Alabama Medicaid Agency

Pharmacy and Therapeutics Committee Meeting

Clinical Packet

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antibacterials
AHFS Class 840404
May 13, 2009

I. Overview

The skin and mucous membrane antibacterials are indicated for the treatment and/or prevention of various skin infections and bacterial vaginosis. Humans are natural hosts for many microorganisms that colonize the skin as normal flora.[1,2] Bacterial infections of the skin are classified as either primary or secondary.[1] 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.

Bacterial vaginosis is estimated to be responsible for 22%-50% of all vaginal infections, followed by candidiasis (17%-39%) and trichomoniasis (4%-35%).[12] Bacterial vaginosis results from replacement of the normal hydrogen peroxide-producing *Lactobacillus* species in the vagina with anaerobic bacteria.[13] 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.[3,5]

Impetigo is a contagious superficial skin infection seen predominantly in children. The most common causative organisms include *S. aureus* and *S. pyogenes*. The goals of therapy include relief of local symptoms, improvement of cosmetic appearance, and prevention of spread and recurrence. Although impetigo usually heals spontaneously within two weeks without scarring, treatment may speed the time to resolution.

Peritonitis is a complication seen in patients treated with peritoneal dialysis, and can result in sepsis and death.[17] 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 and antibiotic protocols have been developed to prevent exit-site infections.[17]

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. Products containing bacitracin and polymyxin B, with or without neomycin, are available over-the-counter. This class was last reviewed in February 2007.

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Bacitracin and polymyxin B‡	ointment, packet	N/A	bacitracin and polymyxin B
Clindamycin	vaginal cream, vaginal suppository	Cleocin®*, Clindesse®	clindamycin
Gentamicin	cream, ointment	N/A	gentamicin
Metronidazole	vaginal gel	MetroGel-Vaginal®*, Vandazole®*	metronidazole, MetroGel-Vaginal®
Mupirocin	ointment	Bactroban®*, Centany®*	mupirocin
Mupirocin calcium	cream	Bactroban®	none
Neomycin, bacitracin, and polymyxin B‡	ointment, packet	N/A	neomycin, bacitracin, and polymyxin B
Neomycin, bacitracin, polymyxin B, and hydrocortisone	ointment	Cortisporin®	none
Neomycin and polymyxin B	irrigation	Neosporin® G.U. Irrigant*	neomycin and polymyxin B

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Neomycin, polymyxin B, and hydrocortisone	cream	Cortisporin®	none
Retapamulin	ointment	Altabax®	none

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
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 antibacterials are summarized in Table 2.

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

Clinical Guideline	Recommendation(s)
The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: **Clinical Management Guidelines for Obstetrician-Gynecologists: Vaginitis[12] (2006)**	• Nonpregnant women with bacterial vaginosis can be treated with vaginal clindamycin, oral clindamycin, vaginal metronidazole, or oral metronidazole products. • The listed alternatives 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.
Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[13] (2006)**	• Recommended regimens for the treatment of bacterial vaginosis in nonpregnant women: o Metronidazole 500 mg orally twice a day for 7 days (OR) o Metronidazole gel, 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days (OR) o Clindamycin cream, 2%, one full applicator (5 g) intravaginally at bedtime for 7 days • Alternative regimens for the treatment of bacterial vaginosis in nonpregnant women: o Clindamycin 300 mg orally twice a day for 7 days (OR) o Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days • The recommended metronidazole regimens are equally efficacious. • Cure rates do not differ between intravaginal clindamycin cream and ovules.
British Association for Sexual Health and HIV, Clinical Effectiveness Group: **National Guideline for the Management of Bacterial Vaginosis[14] (2006)**	• Recommended regimens for bacterial vaginosis: o Metronidazole 400-500 mg twice daily for 5-7 days (OR) o Metronidazole 2 g single dose • Alternative regimens for bacterial vaginosis: o Intravaginal metronidazole gel (0.75%) once daily for 5 days (OR) o Intravaginal clindamycin cream (2%) once daily for 7 days (OR) o Clindamycin 300 mg twice daily for 7 days • All these treatments have been shown to achieve cure rates of 70-80% after 4 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 5 days to 500 mg twice daily for 7 days. The 2 g immediate dose may be slightly less effective at 4 week follow up. • Intravaginal metronidazole gel and clindamycin cream have similar

Clinical Guideline	Recommendation(s)
	efficacy. Theoretically, metronidazole has an advantage because it is less active against lactobacilli than clindamycin. Conversely, clindamycin is more active than metronidazole against most of the bacteria associated with BV. • Oral clindamycin has only been evaluated in one study with short term follow up, and in pregnant women.
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[15] (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 *S. aureus* and *S. 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 5 days each month. This regimen reduces recurrences by ~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 *S. aureus* is a single oral daily dose of 150 mg of this agent for 3 months, which decreases subsequent infections by ~80%.

