks vs placebo	DB, PC, RCT Patients ≥18 years of age with a diagnosis of external anogenital warts	N=45 Treatment: 12 weeks Follow-up 6 months	Primary: Clearance of anogenital warts Secondary: Not reported	Primary: After treatment, 69.7% of patients in the treatment group (all of the female patients and 54.5% of the male patients) had complete clearance of the warts, nine patients had 50 to 90% clearance, and one patient had <50% clearance. After treatment, one patient displayed complete clearance, one patient had 50 to 90% clearance, and the remaining eight patients showed no alteration in lesions. These results are statistically significant in favor of the treatment group (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Haidopoulos et al.[178] (2004) Imiquimod 5% cream applied 3 times per week at bedtime for maximum of 12 weeks or until wart clearing	OL, OS Female patients 16 to 52 years of age with vulvar warts with a median wart area of 55 mm^2	N=73 Treatment: 12 weeks Follow-up 3 months	Primary: Total or partial clearing of the warts Secondary: Not reported	Primary: No improvement was detected in 6% of patients during the 12 week treatment period. Total clearing of the lesions was reported in 71% of patients, 85% of patients reported more than 50% reduction in the size of the lesions, and 8% reported less than 50% reduction in the size of the lesions. In the women experiencing total clearance, 43% reported that the warts were eradicated in the first six weeks of treatment. During the follow-up period, 13% developed recurrent disease and were treated with CO_2 vaporization (17 patients were lost to follow-up during this time). Secondary: Not reported
Stefanaki et al.[179] (2008) Imiquimod 5% cream applied 3 times per week for 12 weeks vs cryotherapy administered once over 3 weeks for 3 consecutive sessions	OL, RCT HIV-negative males with anogenital warts	N=80 12 months	Primary: Clearance of treated warts, recurrence, adverse events Secondary: Not reported	Primary: At the end of three months, irrespective of the type of treatment, 78.8% of the patients demonstrated 100% improvement. Cryotherapy was more effective as 86.7% of the patients showed 100% improvement compared to 68.6% of patients in the imiquimod group. In the imiquimod group, 17.1% of patients did not show any signs of improvement compared to only 2.2% in the cryotherapy group (P=0.019). Patients treated with imiquimod tended to improve earlier than patients on cryotherapy (P=0.012). At the end of the first month, 31.4% of patients on imiquimod demonstrated 100% clearance compared to 20.0% of the patients in the cryotherapy group. At the end of the second month more patients in the imiquimod group (37.1%) were free of the disease compared to the cryotherapy group (22.2%). Initial disease parameters, such as number of warts (P=0.640), color

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.053), location (P=0.101) and duration of lesions (P=0.17), were not statistically different between imiquimod or cryotherapy treatments. At 12 months after the initial visit, the recurrence rate was 41% for the imiquimod and 59% for the cryotherapy group (P=0.138). Treatment with imiquimod was less painful than cryotherapy (P=0.034). Secondary: Not reported
Yan et al.[180] (2006) Imiquimod 5% cream applied 3 times per week until the warts were completely cleared or for a maximum of 16 weeks vs podophyllotoxin 0.5% applied 2-3 times per day for 3 consecutive days followed by a 4-day treatment-free period until the complete shedding of the warts or for a maximum of 4 weeks vs	MA Patients with clinically visible genital warts in the genital, anal, perineal or perianal area	N=473 ≤10 months	Primary: Clearance rate; adverse events Secondary: Not reported	Primary: <u>Imiquimod vs placebo</u> Pooled analysis across three studies including 194 patients in the imiquimod group and 168 in the placebo group showed a statistically significant difference between the two groups (OR, 11.65; 95% CI, 6.05 to 22.44). Patients treated with imiquimod had a much higher cure rate than those who were treated with a placebo. The complete clearance rate was 50.34% in the imiquimod group and the recurrence rate was 13 to 19%. <u>Podophyllotoxin vs placebo</u> Pooled analysis across 9 studies including 479 patients in the podophyllotoxin group and 294 patients in the placebo group revealed a statistically significant difference between the two groups (OR, 16.70; 95% CI, 7.06 to 39.48). Patients treated with podophyllotoxin had a much higher cure rate than those who were treated with a placebo. The complete clearance rate was 56.41% in the podophyllotoxin group and the recurrence rate was 2 to 90%. The clinical cure rates of imiquimod and podophyllotoxin were 50.34 and 56.41%, respectively, without statistically significant differences between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				the two (P>0.05). The most common adverse events of imiquimod were erythema (37%; 70/187), itching (38%; 26/81), erosion (13%; 24/187) and burning (20%; 16/81). Secondary: Not reported
Moresi et al.[181] (2001) Imiquimod 5% cream vs podofilox 0.05% gel	RETRO Infants and young children diagnosed with anogenital warts	N=25 4 months	Primary: Clearing of lesions, adverse effects, and recurrence of lesions with estimated length of wart-free period Secondary: Not reported	Primary: Seventeen patients were treated with podofilox and of those, parents of 15 patients reported resolution of lesions with no recurrence for periods ranging from four months to two years. Adverse reactions reported in the podofilox group included burning (most common), pain, redness, erosions, and edema. Eight patients were treated with imiquimod and of those, parents of six patients reported clearing of lesions which remained clear six to 12 months after therapy ended. Adverse reactions reported in the imiquimod group included itching, redness, and irritation. Half of the patients reported few or no side effects. Secondary: Not reported
Tyring et al.[182] (1998) Podofilox 0.5% gel applied BID for 3 consecutive days followed by 4 days with no treatment vs placebo	DB, MC, PC, RCT Patients ≥18 years of age who were immunocompetent and had at least 2 distinct external anogenital warts	N=326 Treatment: 8 weeks Follow-up: 8 weeks	Primary: Disappearance of treated warts Secondary: Number of warts, wart surface area, individual wart assessment scores, physician assessment of overall response,	Primary: Podofilox gel was significantly better than placebo at clearing anogenital and external genital warts after four and eight weeks of treatment (P<0.001). With additional podofilox gel therapy (four to eight weeks), the proportion of patients with anogenital warts treated successfully increased from 62 to 81 patients (P<0.001). After four and eight weeks of treatment, complete clearance was observed in 38.4 and 44.6% of patients with anogenital warts, respectively. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patient discontinuation due to insufficient response, and recurrence rate of treated warts	Baseline data were higher in the podofilox group in mean wart surface area so absolute changes in this outcome were obscured slightly. The change on percentage of baseline wart area showed a significant effect of podofilox gel at four and eight weeks in the external and anogenital wart populations (P=0.001) and at eight weeks in patients with perianal warts (P=0.03). At four weeks, 41.5% of baseline number of anogenital warts treated with podofilox remained, compared to 89.5% of warts remaining in the placebo group (P=0.001). At eight weeks, 35.9% of baseline anogenital warts treated with podofilox remained compared to 88.4% of warts in the placebo group (P=0.001). Physician assessment of improvement was significantly better at four weeks in the podofilox group compared to the placebo group (73.8% of patients had either moderate or marked improvement or complete clearance compared to 15.1% in the placebo group; P=0.001). This trend continued at week eight (81.1% of patients in the podofilox group compared to 17.2% in the placebo group; P=0.001). Overall, 61.1% of patients in the placebo group discontinued therapy due to insufficient response compared to 8.6% of patients in the podofilox group (P=0.002). At week four, 37% in the placebo group and 1.5% in the podofilox group had discontinued due to insufficient response. After treatment was completed, 30.9% of patients in the podofilox group had recurrence of at least one wart within 12 week, most occurring within the first four weeks. The investigators were not able to compare this to the placebo group since only four patients in this group had their warts clear completely during treatment.
Beutner et al.[183] (1989) Podofilox 0.5% solution applied BID for 3 days	DB, MC, PC, RCT Men ≥18 years of age with a diagnosis of genital warts	N=109 16 weeks	Primary: Change in wart count, change in wart area, and number and percentage of	Primary: At the end of the active treatment phase (week four), 73.6% of warts in the podofilox group were cleared compared to 8.3% in the placebo group and the total wart area was reduced by 82.3% in the podofilox group compared to 4.2% in the placebo group on weeks one to six (P=0.0001 for each). Comparisons could not be made at weeks 12 and 16 because there were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 4 days with no treatment vs placebo			patients completely cleared Secondary: Not reported	patients left in the placebo group. At week six, 82% of warts in the podofilox group had completely cleared and of these, 34% had some evidence of recurrence compared to 13% of warts in the placebo group achieving complete clearance with one wart having evidence of recurrence. Overall, 44.6% of podofilox patients were completely clear at some point in the study compared to zero patients in the placebo group (P<0.001). In the podofilox group, 40% of patients who completely healed did not have a recurrence. Secondary: Not reported
Gilson et al.[184] (2009) Podophyllotoxin 0.15% cream applied BID for 3 days per week for up to 4 weeks vs placebo Patients also received weekly cryotherapy until week 12.	DB, MC, RCT Patients with external anogenital warts	N=140 12 weeks	Primary: Wart clearance at weeks four and 12 Secondary: Not reported	Primary: Clearance rates at week four and week 12 were higher in the imiquimod group (60.0 and 60.0%, respectively) than with cryotherapy alone (45.7 and 45.7%, respectively; RR, 1.31; 95% CI, 0.95 to 1.81). Secondary: Not reported
Baker et al.[185] (1990) Podofilox 0.5% solution applied	OL Women 18 to 46 years of age with a diagnosis of	N=37 10 weeks	Primary: Patients' subjective response to treatment, physicians'	Primary: There was an 83% reduction in the mean wart number and a 79% reduction in the maximum number of warts over the 10 weeks. Approximately 75% of the warts had been eliminated by the end of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for 3 days followed by 4 days without treatment	external anogenital warts involving an area of less than 10 cm^2		objective evaluation of the area, number of warts Secondary: Not reported	treatment period. The percentages of patients who achieved complete clearance at weeks one, two, three, four, six, and 10 were 11.1, 25.0, 29.0, 44.4, 50.0, and 50.0% respectively. After complete clearance, 21.6% of women had new occurrences by week 10. Patients' subjective reports of pain, burning, and itching decreased during treatment, as did physicians' objective reports of inflammation and erosion. Other objective observations by investigators occurred during the first three visits and included edema, odor, skin slough, tenderness, and stinging and no patients described these as severe. Over 80% of patients had none of these additional objective observations. Secondary: Not reported
Greenberg et al.[186] (1991) Podofilox 0.5% solution applied BID for 3 days followed by no treatment for 4 days vs podofilox 0.5% cream applied BID for 3 days followed by no treatment for 4	DB, PC, PG, RCT Women ≥18 years of age with a clinical diagnosis of exophytic vulvar condyloma	N=72 10 weeks	Primary: Percentage of warts that were completely healed at anytime during the study, investigators' overall assessment of treatment response Secondary: Not reported	Primary: There was a significant difference in the percentage of warts cleared in the podofilox groups compared to the placebo group at every week of the study (P<0.042). There was a slight increase in wart count after the week-four study visit, especially in those patients receiving only two treatment cycles. The relapse rate was 33% in those patients achieving complete response, and time to relapse was one to seven weeks. New warts appeared in untreated areas in nine patients in the placebo group and eight patients in the podofilox groups . The investigators' overall assessment of response demonstrated a statistical difference in favor of podofilox at each week (P<0.038).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days vs placebo				Secondary: Not reported
Gross et al.[186] (2007) Sinecatechins 15% ointment applied TID vs sinecatechins 10% cream applied TID vs placebo	DB, MC, RCT Patients ≥18 years of age with 2 to 30 clinically diagnosed external genital warts	N=242 Treatment: 12 weeks Follow-up: 12 weeks	Primary: Clearance of warts; local reactions or adverse effects Secondary: Not reported	Primary: Differences in complete clearance rates between the 10% cream and the placebo groups in male and female patients were not statistically significant (P=0.2693 for males and P=0.6479 for females). When the data for both genders were pooled, the complete clearance rates with the 10% cream were not significantly different from placebo (46.8 vs 37.3%, respectively; P=0.2290). Differences between the 15% ointment and the placebo groups in male and female patients were not statistically significant (P=0.0802 for males and P=0.0678 for females). The complete clearance rate of the 15% ointment group was significantly higher compared to placebo (P=0.0066). There was no significant difference in the complete clearance of all warts (baseline and new warts occurring during treatment). A total of 56.4 and 45.5% of patients of the 15% ointment and 10% cream groups were completely wart-free after 12 weeks of treatment compared to 37.5 and 37.2% of patients of the placebo ointment and cream groups, respectively. Adverse events were observed in only 7.9% of patients, with no serious adverse events reported. Local skin reactions were generally mild to moderate and resolved with continued treatment. Secondary: Not reported
Stockfleth et al.[188] (2008) Sinecatechins 15% ointment applied TID	DB, MC, RCT Patients ≥18 years of age with 2 to 30 clinically diagnosed external genital warts	N=503 Treatment: 16 weeks Follow-up: 12 weeks	Primary: Clearance of warts Secondary: Complete clearance of baseline warts,	Primary: In the sinecatechins 15 and 10% groups, complete clearance of all warts was established in 52.6% (P=0.0143) and in 50.8% of patients (P=0.0280), respectively compared to 37.3% of patients in the placebo group. Secondary: For complete clearance of baseline warts, significant treatment effects

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sinecatechins 10% ointment applied TID vs placebo			total wart number, total wart area, partial clearance, and recurrent and new warts	were observed with sinecatechins 15% (54.6%; P=0.0143) and sinecatechins 10% (52.3%; P=0.0376) compared to placebo (39.2%). Median total wart number decreased to zero in the sinecatechins 15% and 10% groups compared to three in the placebo group (P=0.0007 and P=0.0025, respectively). Median total wart area decreased to zero in both sinecatechins 15% and 10% groups compared to 15 in the placebo group (P=0.0011 and P=0.0010, respectively). During the 12-week treatment-free follow-up period, 5.9 and 4.1% of patients in the sinecatechins 15 and 10% groups had a recurrence of anogenital warts, respectively compared to 2.6% of patients in the placebo group. Most local skin reactions were of mild intensity in all three treatment groups. Serious adverse events occurred in two patients only, one patient in each of the active treatment groups. The patient in the sinecatechins 15% group had an application site reaction with severe local symptoms (redness, edema, burning and pain). The second patient (sinecatechins 10% group) had an unrelated limb injury.
Tatti et al.[189] (2008) Sinecatechins 15% ointment applied TID vs sinecatechins 10% ointment applied TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with 2 to 30 external genital and perianal warts with a total wart area of 12 to 600 mm^2	N=502 Treatment: 16 weeks Follow-up: 12 weeks	Primary: Clearance of warts Secondary: Not reported	Primary: Complete clearance of all external anogenital warts was achieved in 57.2% of patients in the sinecatechins ointment 15% group, 56.3% of patients in the sinecatechins ointment 10% group, and 33.7% of patients in the placebo group (P<0.001). Both genders in both the sinecatechins ointment 15% (women 64.6%; P<0.0048; men 50.0%; P<0.001) and the sinecatechins ointment 10% (women 64.9%; P<0.003; men 48.0%; P<0.003) groups showed statistically significantly higher complete clearance rates of all warts when compared to placebo (women 45.8%; men 23.2%). Clearance rates of at least 50% were reported for 152 (78.4%) patients and 145 (74.0%) patients in the sinecatechins ointment 15% and 10% groups compared to 53 (51.5%) of the placebo patients (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				During the 12-week follow-up period, 6.5 and 8.3% of patients treated with sinecatechins ointment 15 and 10%, respectively, had recurrent warts compared to 8.8% of placebo-treated patients. A total of 3.7, 8.3, and 0% developed new warts in the sinecatechins 15%, sinecatechins 10% and placebo groups, respectively. A total of 87.7, 87.3, and 72.1% of patients experienced application site reactions in the sinecatechins 15%, sinecatechins 10% and placebo groups, respectively. Secondary: Not reported
Tatti et al.[190] (2010) Sinecatechins 15% ointment applied TID (G15%) vs sinecatechins 10% ointment applied TID (G10%) vs placebo	DB, MC, RCT (Pooled analysis of 2 trials) Patients ≥18 years of age with 2 to 30 clinically diagnosed external genital warts	N=1,004 16 weeks	Primary: Clearance of all warts Secondary: Complete clearance of baseline warts, time to complete clearance of both all and baseline warts, partial clearance of both all and baseline warts and incidence of recurrent and new warts	Primary: Complete clearance of all warts was obtained in 53.6% of patients receiving G10% and in 54.9% of patients receiving G15% compared to 35.4% in the placebo group (P<0.001). Secondary: The time to complete clearance of all warts was shorter with G10% and G15% than with placebo (P<0.01). The complete clearance of baseline warts was obtained in significantly more patients receiving G10% and G15% than in the placebo group (P<0.01). Partial clearance of all warts (with clearance levels of at least 50% of all warts) was reached in 76.0 and 77.8% of patients in the G10% and G15% groups compared to 52.2% in the placebo group. The recurrence rates did not differ significantly between groups: 5.8% of patients in the placebo group; 6.5% of patients in the G10% group; 6.8% of patients in the G15% group. Few patients developed new warts during follow-up: 1.4% of patients in the placebo group, 7.0% of patients in the G10% group and 2.4% of patients in the G15% group (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Very few of the adverse events related to study treatment were classified as serious: one patient in the PE10% group developed pustular vulvovaginitis and two patients in the PE15% group had application-site reactions (erythema, burning and pain).
Wound Care				
Wieman et al.[191] (1998) Becaplermin gel 30 µg or 100 µg vs good ulcer care vs placebo In study 1, patients received placebo or becaplermin 30 µg gel. In study 2, patients received becaplermin 30 µg, 100 µg, or placebo. In study 3, patients received becaplermin 100 µg, placebo, or good ulcer care (undefined). In study 4, patients received becaplermin 30 µg or 100 µg.	RCT, PC, MC Patients ≥19 years of age with type 1 or 2 diabetes with at least one but no more than three lower extremity diabetic neuropathic ulcers that extended into the subcutaneous tissue or beyond (stages III and IV as defined in the International Association of Enterostomal Therapy guide to chronic wound staging)	N=922 (4 trials) 20 weeks or until complete ulcer healing was achieved	Primary: Incidence of complete wound healing defined as ulcers without draining and with no dressing required Secondary: Time to complete healing (study 2 only)	Primary: In Study 1, the incidence of complete healing was significantly higher in the becaplermin group compared to the placebo group (P=0.02). In study 2, the incidence of complete healing was 50% in the becaplermin 100 µg group, 36% in the becaplermin 30 µg group, and 35% in the placebo group and was only significant when comparing the 100 µg group to placebo (P=0.01). In study 3, the incidence of complete healing was 44% in the becaplermin 100 µg group, 36% in the placebo group, and 22% in the good ulcer care group. This study was designed to compare good ulcer care to placebo and included a small group of patients receiving becaplermin 100 mcg (N=34). The becaplermin group was not powered for statistical comparison. In study 4, the incidence of complete healing was 36% in the becaplermin group and 32% in the placebo group and was not statistically significant. Secondary: In study 2, the time needed to achieve complete healing was approximately 85 days.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Embil et al.[192] (2000) Becaplermin 100 µg QD	OL, MC Patients ≥18 years of age with type 1 or 2 diabetes, having at least one but no more than two full thickness (stage III or IV as defined by the National Pressure Ulcer Advisory Panel staging system) neuropathic ulcers of the lower extremities	N=134 20 weeks or until complete wound healing	Primary: Percentage of patients achieving complete wound closure within the 20 week treatment period Secondary: Time to achieve complete closure, percentage reduction in ulcer area at each visit, and rate of target ulcer recurrence during the 6-month period following healing	Primary: Complete healing was achieved in 57.5% of patients. Secondary: Complete closure was achieved in a mean of 63 days in those patients achieving complete healing. The percentage of patients achieving ≥50% reduction in ulcer area at week 8 achieved a complete closure at the study end, compared to 13% of patients whose ulcer decreased by <50%. The rate of ulcer recurrence in the 6-month period following healing was 21%.
Landsman et al.[193] (2010) Becaplermin 0.01% gel applied daily and TheraGauze® applied to the wound surface with dressing changes QOD (TG+B) vs TheraGauze® applied to the wound surface	MC, RCT Patients ≥18 years of age with diabetic foot ulcers	N=32 20 weeks	Primary: Rate of wound closure and percentage of wound that close Secondary: Not reported	Primary: After 12 weeks, 46.2% of the wounds achieved closure in the TG and TG+B groups. After 20 weeks, 69.2% of wounds achieved closure with TG+B compared to 61.5% of wounds in the TG group (P=NS). The average rates of wound closure were 0.37 cm^2/week for the TG group and 0.41 cm^2/week for the TG+B group (P=0.34). Very few adverse events and no serious adverse events were noted during this study. The adverse events recorded were two infected wounds (6.3%), one wound lost to follow-up (3.1%), and one worsened wound (3.1%). No amputations were reported for study participants. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with dressing changes QOD (TG)				
Burgos et al.[194] (2000) Collagenase ointment applied at 24-hour intervals vs collagenase ointment applied at 48-hour intervals All patients were entered into an active run-in period with collagenase ointment in order to develop 10 to 30% granulation tissue in the ulcer bed before randomization.	MC, OL, PG, RCT Hospitalized or institutionalized patients ≥55 years of age presenting with stage III pressure ulcers for <1 year	N=102 8 weeks	Primary: Ulcer area Secondary: Assessment of ulcer characteristics and adverse events	Primary: Ulcer area in the 24-hour interval group was reduced from 17.7±18.6 to 12.6±17.0cm^2 compared to from 21.4±20.4 to 15.4±19.9cm^2 in the 48-hour interval group (P=0.0005). No statistically significant differences in ulcer area changes were observed between the two treatment groups (P=0.641). Ulcers showed complete healing (closure and epithelization) in 21 (24.4%) patients (12 in the 24-hour group, nine in the 48-hour group). There were no statistically significant differences between the two treatment groups (P=0.451). The RR of non-healing among the 48-hour interval group as compared to the 24-hour interval group when granulation tissue covered 11 to 30% of the ulcer surface was 1.097 (95% CI, 0.86 to 1.39). Secondary: Analysis of ulcer characteristics by ITT showed a pain intensity decrease in both treatment groups that was statistically significant (P=0.001) only in patients treated at 24-hour intervals. Granulation tissue formation was increased (P<0.0005) and exudate production decreased in both treatment groups (24-hour group, P=0.012; 48-hour group, P=0.04), but differences between treatment groups were not statistically significant. Odor was absent in 70% of ulcers at the time of randomization. Although a reduction in odor intensity was observed in both groups, the difference was not significant. The RR of adverse reaction occurrence was 1.02 (95% CI, 0.21 to 4.80).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Palmieri et al.[195] (1998) Collagenase ointment vs placebo	DB, PC, RCT Patients with chronic ulcers of the lower extremities	N=30 14 days	Primary: Evaluation of wound debridement, granulation, epithelization and inflammation using 5-point scales and by measuring wound size; investigator's rating of clinical global efficacy Secondary: Not reported	Primary: Collagenase was significantly more effective than placebo for debridement, granulation, epithelization, and inflammation (P<0.01). Differences reached statistical significance after six days of treatment for both debridement and inflammation, and after four, five, and eight days for granulation, epithelization and wound size, respectively. The investigator's rating of clinical global efficacy also demonstrated the greater efficacy with collagenase than placebo (P<0.001). Both treatments were well tolerated. Adverse events were minor and consisted of a burning sensation following ointment application and erythema. There were no withdrawals as a result of adverse events in either group. Secondary: Not reported
Ostlie et al.[196] (2012) Collagenase QD for 10 days (mixed with polymyxin for antibacterial coverage) vs silver sulfadiazine QD for 10 days Both groups were treated with silver sulfasalazine for the first days of debridement	RCT Patients two months to 18 years of age with partial thickness burns	N=100 12 days	Primary: Need for skin grafting Secondary: None reported	Primary: There was no significant difference in the proportion of patients that required skin grafting between the collagenase and silver sulfasalazine groups (32 vs 36%; P=0.68). Secondary: None reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by the study drug.				
Ramundo et al.[197] (2009) Collagenase vs petrolatum-based or other ointment, autolytic debridement via a hydrogel or polyacrylate dressing, surgical excision, silver sulfadiazine, and alternative enzymatic agents (papain-urea and trypsin-chymotrypsin)	SR Patients with pressure ulcers, leg ulcers, or burn wounds	N=376 (11 trials) Variable duration	Primary: Safety and efficacy of collagenase Secondary: Not reported	Primary: Collagenase ointment was more effective than inactive ointment for debridement of necrotic tissue from pressure ulcers, leg ulcers, and partial-thickness burn wounds. Collagenase was more effective as a debriding agent than silver sulfadiazine cream and equal to a fibrinolysin/DNAase ointment. Equivocal results were found in two studies comparing collagenase to autolytic debridement, but the quality of these studies is not sufficient to allow us to reach definitive conclusions. Results suggest that collagenase may remove slough more rapidly than a trypsin/chymotrypsin debriding ointment, but another study found that collagenase ointment removed necrotic tissue more slowly than a papain-urea ointment. However, there was no significant difference in wound closure between collagenase ointment and papain-urea ointment. Results of a comparison cohort study suggest that debridement with collagenase is similar to surgical excision alone in children with partial-thickness burns. Treatment with collagenase may reduce the need for excision if the techniques are combined. Only one study reported wound healing outcomes as well as time to complete debridement. Treatment of partial-thickness burns covering less than 25% of total body surface healed more quickly using collagenase compared to silver sulfadiazine. Secondary: Not reported
Miscellaneous				
Barikbin et al.[198] (2009) Betamethasone	DB, RCT Patients 20 to 53 years of age with	N=10 8 weeks	Primary: Clinical severity score	Primary: Before treatment, mean disease severity was 4.2 in the pimecrolimus group and 4.4 in the betamethasone group. Following eight weeks of therapy, the mean disease severity was 0.67 and 1.2 in the pimecrolimus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valerate 0.1% cream applied BID vs pimecrolimus 1% cream applied BID	moderate to severe discoid lupus erythematosus of the face		Secondary: Not reported	and betamethasone groups, respectively. The mean clinical severity scores decreased 86% and 73% in the pimecrolimus and betamethasone groups, respectively (both, P=0.043). There was no significant difference between the groups in terms of therapeutic efficacy (P=0.1). There were no recurrences at the eight-week follow-up. Secondary: Not reported
Goldstein et al.[199] (2011) Clobetasol 0.05% cream daily vs pimecrolimus 1% cream applied BID	DB, RCT Female patients ≥18 years of age with biopsy-proven active vulvar lichen sclerosus	N=38 12 weeks	Primary: Change in inflammation as assessed by biopsy Secondary: Change in pruritus and burning/pain as assessed by patients using a VAS, clinical evaluation of an investigator global assessment of the severity of the disease, clinical evaluation of lichenification, and clinical evaluation of ulceration/fissuring	Primary: The improvement in inflammation was significant both for the clobetasol and pimecrolimus groups (P=0.001 and P=0.008, respectively). Clobetasol was found to be more effective in improving inflammation compared to pimecrolimus (P=0.015). There were nine nonresponders (i.e., no improvement in inflammation), one in the clobetasol group and eight in the pimecrolimus group. Secondary: The mean change in the VAS-pruritus score in the clobetasol and pimecrolimus groups were 4.5 and 3.5, respectively (P=0.319). The mean change in VAS-burning/pain score in the clobetasol and pimecrolimus groups was 3.7 and 3.8, respectively (P=0.932). Clobetasol and pimecrolimus were found to be effective in decreasing both the total score on the investigator global assessment (P=0.001) and all three subscales (severity of disease, P=0.001; lichenification, P=0.001; and ulceration, P=0.025). No adverse events were reported and no herpetic events occurred.
Koc et al.[200] (2009) Ketoconazole 2% cream applied BID	OL, RCT Patients with mild to moderate seborrheic dermatitis	N=48 6 weeks	Primary: Treatment efficacy (symptoms of erythema, scaling and infiltration)	Primary: In both treatment groups, there was a significant decrease in erythema, scaling and infiltration criteria (P<0.05). Clinical improvements were as follows: 81.4 and 78.3% for erythema, 86.1 and 87.2% for scaling, and 93.3 and 94.6% for infiltration in the pimecrolimus and ketoconazole groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pimecrolimus 1% cream applied BID			Secondary: Not reported	The mean percentage decrease in the total clinical severity scores was 86.2 and 86.1% in the pimecrolimus and ketoconazole groups, respectively (P>0.05). Adverse events were observed in 12 patients in the pimecrolimus group and four patients in the ketoconazole group. Burning sensation, pruritus, irritation, and erythema were more common in the pimecrolimus group than in the ketoconazole group (P<0.05). Secondary: Not reported
Köse et al.[201] (2010) Mometasone 0.1% cream applied daily vs pimecrolimus 1% cream applied BID	OL, SC Patients with stable vitiligo	N=50 12 weeks	Primary: Response to treatment Secondary: Not reported	Primary: Patients receiving mometasone had a better response to treatment than patients in the pimecrolimus group (P=0.008 in the PP population). Lesion size decreased from 19.20 to 16.85 cm^2 in the pimecrolimus group (P=0.002) and from 18.65 to 10.45 cm^2 in the mometasone group (P<0.001). There was no significant difference between the treatment groups (P=0.154). Complete remission occurred in three patients (15%) receiving mometasone. There were no patients who achieved complete remission in the pimecrolimus group (P=0.018 in the PP population). Moderate and marked responses were recorded in 11 patients (55%) in the mometasone group and in seven patients (35%) in the pimecrolimus group. No change and minimal responses were observed in six patients (30%) in the mometasone group, and in 13 patients (65%) in the pimecrolimus group. After six months, three patients (15%) in the pimecrolimus group and four patients (20%) in the mometasone group showed some areas of depigmentation over re-pigmented vitiliginous lesions. Initial repigmentation started after 9.25 weeks in the mometasone group and after 11.25 weeks in the pimecrolimus group (P=0.064 in the PP population). The mean repigmentation rate was 65% in the mometasone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group and 42% in the pimecrolimus group at the end of therapy. Both agents were well tolerated. The reported adverse events with mometasone were atrophy, telangiectasia, and erythema. Patients receiving pimecrolimus reported a burning sensation and pruritus. Secondary: Not reported
Rigopoulos et al.[202] (2009) Betamethasone valerate 0.1% ointment applied BID vs tacrolimus 0.1% ointment applied BID vs placebo	OL, RCT Patients with chronic paronychia	N=45 Treatment: 3 weeks Follow-up: 6 weeks	Primary: Treatment response Secondary: Not reported	Primary: Eight patients in the betamethasone group were considered as cured, two as improved and four as nonresponders at the end of the treatment period. Thirteen patients in the tacrolimus group were considered as cured and one as improved at the end of the treatment period. Nine patients in the placebo group were considered as stable and six failed to respond. Patients in the betamethasone and tacrolimus groups had greater cure or improvement rates compared to patients in the placebo group (P<0.001). Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QAM= every morning, QD=once daily, QID=four times daily, QHS=every bedtime, QOD=every other day. QPM=every evening, TID=three times daily
Study abbreviations: CI=confidence interval, CS=comparative study, DB=double-blind, ES=extension study, HR=hazard ratio, IB=investigator-blinded, ITT=intention to treat, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SR=systematic review
Miscellaneous abbreviations: ACTG=AIDS Clinical Trials Group, AD=atopic dermatitis, AK=actinic keratosis, BCC=basal cell carcinoma, BPI=brief pain inventory, BSA=body surface area, CA=Composite Assessment of Index Lesion Disease Severity, CCR=clinical complete response, CGIC=Investigator-Related Clinical Impression of Change, CLNS=Cumulative Lesion Number Score, CTCL=cutaneous T-cell lymphoma, DLQI=Dermatology Life Quality Index, EASI=Eczema Area and Severity Index, ESI=erythema, scaling, and induration, GII=Global Improvement Indices, GSS=Global Severity Score, HIV=human immunodeficiency virus, HIV-DSP= Human Immunodeficiency Virus Associated Distal Sensory Polyneuropathy, IAS=Investigator Assessment Scale, IDQOL= Infants' Dermatitis Quality of Life Index, IGA=Investigator's Global Assessment, IGADA=Investigator Global Atopic Dermatitis Assessment, IGII=Investigators' Global Improvement Index, IGIP=Investigator Global Integrated Photodamage, ISGA=Investigator Static Global Assessment, KS=Kaposi's Sarcoma, mEASI=Modified Eczema Area and Severity Index, mLEASI=Modified Local Eczema Area and Severity Index, MPSS=Modified Psoriasis Severity Score, MTX=methotrexate, NPRS=Numeric Pain Rating Scale, NAPSI=Nail Psoriases Severity Index, ODS=overall disease severity, PASI=Psoriasis Area and Severity Index, PD=progressive disease, PDI=Psoriasis Disability Index, PDT=photodynamic therapy, PGA=Physicians Global Assessment of Clinical Condition, PGIC=Patient Global Impression of Change, PGII=Patient Global Improvement Index, PHN=post-herpetic neuralgia, PR=partial response, PRA=partial response area, PRH=partial response height, PQoL-12=Psoriasis Quality of Life Questionnaire, PQoL-AD=Quality-f-Life Questionnaire for Parents of Children with Atopic Dermatitis, PSSI=Psoriasis Scalp Severity Index, PTH=parathyroid, PUVA=psoralen