International Society for Peritoneal Dialysis (ISPD) Guideline: **Peritoneal Dialysis-Related Infections: 2005 Update[17] (2005)**	• Prevention of catheter infections (and thus peritonitis) is the primary goal of exit-site care. Antibiotic protocols against *S. aureus* are effective in reducing the risk of *S. aureus* catheter infections.
	• Antibiotic Protocol Options for Preventing Exit-Site Infections:
	  o Mupirocin:
	  ▪ Daily after cleansing in all patients
	  ▪ Daily after cleansing in carriers only
	  ▪ In response to a positive exit-site culture for *Staphylococcus aureus* denoting carriage
	  o Gentamicin cream:
	  ▪ Daily in all patients after cleansing
	• Mupirocin ointment should be avoided in patients with polyurethane catheters and mupirocin cream should be substituted.

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[3-11,18-30]

Indication	Bacitracin, Polymyxin B	Clinda-mycin	Gent-amicin	Metro-nidazole	Mupirocin	Mupirocin Calcium	Neomycin, Bacitracin, Polymyxin B	Neomycin, Bacitracin, Polymyxin B, Hydro-cortisone	Neomycin, Polymyxin B	Neomycin, Polymyxin B, Hydro-cortisone	Retap-amulin
Treatment of primary and secondary skin infections			✔								
Treatment of secondarily infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*						✔					
Topical treatment of impetigo due to *S. aureus* and *S. pyogenes*					✔						✔
Treatment of bacterial vaginosis		✔		✔							
First aid to help reduce the risk of skin infection in minor cuts, scrapes, and burns	✔						✔				
Treatment of corticosteroid-responsive dermatoses with secondary infection								✔		✔	
Urinary bladder irrigant									✔		

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antibacterials[3-11,18-30]

Generic Name(s)	Onset (hours)	Time to Peak (hours)	Absorption (%)	Active Metabolites	Half-Life (hours)	Protein Binding (%)
Bacitracin	No data	No data	No data	No	1.5	No data
Clindamycin	No data	1-3	0.6-11	Yes Clindamycin sulfoxide, N-dimethyl clindamycin	1.5-5.3	60-95
Gentamicin*	No data	No data	5	No	1.5-4	0-30
Hydrocortisone	168	No data	No data	No	1-2	90
Metronidazole	No data	8-12	2-56	Yes 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitro-imidazole	6-14	<20
Mupirocin	48-72	24	No measureable absorption	No	0.28-0.58	95-97
Mupirocin calcium	48-72	24	0.24-3.3	No	0.28-0.58	95-97
Neomycin	No data	No data	No measurable absorption	No	3	0-88
Polymyxin B	No data	No data	No data	No	4.5-6	No data
Retapamulin	No data	No data	No data	No	No data	94

*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[19]

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

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[3-11,18-30]