ultraviolet A, QOL=quality of life, sBCC=superficial basal cell carcinoma, SCC=squamous cell carcinoma, SCOR-AD=Severity Scoring of Atopic Dermatitis, SD=stable disease, SF-MPQ=Short Form McGill Pain Questionnaire, TAS=target area score, TLNS=Target Lesion Number Score, TNM=tumor nodes metastasis, TOC=test of cure, TSS=Total Severity Score, TTS=total thickness score, UVA=ultraviolet A, UVB=ultraviolet B, VAS=visual analog scale, VAS-BP=burning/pain visual analog scale, VAS-PR=pruritics visual analog scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 16. Relative Cost of the Skin and Mucous Membrane Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Acitretin	oral capsule	Soriatane®*	$$$$$	$$$$$
Alitretinoin	gel	Panretin®	$$$$$	N/A
Becaplermin	gel	Regranex®	$$$$$	N/A
Bexarotene	gel	Targretin®	$$$$$	N/A
Calcipotriene	cream, foam, ointment, solution	Dovonex®*, Sorilux®	$$$$$	$$$$$
Calcitriol	ointment	Vectical®*	$$$$$	N/A
Collagenase	ointment	Santyl®	$$$$$	N/A
Diclofenac	gel	Solaraze®	$$$$$	N/A
Fluorouracil	cream, solution	Carac®, Efudex®*	$$$$-$$$$$	$$$$
Formaldehyde	solution	N/A	$$$	N/A
Imiquimod	cream	Aldara®*, Zyclara®	$$$$$	$$$$$
Ingenol mebutate	gel	Picato®	$$$$$	N/A
Nitroglycerin	ointment	Rectiv®	$$$$$	N/A
Pimecrolimus	cream	Elidel®	$$$$$	N/A
Podofilox	gel, solution	Condylox®*	$$$$-$$$$$	$$$
Podophyllum resin	liquid	Podocon-25®	$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Sinecatechins	ointment	Veregen®	$$$$$	N/A
Tacrolimus	ointment	Protopic®	$$$$$	N/A
Tazarotene	cream, gel	Tazorac®	$$$$-$$$$$	N/A
Combination Products				
Calcipotriene and betamethasone	ointment, suspension	Taclonex®	$$$$$	N/A
Capsaicin and skin cleanser	kit	Qutenza®	$$$$$	N/A
Mucositis, stomatitis combination	wafer	Mucotrol®	$$$$$	N/A
Thrombin, fibrinogen, aprotinin, and calcium chloride	kit, syringe	Artiss®, Artiss® Duploject	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The miscellaneous skin and mucous membrane agents are approved for the treatment of actinic keratoses, atopic dermatitis, basal cell carcinoma, cutaneous T-cell lymphoma, Kaposi's sarcoma, mucositis, pain associated with anal fissure, postherpetic neuralgia, psoriasis, warts and wounds.[1-29] The wide variety of products, as well as the range of Food and Drug Administration (FDA)-approved indications, makes direct comparisons difficult. Alitretinoin, calcipotriene, calcitriol, fluorouracil, imiquimod and podofilox are available in a generic formulation.

Diclofenac, fluorouracil, imiquimod and ingenol mebutate are approved for the treatment of actinic keratosis. Topical therapies (e.g., cryotherapy, 5-fluorouracil, diclofenac, imiquimod, photodynamic therapy) are all acceptable treatment options for patients with actinic keratosis, and guidelines do not give preference to one topical agent over another.[30,37] Clinical trials have demonstrated a significant reduction in actinic keratosis lesions with diclofenac, fluorouracil, imiquimod and ingenol compared to placebo.[56-58,62,63,67-74,75,77] In a 12-week comparative study, diclofenac and imiquimod were found to be equally effective.[60] Two studies evaluated the effects of fluorouracil and imiquimod on clinical and histological outcomes. Fluorouracil was found to be more effective than imiquimod in a 24-week study.[66] A second study demonstrated similar initial clearance rates with fluorouracil and imiquimod at the end of the active treatment phase; however, the 12-month sustained clearance rates were significantly higher with imiquimod compared to fluorouracil.[76]

Pimecrolimus and tacrolimus are approved for the treatment of atopic dermatitis. Pimecrolimus is only indicated for the treatment of mild to moderate disease; whereas, tacrolimus is indicated for the treatment of moderate to severe disease. For the treatment of atopic dermatitis, emollients are considered the standard of care.[31-36] They are steroid-sparing and are useful for both prevention and maintenance therapy. Topical corticosteroids provide symptomatic relief and are safe to use in the short term. Topical calcineurin inhibitors are second-line therapy in patients who have failed to respond adequately to other topical treatments, or when those treatments are not advisable.[23,27,31-34] According to the prescribing information, the long-term safety of topical calcineurin inhibitors has not been established.[23,28] Rare cases of malignancy have been reported in patients treated with topical calcineurin inhibitors, although a causal relationship has not been established. Pimecrolimus 1% and tacrolimus 0.03% were found to be equally effective in patients with mild to moderate atopic dermatitis.[90,99,102] Clinical trials have also compared pimecrolimus 1% and tacrolimus 0.1% in patients with moderate to severe disease. Patients receiving tacrolimus had a higher treatment success rate following six weeks of therapy than those receiving pimecrolimus.[97-99] There were no studies found in the medical literature that directly compared pimecrolimus 1% and tacrolimus 0.03% in patients with moderate to severe atopic dermatitis.

Fluorouracil and imiquimod are approved for the treatment of superficial basal cell carcinoma. The goal of therapy is to eradicate the tumor in a manner that will be the most acceptable to the patient.[37,38] Surgery is often the most effective way to eradicate the tumor.[37,38] The National Comprehensive Cancer Network guidelines recommend the use of topical therapies (e.g., cryotherapy, 5-fluorouracil, imiquimod, photodynamic therapy) in patients with low-risk superficial basal cell carcinoma when surgery or radiation is contraindicated or

impractical.[36] There are relatively few studies that compare the different skin cancer treatments. Several trials have demonstrated the efficacy of imiquimod and fluorouracil in the treatment of superficial basal cell carcinoma; however, there were no studies found in the medical literature that directly compared these agents.[108-115]

Bexarotene is approved for the treatment of lesions in patients with cutaneous T-cell lymphoma. Guidelines recommend skin-directed therapies (localized or generalized) as initial treatment in patients with patch/plaque cutaneous T-cell lymphoma.[39,40] According to the National Comprehensive Cancer Network guidelines, treatment options for patients with stage IA disease include topical corticosteroids, nitrogen mustard or carmustine, topical retinoids (bexarotene or tazarotene), topical imiquimod and phototherapy.[40] Patients with stage IB-IIA disease require generalized skin treatment. Topical retinoids are not recommended for generalized skin involvement since they can cause irritation.[40] Patients with stage IIB or higher disease will require systemic therapy.[39,40] Bexarotene was evaluated in two open-label studies in patients with early stage (Stage IA-IIA) cutaneous T-cell lymphoma.[117,118] In the phase I-II dose-finding study, the overall response rate was 63%, with 21% of patients achieving complete response.[117] In the phase III study, the overall response rate was 44%, with 8% of patients achieving complete response. Patients in the phase III trial were refractory to, or intolerant to, at least two prior therapies.[118]

Alitretinoin is approved for the treatment of cutaneous lesions in patients with acquired immunodeficiency syndrome-related Kaposi's sarcoma, and it has been shown to be more effective than placebo in clinical trials.[119,120] Alitretinoin should not be used when systemic anti-Kaposi's sarcoma therapy is required (e.g., more than 10 new Kaposi's sarcoma lesions in the prior month, symptomatic lymphedema, symptomatic pulmonary Kaposi's sarcoma, or symptomatic visceral involvement).[4]