Adverse Events	Bacitracin, Polymyxin B	Clinda-mycin	Genta-micin	Metro-nidazole	Mupirocin	Mupirocin Calcium	Neomycin, Bacitracin, Polymyxin B	Neomycin, Bacitracin, Polymyxin B, Hydrocortisone	Neomycin, Polymyxin B	Neomycin, Polymyxin B, Hydrocortisone	Retap-amulin
Central Nervous System											
Ataxia	-	-	✔	-	-	-	-	-	-	-	-
Dizziness	-	-	✔	2	✔	-	-	-	-	-	-
Depression	-	-	-	✔	-	-	-	-	-	-	-
Fatigue	-	-	-	✔	-	-	-	-	-	-	-
Headache	-	1-10	✔	5-9	2-9	-	-	-	-	-	1-2
Insomnia	-	-	-	<1	-	-	-	-	-	-	-
Neurotoxicity	-	-	✔	-	-	-	-	-	-	-	-
Pyrexia	-	-	-	-	-	-	-	-	-	-	1
Dermatological											
Acne	--	-	-	<1	-	-	-	-	-	-	-
Burning	1-10	6-11	-	✔	1-4	-	-	✔	✔	✔	-
Cellulitis	-	-	-	-	✔	-	-	-	-	-	-
Contact dermatitis	✔	-	-	-	✔	✔	✔	✔	✔	✔	✔
Dermatitis	-	✔	-	-	<1	-	-	-	-	-	-
Dryness	-	18-23	-	✔	✔	-	-	-	-	-	-
Eczema	-	-	-	-	-	-	-	-	-	-	1
Edema	-	-	✔	-	✔	✔	-	-	-	-	-
Erythema	1-10	7-16	1-10	✔	<1	✔	-	✔	✔	✔	✔
Failure to heal	-	-	-	-	-	✔	-	-	-	-	-
Folliculitis	-	1-10	-	-	-	-	-	-	-	-	-
Irritation	-	-	✔	✔	-	✔	✔	-	-	-	1
Oiliness	-	>10	-	-	-	-	-	-	-	✔	-
Pain	-	-	-	<1	1-2	-	-	-	✔	✔	✔
Peeling of skin	-	7-11	-	-	-	-	-	-	-	-	-
Pruritus	1-10	7-11	1-10	✔	1-2	✔	✔	-	✔	✔	1-2
Rash	1-10	✔	1-10	✔	1	-	✔	✔	✔	✔	-
Stinging	-	-	-	-	1-2	-	-	-	✔	✔	-
Sweating	-	-	-	<1	-	-	-	-	-	-	-
Swelling	1-10	-	-	-	✔	✔	-	-	✔	✔	-

Adverse Events	Bacitracin, Polymyxin B	Clinda-mycin	Genta-micin	Metro-nidazole	Mupirocin	Mupirocin Calcium	Neomycin, Bacitracin, Polymyxin B	Neomycin, Bacitracin, Polymyxin B, Hydrocortisone	Neomycin, Polymyxin B	Neomycin, Polymyxin B, Hydrocortisone	Retap-amulin
Urticaria	-	-	-	<1	-	-	-	✔	✔	✔	-
Gastrointestinal											
Abdominal pain	-	1-10	-	-	-	-	-	-	-	-	-
Anorexia	-	-	-	<1	-	-	-	-	-	-	-
Bloating	-	-	-	✔	-	-	-	-	-	-	-
Constipation	-	1	-	<1	-	-	-	-	-	-	-
Cramping	-	-	-	✔	-	-	-	-	-	-	-
Decreased appetite	-	-	-	1	-	-	-	-	-	-	-
Diarrhea	-	1-10	-	1	-	-	-	-	-	-	1
Dyspepsia	-	✔	-	<1	-	-	-	-	-	-	-
Gas	-	-	-	✔	-	-	-	-	-	-	-
Gingivitis	-	-	-	<1	-	-	-	-	-	-	-
Nausea	-	1-10	-	4	5	-	-	-	-	-	1
Taste perversion	-	-	-	2	<1	-	-	-	-	-	-
Vomiting	-	1-10	-	4	-	-	-	-	-	-	-
Genitourinary											
Bladder irritation	-	-	-	-	-	-	-	✔	-	-	-
Breast enlargement	-	-	-	<1	-	-	-	-	-	-	-
Dark urine	-	-	-	✔	-	-	-	-	-	-	-
Dysuria	-	-	-	<1	-	-	-	-	-	-	-
Labial edema	-	-	-	<1	-	-	-	-	-	-	-
Leucorrhea	-	-	-	<1	-	-	-	-	-	-	-
Menorrhagia	-	-	-	<1	-	-	-	-	-	-	-
Nephrotoxicity	-	-	✔	-	-	-	-	✔	-	-	-
Pelvic discomfort	-	-	-	3	-	-	-	-	-	-	-
Pyelonephritis	-	-	-	<1	-	-	-	-	-	-	-
Salpingitis	-	-	-	<1	-	-	-	-	-	-	-
Urinary tract infection	-	1	-	<1	-	-	-	-	-	-	-
Vaginal burning	-	-	-	✔	-	-	-	-	-	-	-
Vaginal discharge	-	1	-	12	-	-	-	-	-	-	-
Vaginal irritation	-	-	-	9	-	-	-	-	-	-	-
Vaginosis, fungal	-	14	✔	10	-	-	-	-	-	-	-
Vaginal pain	-	2	✔	-	-	-	-	-	-	-	-
Vulvovaginal pruritus	-	3	✔	-	-	-	-	-	-	-	-