Capsaicin 8% patch is approved for the treatment of neuropathic pain associated with postherpetic neuralgia. According to the European Federation of Neurological Societies guidelines, tricyclic antidepressants, gabapentin and pregabalin are recommended as first-line therapy for the treatment of postherpetic neuralgia. Topical lidocaine may be considered as initial therapy in elderly patients, especially if there are concerns related to central nervous system effects of oral medications. Second-line therapies include strong opioids and capsaicin.[41] Clinical trials demonstrated a greater reduction in pain scores following the application of an 8% capsaicin patch compared to a 0.04% capsaicin patch.[122-126] There were no studies found in the medical literature that directly compared the 8% capsaicin patch to other treatments for postherpetic neuralgia. Capsaicin may produce severe irritation of the eyes, skin, respiratory tract and mucous membranes; therefore, the patch much be administered by a health care provider.[11]

Acitretin, calcipotriene, calcipotriene-betamethasone, calcitriol and tazarotene are approved for the treatment of psoriasis. Acitretin is available as an oral capsule, while the other agents are topical formulations. There are numerous topical and systemic therapies available for the treatment of psoriasis. The selection of therapy should take into consideration the disease severity, location of the lesions, and patient preference. Patients with mild to moderate disease can often be treated with a topical agent, while those with moderate to severe disease may need systemic therapy.[47,48] Topical agents are also used adjunctively for resistant lesions in patients who are being treated with ultraviolet light or systemic medications. Topical preparations that are effective for the treatment of psoriasis include corticosteroids, tar-based products, dithranol preparations, vitamin A analogs and vitamin D analogs. Emollients should also be used to soften scaling and reduce irritation. Guidelines do not give preference to one topical agent over another.[47,48] As demonstrated in clinical trials, calcipotriene is an effective and safe treatment for the management of psoriasis.[131,132,135-139,158] The combination of calcipotriene and betamethasone was more effective than monotherapy with either agent alone.[46,47,143-147,149,152-155] There were no studies found in the medical literature that directly compared the calcipotriene-betamethasone combination product with the coadministration of calcipotriene and betamethasone as separate formulations. Calcitriol has also been shown to be an effective treatment option for patients with psoriasis in several clinical trials.[160-165] It appears to cause less irritation than calcipotriene, especially in sensitive areas of the skin.[46,47,164,165] Tazarotene has been shown to be as effective as calcipotriene, clobetasol and coal tar.[170-175] Acitretin is an effective systemic agent for the treatment of severe psoriasis; however, it is teratogenic and its use is limited in female patients of childbearing potential.[48,45,127-130]

Imiquimod, podofilox, podophyllum resin, and sinecatechins are approved for the treatment of external anogenital warts. According to the Centers for Disease Control and Prevention and British Association for Sexual Health and human immunodeficiency virus guidelines, there is no evidence to suggest that any of the available treatments are

more effective than any other.[49,50] The selection of therapy should be based on the size, number and location of the warts, patient preference, adverse events and provider experience. Imiquimod, podofilox and sinecatechins are patient-administered treatments, whereas podophyllum resin is applied by health care professionals. Clinical trials have demonstrated that all of these agents are effective for the treatment of external anogenital warts.[177-190]

Becaplermin is approved for the treatment of lower extremity diabetic ulcers. The management of ulcers includes debridement, moisture balance, inflammation and infection control, pressure relief and local wound care.[52-54] The efficacy of becaplermin in patients with lower extremity diabetic ulcers was assessed in four clinical trials.[191-193] Two studies demonstrated a higher incidence of complete wound healing with becaplermin compared to placebo, whereas a third study found no difference. The fourth study was not adequately powered to detect a difference between the treatment groups. According to the prescribing information, there was an increased rate of mortality secondary to malignancy observed in patients treated with 3 or more tubes of becaplermin in a retrospective cohort study.[191] Becaplermin should only be used when the benefits outweigh the risks and with caution in patients with known malignancy. Collagenase is approved for debriding chronic dermal ulcers and severely burned areas; however, there are very few published studies comparing its use with other agents or debridement techniques.[194-197]

At this time, there is not a role for the miscellaneous skin and mucous membrane agent**s** in general use. Because these agents have narrow indications with limited usage, they should be available for special needs/circumstances that require medical justification through the prior authorization process. After clinical circumstances are explored, proper medical justification will provide patient access to these agents.

Therefore, all brand miscellaneous skin and mucous membrane agents within the class reviewed are comparable to each other and to the generics in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous skin and mucous membrane agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Nov]. Available from: http://online.factsandcomparisons.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Nov]. Available from: http://www.thomsonhc.com/.
3. Soriatane® [package insert]. Research Triangle Park (NC): Stiefel Laboratories, Inc.; 2011 Mar.
4. Panretin® [package insert]. Woodcliff Lake (NJ): Eisai Inc.; 2009 Jul.
5. Regranex® [package insert]. Forth Wroth (TX): Healthpoint, Ltd.; 2012 Sep.
6. Targretin® [package insert]. Woodcliff Lake (NJ): Eisai Inc.; 2012 Mar.
7. Dovonex® cream [package insert]. Parsippany (NJ): Leo Laboratories Ltd.; 2009 Dec.
8. Sorilux® [package insert]. Research Triangle Park (NC): Stiefel Laboratories, Inc.; 2013 Sep.
9. Taclonex® [package insert]. Parsippany (NJ): LEO Pharma Inc.; 2012 Oct.
10. Vectical® [package insert]. Fort Worth (TX): Galderma Laboratories, L.P.; 2012 Jul.
11. Qutenza® [package insert]. Ardsley (NY): Acorda Therapeutics, Inc; 2013 Jul.
12. Santyl® [package insert]. Fort Worth (TX): Healthpoint Biotherapeutics; 2012 Aug.
13. Solaraze® [package insert]. Melville (NY): PharmaDerm; 2012 Jan.
14. Carac® [package insert]. Bridgewater (NJ): Valeant Pharmaceuticals North America; 2012 Aug.
15. Efudex® [package insert]. Costa Mesa (CA): Valeant Pharmaceuticals; 2006 Aug.
16. Fluoroplex® [package insert]. West Chester (PA): Aqua Pharmaceuticals; 2012 Mar.
17. Formaldehyde [package insert on the internet]. Rochester (NY): Rochester Pharmaceuticals; 2013 Jun [cited 2013 Nov]. Available at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=06ab03b5-07ed-4087-9f04-7a4ea2743169.
18. Aldara® [package insert]. Scottsdale (AZ): Medicis; 2012 Jan.
19. Zyclara® [package insert]. Scottsdale (AZ): Medicis; 2012 Feb.
20. Picato® [package insert].]. Parsippany (NJ): LEO Pharma Inc.; 2012 Jan.
21. Mucosal barrier gel: drug information. In Basdow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Dec 6]. Available from: http://www.utdol.com/utd/index.do.
22. Rectiv® [package insert]. Bridgewater (NJ): Aptalis Pharma US, Inc.; 2013 Jul.
23. Elidel® [package insert]. Bridgewater,(NJ): Valeant Pharmaceuticals North America; 2011 Aug.
24. Condylox® [package insert]. Parsippany (NJ): Watson Pharma, Inc.; 2011Mar.
25. Podocon-25® [package insert]. Minneapolis (MN): Perrigo; 2012 May.
26. Veregen® [package insert]. Melville (NY): PharmaDerm; 2012 Nov.
27. Protopic® [package insert]. Northbrook (IL): Astellas Pharma US, Inc.; 2012 May.
28. Tazorac® [package insert]. Irvine (CA): Allergan, Inc.; 2011 Mar.
29. Artiss® [package insert]. Westlake Village (CA): Baxter Healthcare Corporation; 2011 Aug.
30. de Berker D, McGregor JM, Hughes BR. British Association of Dermatologists Therapy Guidelines and Audit. Guidelines for the management of actinic keratoses. Br J Dermatol 2007 Feb;156(2):222-30.
31. Scottish Intercollegiate Guidelines Network (SIGN). Management of atopic eczema in primary care. Edinburgh: SIGN; 2011. (SIGN publication no. 125). Available at: http://www.sign.ac.uk/pdf/sign125.pdf. Accessed December 2013.
32. Primary Care Dermatology Society & British Association of Dermatologists. Guidelines for the management of atopic eczema. Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PCDS-BAD%20Eczema%20reviewed%202010.pdf. Accessed December 2013.
33. Darsow U, Wollenberg A, Simon D, et al. Position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol. 2009;24:317-28.
34. National Collaborating Centre for Women's and Children's Health. Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Dec. 39 p. Available at: http://www.nice.org.uk/nicemedia/live/11901/38597/38597.pdf. Accessed December 2013.
35. Schneider L, Tiles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: A practice parameter update 2012. J Allergy Clin Immunol. 2013;131:295-9.
36. Hanifin J, Cooper K, Ho V, et al. Guidelines of care for atopic dermatitis. J Am Acad Dermatol. 2004;50(3):391-404.