Adverse Events	Bacitracin, Polymyxin B	Clinda-mycin	Genta-micin	Metro-nidazole	Mupirocin	Mupirocin Calcium	Neomycin, Bacitracin, Polymyxin B	Neomycin, Bacitracin, Polymyxin B, Hydrocortisone	Neomycin, Polymyxin B	Neomycin, Polymyxin B, Hydrocortisone	Retap-amulin
Hematologic											
Blood dyscrasias	-	✔	✔	1-2	✔	-	-	-	-	-	-
Musculoskeletal											
Back pain	-	1-2	-	<1	-	-	-	-	-	-	-
Neuromuscular blockade	-	✔	-	-	-	-	-	✔	-	-	-
Gait instability	-	-	✔	-	-	-	-	-	-	-	-
Respiratory											
Apnea	-	-	-	-	-	-	✔	-	-	-	-
Asthma	-	-	-	<1	-	-	-	-	-	-	-
Cough	-	-	-	-	2	-	-	-	-	-	-
Dyspnea	-	-	✔	-	-	-	-	-	-	-	-
Nasopharyngitis	-	1	-	-	1-4	-	-	-	-	-	1
Respiratory tract infection	-	-	-	-	5	-	-	-	-	-	-
Rhinitis	-	-	-	<1	1-6	-	-	-	-	-	-
Miscellaneous											
Allergy	1-10	1-10	✔	<1	-	✔	-	-	✔	✔	-
Alopecia	-	-	✔	-	-	-	-	-	-	-	-
Increased creatinine phosphokinase	-	-	-	-	-	-	-	-	-	-	<1
Flu syndrome	-	-	-	<1	-	-	-	-	-	-	-
Fungal infection	-	-	-	9	-	-	-	-	-	-	-
Ototoxicity	-	-	✔	-	-	-	-	✔	✔	✔	-
Photosensitivity	-	-	✔	-	-	-	-	-	-	-	-
Secondary infection	-	-	-	-	-	-	✔	-	✔	✔	-
Sensitization to neomycin	-	-	-	-	-	-	-	-	✔	✔	-

✔ Percent not specified
\- Event not reported

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[3-11,18-30]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Bacitracin and polymyxin B	Apply to the affected area 1-3 times daily.	Apply to the affected area 1-3 times daily.	Ointment: bacitracin 500 units/g and polymyxin B 10,000 units/g
Clindamycin	Vaginal cream: Cleocin®: Insert one applicatorful intravaginally once daily for 3-7 consecutive days. Clindesse®: Insert one applicatorful intravaginally once Vaginal suppository: Insert once daily for 3 consecutive days.	Safety and efficacy in children have not been established	Vaginal cream: 2% Vaginal suppository: 100 mg
Gentamicin	Cream: Apply to the affected area 3-4 times daily. Ointment: Apply to the affected area 3-4 times daily.	Cream: Apply to the affected area 3-4 times daily. Ointment: Apply to the affected area 3-4 times daily.	Cream: 0.1% Ointment: 0.1%
Metronidazole	Insert one applicatorful 1-2 times daily for 5 days.	Safety and efficacy in children have not been established.	Vaginal gel: 0.75%
Mupirocin	Apply to the affected area 3 times daily	Apply to the affected area 3 times daily.	Ointment: 2%
Mupirocin calcium	Apply to the affected area 3 times daily for 10 days	Apply to the affected area 3 times daily for 10 days	Cream: 2%
Neomycin, bacitracin, and polymyxin B	Apply to the affected area 1-3 times daily	Apply to the affected area 1-3 times daily	Ointment: Bacitracin 400 units/g, neomycin 3.5 mg/g, polymyxin B 5000 units/g
Neomycin, bacitracin, polymyxin B, and hydrocortisone	Apply to the affected area 2-4 times daily	Apply to the affected area 2-4 times daily	Ointment: 1.0%
Neomycin and polymyxin B	1 mL irrigant added to 1 L of saline solution. 1 L of irrigant daily for up to 10 days.	1 mL irrigant added to 1 L of saline solution. 1 L of irrigant daily for up to 10 days.	Irrigation solution: neomycin 40 mg/ml and polymyxin B 200,000 units/ml
Neomycin, polymyxin B, and hydrocortisone	Apply to the affected area 2-4 times daily.	2 years of age and older: Apply to the affected area 1-4 times daily.	Cream: 0.5%
Retapamulin	Apply to affected area (up to 100 cm^2 in total area) twice daily for 5 days.	≥9 months of age: Apply to affected area (up to 2% total body surface area) twice daily for 5 days.	Ointment: 1%