37. National Comprehensive Cancer Network. Practice Guidelines in Oncology. Basal Cell and Squamous Cell Skin Cancers [guideline on the Internet]. National Comprehensive Cancer Network 2013 Jul 26 [cited 2013 Dec 6]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
38. Telfer NR, Colver GB, Morton CA. British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. Br J Dermatol. 2008 Jul;159(1):35-48.
39. National Comprehensive Cancer Network. Practice Guidelines in Oncology. Non-Hodgkin's Lymphomas [guideline on the Internet]. National Comprehensive Cancer Network 2013 Sep 6 [cited 2013 Dec 6]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site
40. Whittaker S, Marsden J, Spittle M, Jones R. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol. 2003;149(6):1095-107.
41. Attal N, Cruccu G, Haanpää M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol. 2006;13:1153-69.
42. Centre for Clinical Practice. Neuropathic pain. The pharmacological management of neuropathic pain in adults in non-specialist settings. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Mar. 155 p. (Clinical guideline; no. 96) [cited 2013 Nov 23]. Available from: http://www.nice.org.uk/nicemedia/live/12948/47949/47949.pdf.
43. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, et al. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. Mayo Clin Proc. 2010;85(3)(suppl):s3-s14.
44. Dworkin RH, Johnson RW, Breuer J, Gnann JW, et al. Recommendations for the management of herpes zoster. Infectious Diseases Society of America. Clin Infect Dis. 2007;44 Suppl 1:S1-26.
45. Dubinsky R, Kabbani H, El-Chami Z, Boutwell C, Ali H, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2004;63:959-65.
46. Ormerod AD, Campalani E, Goodfield MJ, et al. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. Br J Dermatol. 2010;162:952-63.
47. Menter A, Korman NJ, Elmets CA, et al.; American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60:643-59.
48. British Association of Dermatologists & Primary Care Dermatology Society. Recommendations for the initial management of psoriasis. Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/BAD-PCDS%20Psoriasis%20reviewed%202010.pdf. Accessed December 2013.
49. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep. 2010;59(RR-12):1-110.
50. Clinical Effectiveness Group, British Association for Sexual Health and HIV (BASHH). United Kingdom national guideline on the management of anogenital warts. London (UK): British Association for Sexual Health and HIV (BASHH); 2007. Available at: http://www.bashh.org/documents/86/86.pdf. Accessed December 2013.
51. Sterling JC, Handfield-Jones S, Hudson PM; British Association of Dermatologists. Guidelines for the management of cutaneous warts. Br J Dermatol. 2001;144(1):4-11.
52. Apelqvist J, Bakker K, van Houtum W, et al., International Working Group on the Diabetic Foot. Practical guidelines on the management and prevention of the diabetic foot; 2007. Diabetes Metab Res Rev. 2008;24(Suppl 1):S181–7.
53. Frykberg RG, Zgonis T, Armstrong DG, et al. American College of Foot and Ankle Surgeons. Diabetic foot disorders: a clinical practice guideline. J Foot Ankle Surg. 2006;45:52-66.
54. Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999,Boston, Massachusetts. American Diabetes Association. Diabetes Care. 1999 Aug;22(8):1354-1360.
55. Multinational association of Supportive Care in Cancer/Society of Oral Oncology. Mucositis [guideline on the internet]. Hillerod Denmark: 2013 [cited 2013 Dec 11] Available from http://www.mascc.org/mucositis-guidelines.
56. Wolf J, Taylor R, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. Int J Dermatol. 2001;40:709-13.
57. Ulrich C, Johannsen A, Röwert-Huber J, et al. Results of a randomized, placebo-controlled safety and efficacy study of topical diclofenac 3% gel in organ transplant patients with multiple actinic keratoses. Eur J Dermatol. 2010;20:482-8.

58. Van der Geer S, Krekels GA. Treatment of actinic keratoses on the dorsum of the hands: ALA-PDT vs diclofenac 3% gel followed by ALA-PDT. A placebo-controlled, double-blind, pilot study. J Dermatolog Treat. 2009;20:259-65.
59. Nelson C, Rigel D, Smith S, Swanson N, Wolf J. Phase IV, open-label assessment of the treatment of actinic keratosis with a 3.0% diclofenac sodium topical gel (Solaraze™). J Drugs Dermatol. 2004;3(4):401-7.
60. Nelson CG, Spencer J, Nelson CG. A single-arm, open-label efficacy and tolerability study of diclofenac sodium 3% gel for the treatment of actinic keratosis of the upper and lower lip. J Drugs Dermatol. 2007 Jul;6(7):712-7.
61. Kose O, Koc E, Erbil AH, et al. Comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% imiquimod cream in the treatment of actinic keratosis. J Dermatolog Treat. 2008;19:159-63.
62. Jorizzo J, Stewart D, Bucko A, et al. Randomized trial evaluating a new 0.5% fluorouracil formulation demonstrates efficacy after one-, two-, or four-week treatment in patients with actinic keratosis. Cutis. 2002;70:335-9.
63. Jorizzo J, Weiss J, Furst K, VandePil C, Levy S. Effect of a one-week treatment with 0.5% topical fluorouracil on occurrence of actinic keratosis after cryosurgery: a randomized, vehicle-controlled clinical trial. Arch Dermatol. 2004;140:813-6.
64. Loven K, Stein L, Furst K, Levy S. Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratosis. Clin Ther. 2002;24(6):990-1000.
65. Stough D, Bucko AD, Vamvakias G, et al. Fluorouracil cream 0.5% for actinic keratoses on multiple body sites: an 18-month open-label study. Cutis. 2010;85:267-73.
66. Tanghetti E, Werschler P. Comparison of 5% 5-fluorouracil cream and 5% imiquimod cream in the management of actinic keratoses on the face and scalp. J Drugs Dermatol. 2007;6:144-7.
67. Jorizzo JL, Markowitz O, Lebwohl MG, et al. A randomized, double-blinded, placebo-controlled, multicenter, efficacy and safety study of 3.75% imiquimod cream following cryosurgery for the treatment of actinic keratoses. J Drugs Dermatol. 2010;9:1101-8.
68. Swanson N, Abramovits W, Berman B, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. J Am Acad Dermatol. 2010;62:582-90.
69. Shaffelburg M. Treatment of actinic keratoses with sequential use of photodynamic therapy; and imiquimod 5% cream. J Drugs Dermatol. 2009;8:35-9.
70. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol. 2004;50(5):714-21.
71. Stockfleth E, Meyer T, Benninghoff B, et al. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. Arch Dermatol. 2002;138:1498-502.
72. Stockfleth E, Christophers E, Benninghoff B, Sterry W. Low incidence of new actinic keratoses after topical 5% imiquimod cream treatment: a long-term follow-up study. Arch Dermatol. 2004;140:42.
73. Zeichner JA, Stern DW, Uliasz A, et al. Placebo-controlled, double-blind, randomized pilot study of imiquimod 5% cream applied once per week for 6 months for the treatment of actinic keratoses. J Am Acad Dermatol. 2009;60:59-62.
74. Lee P, Harwell W, Loven K, et al. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. Dermatol Surg. 2005;31(6):659-63.
75. Korman N, May R, Ling M, et al. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. Arch Dermatol. 2005;141:467-73.
76. Krawtchenko N, Roewert-Huber J, Ulrich M, et al. A randomized study of topical 5% imiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. Br J Dermatol. 2007;157(Suppl 2):34-40.
77. Sotiriou E, Apalla Z, Maliamani F, et al. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs 5% imiquimod cream for actinic keratoses on the upper extremities. J Eur Acad Dermatol Venereol. 2009;23:1061-5.
78. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012 Mar 15;366(11):1010-9. doi: 10.1056/NEJMoa1111170.
79. Gollnick H, Kaufmann R, Stough D, et al. Pimecrolimus cream 1% in the long-term management of adult atopic dermatitis: prevention of flare progression. A randomized controlled trial. Br J Dermatol. 2008;158:1083-93.

80. Sigurgeirsson B, Ho V, Ferrándiz C, et al. Effectiveness and safety of a prevention-of-flare-progression strategy with pimecrolimus cream 1% in the management of pediatric atopic dermatitis. J Eur Acad Dermatol Venereol. 2008;22:1290-301.
81. Zuberbier T, Heinzerling L, Bieber T, et al. Steroid-sparing effect of pimecrolimus cream 1% in children with severe atopic dermatitis. Dermatology. 2007;215:325-30.
82. Zuberbier T, Bräutigam M. Long-term management of facial atopic eczema with pimecrolimus cream 1% in pediatric patients with mild to moderate disease. J Eur Acad Dermatol Venereol. 2008;22:718-21.
83. Murrell DF, Calvieri S, Ortonne JP, et al. A randomized controlled trial of pimecrolimus cream 1% in adolescents and adults with head and neck atopic dermatitis and intolerant of, or dependent on, topical corticosteroids. Br J Dermatol. 2007;157:954-9.
84. Kapp A, Papp K, Bingham A, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a non-steroid anti-inflammatory drug. J Allerg Clin Immunol. 2002;110(2):277-84.
85. Staab D, Kaufman S, Brautigam M. Treatment of infants with atopic eczema with pimecrolimus cream 1% improves parents' quality of life: a multicenter, randomized trial. Pediatr Allergy Immunol. 2005;16:527-33.
86. Kaufman R, Bieber T, Helgesen A, et al. Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: a randomized trial. Allergy. 2006;61:375-81.
87. Hoeger PH, Lee KH, Jautova J, Wohlrab J, Guettner A, Mizutanis G, et al. The treatment of facial atopic dermatitis in children who are intolerant of, or dependent on, topical corticosteroids: a randomized, controlled clinical trial. Br J Dermatol. 2009;160:415-22.
88. Papp K, Werfel T, Folster-Holst R, Ortonne J, et al. Long-term control of atopic dermatitis with pimecrolimus cream 1% in infants and young children: a two-year study. J Am Acad Dermatol. 2005;52(2):240-6.
89. Meurer M, Eichenfield LF, Ho V, et al. Addition of pimecrolimus cream 1% to a topical corticosteroid treatment regimen in pediatric patients with severe atopic dermatitis: a randomized, double-blind trial. J Dermatolog Treat. 2010;21:157-66.
90. Kempers S, Boguniewicz M, Carter E, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. J Am Acad Dermatol. 2004;51(4):515-25.
91. Doss N, Kamoun MR, Dubertret L, et al. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate-to-severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs fluticasone 0.005% ointment. Pediatr Allergy Immunol. 2010;21:321-9.
92. Doss N, Reitamo S, Dubertret L, et al. Superiority of tacrolimus 0.1% ointment compared to fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. Br J Dermatol 2009;161:427-34.
93. Reitamo S, Ortonne J, Sand C, et al. A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol. 2005;152:1282-9.
94. Poole CD, Chambers C, Allsopp R, et al. Quality of life and health-related utility analysis of adults with moderate and severe atopic dermatitis treated with tacrolimus ointment vs topical corticosteroids. J Eur Acad Dermatol Venereol. 2010;24:674-8.
95. Mandelin J, Remitz A, Virtanen H, et al. One-year treatment with 0.1% tacrolimus ointment vs a corticosteroid regimen in adults with moderate to severe atopic dermatitis: A randomized, double-blind, comparative trial. Acta Derm Venereol. 2010;90:170-4.
96. Kubota Y, Yoneda K, Nakai K, et al. Effect of sequential applications of topical tacrolimus and topical corticosteroids in the treatment of pediatric atopic dermatitis: an open-label pilot study. J Am Acad Dermatol. 2009;60:212-7.
97. Fleischer A, Abramovits W, Breneman D, et al. Tacrolimus ointment is more effective than pimecrolimus cream in adult patients with moderate to very severe atopic dermatitis. J Dermatolog Treat. 2007;18:151-7.
98. Abramovits W, Fleischer A, Jaracz E, et al. Adult patients with moderate atopic dermatitis: tacrolimus ointment vs pimecrolimus cream. J Drugs Dermatol. 2008;7:1153-8.
99. Paller A, Lebwohl M, Fleischer A, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. J Am Acad Dermatol. 2005;52(5):810-22.
100. Kirsner RS, Heffernan MP, Antaya R, et al. Safety and efficacy of tacrolimus ointment vs pimecrolimus cream in the treatment of patients with atopic dermatitis previously treated with corticosteroids. Acta Derm Venereol. 2010;90:58-64.

101. Yin Z, Xu J, Luo D. Efficacy and tolerance of tacrolimus and pimecrolimus for atopic dermatitis: a meta-analysis. J Biomed Res. 2011 Nov;25(6):385-91.
102. Bieber T, Vick K, Fölster-Holst R, Belloni-Fortina A, Städtler G, Worm M, et al. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. Allergy. 2007;62(2):184-9.
103. Ashcroft D, Dimmock P, Garside R, Stein K, Williams H. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. BMJ. 2005;330(7490):516-24.
104. El-Batawy MM, Bosseila MA, Mashaly HM, et al. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. J Dermatol Sci. 2009;54:76-87.
105. Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. J Dermatolog Treat. 2010;21:144-56.
106. Hui RL, Lide W, Chan J, et al. Association between exposure to topical tacrolimus or pimecrolimus and cancers. Ann Pharmacother. 2009;43:1956-63.
107. Gross K, Kircik L, Kricorian G. 5% 5-Fluorouracil cream for the treatment of small superficial Basal cell carcinoma: efficacy, tolerability, cosmetic outcome, and patient satisfaction. Dermatol Surg. 2007;33:433-9.
108. Romagosa R, Saap L, Givens M, et al. A pilot study to evaluate the treatment of basal cell carcinoma with 5-fluorouracil using phosphatidyl choline as a transepidermal carrier. Dermatol Surg. 2000;26(4):338-40.
109. Schulze H, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. Br J Dermatol. 2005;152:939-47.
110. Geisse J, Caro I, Lindholm J, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol. 2004;50(5):722-33.
111. Marks R, Owens M, Walters S. Efficacy and safety of 5% imiquimod cream in treating patients with multiple superficial basal cell carcinomas. Arch Dermatol. 2004;140:1284-5.
112. Gollnick H, Barona C, Frank R, et al. Recurrence rate of superficial basal cell carcinoma following successful treatment with imiquimod 5% cream: interim two-year results from an ongoing five-year follow-up study in Europe. Eur J Dermatol. 2005;15(5):374-81.
113. Gollnick H, Barona CG, Frank RG, et al. Recurrence rate of superficial basal cell carcinoma following treatment with imiquimod 5% cream: conclusion of a five-year long-term follow-up study in Europe. Eur J Dermatol. 2008;18:677-82.
114. Quirk C, Gebauer K, De'Ambrosis B, et al. Sustained clearance of superficial basal cell carcinomas treated with imiquimod cream 5%: results of a prospective five-year study. Cutis. 2010;85:318-24.
115. Peris K, Campione E, Micantonio T, et al. Imiquimod treatment of superficial and nodular basal cell carcinoma: 12-week open-label trial. Dermatol Surg. 2005:31(3):318-23.
116. Garcia-Martin E, Idoipe M, Gil LM, et al. Efficacy and tolerability of imiquimod 5% cream to treat periocular basal cell carcinomas. J Ocul Pharmacol Ther. 2010;26:373-9.
117. Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. Arch Dermatol. 2002;138:325-32.
118. Heald P, Mehlmauer M, Martin A, et al. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol. 2003;49(5):801-15.
119. Walmsley S, Northfelt D, Melosky B, et al. Treatment of AIDS-related Kaposi ’s sarcoma with topical alitretinoin (9-cis-retinoic acid) gel. J Acquir Immune Defic Syndr. 1999;22(3):235-53.
120. Bodsworth N, Bloch M, Bower M, et al. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi’s sarcoma. Am J Clin Dermatol. 2001;2:77-8.
121. Backonja M, Wallace MS, Blonsky ER, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind study. Lancet Neurol. 2008;7:1106-12.
122. Irving GA, Backonja MM, Dunteman E, et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. Pain Med. 2011;12:99-109.
123. Webster L, Malan P, Tuchman M, et al. A multicenter, randomized, double-blind, controlled dose finding study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. J Pain 2010;11:972-82.
124. Webster LR, Tark M, Rauck R, et al. Effect of duration of postherpetic neuralgia on efficacy analyses in a multicenter, randomized, controlled study of NGX-4010, an 8% capsaicin patch evaluated for the treatment of postherpetic neuralgia. BMC Neurol. 2010;10:92.

125. Backonja MM, Malan TP, Vanhove GF, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open-label extension. Pain Med. 2010;11:600-8.
126. Simpson DM, Gazda S, Brown S, et al. Long-term safety of NGX-4010, a high-concentration capsaicin patch, in patients with peripheral neuropathic pain. J Pain Symptom Manage. 2010;39:1053-64.
127. Tosti A, Ricotti C, Romanelli P, et al. Evaluation of the efficacy of acitretin therapy for nail psoriasis. Arch Dermatol. 2009;145:269-71.
128. Rim JH, Park JY, Choe YB. The efficacy of calcipotriol+acitretin combination therapy for psoriasis: comparison with acitretin monotherapy. Am J Clin Dermatol. 2003;4:507-10.
129. van de Kerkhof PC, Cambazard F, Hutchinson PE et al. The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. Br J Dermatol. 1998;138**:**84-9.
130. Mittal R, Malhotra S, Pandhi P, et al. Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. Arch Dermatol. 2009;145:387-93.
131. Veronikis I, Malabanan A, Holick M. Comparison of calcipotriene (Dovonex) with a coal tar emulsion (Exorex) in treating psoriasis in adults: a pilot study. Arch Dermatol. 1999;135(4):474-5.
132. Alora-Palli MB, Perkins AC, Van Cott A, et al. Efficacy and tolerability of a cosmetically acceptable coal tar solution in the treatment of moderate plaque psoriasis: a controlled comparison with calcipotriene (calcipotriol) cream. Am J Clin Dermatol. 2010;11:275-83.
133. Feldman SR, Matheson R, Bruce S, Grande K, Markowitz O, Kempers S, et al.; U0267-301 & 302 Study Investigators. Efficacy and safety of calcipotriene 0.005% foam for the treatment of plaque-type psoriasis: results of two multicenter, randomized, double-blind, vehicle-controlled, phase III clinical trials. Am J Clin Dermatol. 2012 Aug 1;13(4):261-71.
134. Feldman SR, Mills M, Brundage T, Eastman WJ. A multicenter randomized, double-blind study of the efficacy and safety of calcipotriene foam, 0.005%, vs vehicle foam in the treatment of plaque-type psoriasis of the scalp. J Drugs Dermatol. 2013 Mar;12(3):300-6.
135. Sharma V, Kaur I, Kumar B, et al. Calcipotriol vs coal tar: a prospective randomized study in stable plaque psoriasis. Int J Dermatol. 2003;42:834-8.
136. Thaci D, Daiber W, Boehncke W, et al. Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety, and acceptance in 3,396 patients. Dermatology. 2001;203:153-6.
137. Reygagne P, Mrowietz U, Decroix J, et al. Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. J Dermatologic Treatment. 2005;16:31-6.
138. Tosti A, Piraccini B, Cameli N, et al. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. Br J Dermatol. 1998;139:655-9.
139. Crosti C, Finzi A, Mian E, Scarpa C, et al. Calcipotriol in psoriasis vulgaris: a controlled trial comparing betamethasone dipropionate and salicylic acid. Int J Dermatol. 1997;36:537-41.
140. Parslew R, Traulsen J. Efficacy and local safety of a calcipotriol/betamethasone dipropionate ointment in elderly patients with psoriasis vulgaris. Eur J Dermatol. 2005;15(1):37-9.
141. Tyring S, Mendoza N, Appell M, et al. A calcipotriene/betamethasone dipropionate two-compound scalp formulation in the treatment of scalp psoriasis in Hispanic/Latino and Black/African American patients: results of the randomized, eight-week, double-blind phase of a clinical trial. Int J Dermatol. 2010;49:1328-33.
142. Menter A, Gold LS, Bukhalo M, Grekin S, Kempers S, Boyce BM, et al. Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: a randomized, double-blind, vehicle-controlled trial. J Drugs Dermatol. 2013 Jan;12(1):92-8.
143. Singh S, Reddy D, Pandey S. Topical therapy for psoriasis with the use of augmented betamethasone and calcipotriene on alternate weeks. J Am Acad Dermatol. 2000;43(1):61-5.
144. Douglas W, Poulin Y, Decroix J, et al. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Derm Venereol. 2002;82:131-5.
145. Kaufman R, Bibby A, Bissonnette R, et al. A new calcipotriol/betamethasone dipropionate formulation (Daivobet™) is an effective once-daily treatment for psoriasis vulgaris. Dermatology. 2002;205:389-93.
146. Papp K, Guenther L, Boyden B, et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. J Am Acad Dermatol. 2003;48(1):48-54.
147. Guenther L, Cambazard F, van de Kerkhof P, et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment

of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. Br J Dermatol. 2002;147:316-23.
148. van de Kerkhof P. The impact of a two-compound product containing calcipotriol and betamethasone dipropionate (Daivobet®/Dovobet®) on the quality of life in patients with psoriasis vulgaris: a randomized controlled trial. Br J Dermatol. 2004;151:663-8.
149. Kragballe K, Noerrelund K, Lui H, et al. Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. 2004;150:1167-73.
150. van de Kerkhof P, Wasel N, Kragballe K, Cambazard F, Murray S. A two-compound product containing calcipotriol and betamethasone dipropionate provides rapid, effective treatment of psoriasis vulgaris regardless of baseline disease severity. Dermatology. 2005;210:294-9.
151. Menter A, Abramovits W, Colón LE, et al. Comparing clobetasol propionate 0.05% spray to calcipotriene 0.005% betamethasone dipropionate 0.064% ointment for the treatment of moderate to severe plaque psoriasis. J Drugs Dermatol. 2009;8:52-7.
152. Luger TA, Cambazard F, Larsen FG et al. A study of the safety and efficacy of calcipotriol and betamethasone dipropionate scalp formulation in the long-term management of scalp psoriasis. Dermatology. 2008;217:321-8.
153. Saraceno R, Andreassi L, Ayala F, et al. Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet) vs calcipotriol (Daivonex) in the treatment of psoriasis vulgaris: a randomized, multicentre, clinical trial. J Dermatolog Treat. 2007;18:361-5.
154. van de Kerkhof PC, Hoffmann V, Anstey A, et al. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared to each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. Br J Dermatol. 2009;160:170-6.
155. Jemec GB, Ganslandt C, Ortonne JP, et al. A new scalp formulation of calcipotriene plus betamethasone compared to its active ingredients and the vehicle in the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. J Am Acad Dermatol. 2008 Sep;59(3):455-63.
156. White S, Vender R, Thaçi D, et al. Use of calcipotriene cream (Dovonex cream) following acute treatment of psoriasis vulgaris with the calcipotriene/betamethasone dipropionate two-compound product (Taclonex): a randomized, parallel-group clinical trial. Am J Clin Dermatol. 2006;7:177-84.
157. Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet/Daivobet/Taclonex) in the treatment of psoriasis vulgaris. Br J Dermatol. 2006;154:1155-60.
158. De Jong E, Mork N, Seijger M, et al. The combination of calcipotriol and methotrexate compared to methotrexate and vehicle in psoriasis: results of a multicentre placebo-controlled randomized trial. Br J Dermatol. 2003;148:318-25.
159. Torras H, Aliaga A, Lopez-Estebaranz J, et al. A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. J Dermatol Treat. 2004;15:98-103.
160. Lebwohl M, Menter A, Weiss J, et al. Calcitriol 3 µg/g ointment in the management of mild to moderate plaque type psoriasis: results from 2 placebo-controlled, multicenter, randomized double-blind, clinical studies. J Drugs Dermatol. 2007;6:428-35.
161. Lebwohl M, Ortonne JP, Andres P, et al. Calcitriol ointment 3 µg/g is safe and effective over 52 weeks for the treatment of mild to moderate plaque psoriasis. Cutis. 2009;83:205-12.
162. Langner A, Ashton P, Van De Kerkhof PC, et al. A long-term multicentre assessment of the safety and tolerability of calcitriol ointment in the treatment of chronic plaque psoriasis. Br J Dermatol. 1996;135:385-9.
163. Bourke JF, Iqbal SJ, Hutchinson PE, et al. A randomized double-blind comparison of the effects on systemic calcium homeostasis of topical calcitriol (3 µg/g) and calcipotriol (50 µg/g) in the treatment of chronic plaque psoriasis vulgaris. Acta Derm Venereol. 1997;77:228-30.
164. Zhu X, Wang B, Zhao G, et al. An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3 µg/g ointment vs calcipotriol 50 µg/g ointment in subjects with mild to moderate chronic plaque-type psoriasis. J Eur Acad Dermatol Venereol. 2007;21:466-72.
165. Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 µg g(-1) ointment and calcipotriol 50 µg g(-1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. Br J Dermatol. 2003;148:326-33..
166. Camarasa JM, Ortonne JP, Dubertret L. Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. J Dermatolog Treat. 2003;14:8-13.

167. Liao YH, Chiu HC, Tseng YS, et al. Comparison of cutaneous tolerance and efficacy of calcitriol 3 µg g(-1) ointment and tacrolimus 0.3 mg g(-1) ointment in chronic plaque psoriasis involving facial or genitofemoral areas: a double-blind, randomized controlled trial. Br J Dermatol. 2007;157:1005-12.
168. Lahfa M, Mrowietz U, Koenig M, et al. Calcitriol ointment and clobetasol propionate cream: a new regimen for the treatment of plaque psoriasis. Eur J Dermatol. 2003;13:261-5.
169. Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs clobetasol propionate 0.05% cream: a double-blind study. Acta Derm Venereol. 2007;87(2):167-8.
170. Angelo JS, Kar BR, Thomas J. Comparison of clinical efficacy of topical tazarotene 0.1% cream with topical clobetasol propionate 0.05% cream in chronic plaque psoriasis: a double-blind, randomized, right-left comparison study. Indian J Dermatol Venereol Leprol. 2007;73:65.
171. Kumar U, Kaur I, Dogra S, et al. Topical tazarotene vs coal tar in stable plaque psoriasis. Clin Exp Dermatol. 2010;35:482-6.
172. Tzung T, Wu J, Hsu N, Chen Y, Ger L. Comparison of tazarotene 0.1% gel plus petrolatum once daily vs calcipotriol 0.005% ointment twice daily in the treatment of plaque psoriasis. Acta Derm Venereol. 2005;85:236-9.
173. Schiener R, Behrens-Williams S, Pillekamp H, et al. Calcipotriol vs tazarotene as combination therapy with narrowband ultraviolet B (311 nm): efficacy in patients with severe psoriasis. Br J Dermatol. 2000;143:1275-8.
174. Guenther L, Poulin Y, Pariser D. A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1% cream once daily vs calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. 2000;22(10):1225-38.
175. Bowman P, Maloney J, Koo J. Combination of calcipotriene (Dovonex) ointment and tazarotene (Tazorac) gel vs clobetasol ointment in the treatment of plaque psoriasis: a pilot study. J Am Acad Dermatol. 2002;46(6):907-13.
176. Griswold J, Cross J, Luterman A, et al. Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study. J Burn Care Res. 2008;29:293-303.
177. Arican O, Guneri F, Bilgic K, Karaoglu A. Topical imiquimod 5% cream in external anogenital warts: a randomized, double-blind, placebo-controlled study. J Dermatol. 2004;31(8):627-31.
178. Haidopolous D, Diakomanolis E, Rodolakis A, et al. Safety and efficacy of locally applied imiquimod cream 5% for the treatment of condylomata acuminate of the vulva. Arch Gynecol Obstet. 2004;270:240-3.
179. Stefanaki C, Katzouranis I, Lagogianni E, et al. Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. Int J STD AIDS. 2008;19:441-4.
180. Yan J, Chen S, Wang H, et al. Meta-Analysis of 5% Imiquimod and 0.5% Podophyllotoxin in the treatment of condylomata acuminata. Dermatology. 2006;213:218-23.
181. Moresi J, Herbert C, Cohen B. Treatment of anogenital warts in children with topical 0.05% podofilox gel and 5% imiquimod cream. Pediatric Dermatol. 2001;18(5):448-52.
182. Tyring S, Edwards L, Cherry L, et al. Safety and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. Arch Dermatol. 1998;134(1):33-8.
183. Beutner K, Conant M, Friedman-Kien A, et al. Patient-applied podofilox for treatment of genital warts. Lancet. 1989;1(8642):831-4.
184. Gilson RJ, Ross J, Maw R, et al. A multicentre, randomized, double-blind, placebo controlled study of cryotherapy vs cryotherapy and podophyllotoxin cream as treatment for external anogenital warts. Sex Transm Infect. 2009;85:514-9.
185. Baker D, Douglas J, Buntin D, et al. Topical podofilox for the treatment of condylomata acuminate in women. Obstet Gynecol. 1990;76(4):656-9.
186. Greenberg M, Rutledge L, Reid R, et al. A double-blind, randomized trial of 0.5% podofilox and placebo for the treatment of genital warts in women. Obstet Gynecol. 1991;77(5):735-9.
187. Gross G, Meyer KG, Pres H, et al. A randomized, double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. J Eur Acad Dermatol Venereol. 2007;21:1404-12.
188. Stockfleth E, Beti H, Orasan R, et al. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. Br J Dermatol. 2008;158:1329-38.
189. Tatti S, Swinehart J, Thielert C, et al. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. Obstet Gynecol. 2008;111:1371-9.
190. Tatti S, Stockfleth E, Beutner KR, et al. Polyphenon E: a new treatment for external anogenital warts. Br J Dermatol. 2010;162:176-84.
191. Wieman T, et al. Clinical efficacy of becaplermin (rhPDGF-BB) gel. Am J Surg. 1998;176(2A):74S-79S.

192. Embil J, Papp K, Sibbald G, et al. Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy. Wound Repair Regen. 2000;8(3):162-168.
193. Landsman A, Agnew P, Parish L, et al. Diabetic foot ulcers treated with becaplermin and TheraGauze, a moisture-controlling smart dressing: a randomized, multicenter, prospective analysis. J Am Podiatr Med Assoc 2010;100:155-60.
194. Burgos A, Gimenez J, Moreno E, et al: Collagenase ointment application at 24- vs 48-hour intervals in the treatment of pressure ulcers: a randomized multicentre study. Clin Drug Invest. 2000;19:399-407.
195. Palmieri B, Magri M. A new formulation of collagenase ointment (iruxol((r)) mono) in the treatment of ulcers of the lower extremities: a randomized, placebo-controlled, double-blind study. Clin Drug Investig. 1998;15:381-7.
196. Ostlie DJ, Juang D, Aguayo P, Pettiford-Cunningham JP, Erkmann EA, Rash DE, et al. Topical silver sulfadiazine vs collagenase ointment for the treatment of partial thickness burns in children: a prospective randomized trial. J Pediatr Surg. 2012 Jun;47(6):1204-7.
197. Ramundo J, Gray M. Collagenase for enzymatic debridement: a systematic review. J Wound Ostomy Continence Nurs. 2009;36(6 Suppl):S4-11.
198. Barikbin B, Givrad S, Yousefi M, et al. Pimecrolimus 1% cream vs betamethasone 17-valerate 0.1% cream in the treatment of facial discoid lupus erythematosus: a double-blind, randomized pilot study. Clin Exp Dermatol. 2009;34:776-80.
199. Goldstein AT, Creasey A, Pfau R, et al. A double-blind, randomized controlled trial of clobetasol vs pimecrolimus in patients with vulvar lichen sclerosus. J Am Acad Dermatol. 2011;64:e99-104.
200. Koc E, Arca E, Kose O, et al. An open, randomized, prospective, comparative study of topical pimecrolimus 1% cream and topical ketoconazole 2% cream in the treatment of seborrheic dermatitis. J Dermatolog Treat. 2009;20:4-9.
201. Köse O, Arca E, Kurumlu Z. Mometasone cream vs pimecrolimus cream for the treatment of childhood localized vitiligo. J Dermatolog Treat. 2010;21:133-9.
202. Rigopoulos D, Gregoriou S, Belyayeva E, et al. Efficacy and safety of tacrolimus ointment 0.1% vs betamethasone 17-valerate 0.1% in the treatment of chronic paronychia: an unblinded randomized study. Br J Dermatol. 2009;160:858-60.