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
Prophylaxis of Skin and Soft Tissue Infections				
Maddox et al.[16] (1985) Bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound TID vs. placebo	RCT, DB Children with minor wounds	N=59 15 weeks	Primary: Prevention of streptococcal pyoderma	Primary: Eighty-one percent of the 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 with 15% of children treated with bacitracin, neomycin sulfate, and polymyxin B (NNT=32; P=0.01).
Dire et al.[56] (1995) Bacitracin zinc, applied to the wound TID vs. bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound TID vs. silver sulfadiazine, applied to the	RCT, DB, PC, PRO Patients with uncomplicated soft tissue wound admitted to the emergency department (ED) within 12 hours of injury	N=426	Primary: Wound infection rates	Primary: Wound infection rates were 17.6% (19/108) for petrolatum, 5.5% (6/109) for bacitracin (number needed to treat [NNT] =8), 4.5% (5/110) for bacitracin, neomycin sulfate, and polymyxin B (NNT=8), and 12.1% (12/99) 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 (0.9%) developed a hypersensitivity reaction to bacitracin, neomycin sulfate, and polymyxin B.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
wound TID vs. petrolatum, applied to the wound TID				
Hood et al.[55] (2004) Mupirocin topical ointment, applied to the wound TID vs. neomycin, bacitracin, and polymyxin B ointment applied to the wound TID	RCT, AC Emergency department (ED) patients with uncomplicated soft tissue wound 24 hours or less before study enrollment	N=99 7 days	Primary: Presence of infection 7 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).
Treatment of Skin and Soft Tissue Infections				
D'Amico et al.[49] (1998) Topical antibacterial regimens (e.g., polymyxin, tobramycin, amphotericin, nystatin, neomycin, gentamycin, vancomycin) vs.	MA All randomized controlled trials evaluating the effect of antibiotic prophylaxis on the prevention of respiratory tract infections and deaths in critically ill adult patients in intensive care unit (ICU)	N=5727 33 trials	Primary: Prevention of respiratory tract infection and mortality	Primary: The prevalence of respiratory infections was 16% among treated patients and 36% among controls in trials that used a combination of topical plus systemic antibiotics and 18% and 28%, respectively, in trials that tested the effectiveness of topical prophylaxis alone. ($P<0.05$ in 21/32 comparisons). There was a strong protective effect of the combination of topical and systemic treatment (OR 0.35; 95% CI, 0.29-0.41). There was a protective effect in trials that tested topical antibiotics (OR 0.56; 95% CI, 0.46-0.68). The results suggest that 5 (4 to 5) and 9 (7 to 13) patients would need to be treated to prevent one infection, depending on whether a combination of topical and systemic drugs or a topical antibiotic only

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topical antibacterial regimens in addition to systemic antibacterial regimens (e.g., cefotaxime, ceftriaxone, ciprofloxacin, ceftazidime) vs. placebo				is tested. The mortality was 24% in treated patients and 30% in controls for trials that tested a combination of topical plus systemic antibiotics (OR 0.80; 95% CI, 0.69-0.93). Twenty three patients (14 to 68) would need to be treated to prevent one death. The mortality was 26% in control and treated patients for trials that tested the effectiveness of topical treatment (OR 1.01; 95% CI 0.84-1.22). There was no difference in mortality between patients receiving prophylaxis with topical antibacterial regimen and placebo (26% in both groups; OR, 1.01; 95% CI, 0.84-1.22).
Leyden et al.[57] (1987) Bacitracin, neomycin sulfate, and polymyxin B "triple-antibiotic" ointment (Neosporin®), applied to the wound BID vs. bacitracin and polymyxin B ointment (Polysporin®), applied to the wound BID vs.	RCT, OL, AC 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, *S. aureus* count after 2 applications of each test agent	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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 vs. wound protectant, applied to the				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
wound BID vs. no treatment				
Berger et al.[58] (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. nonocclusive gauze dressing	RCT, AC, PG Healthy volunteers >18 years of age, with dermabrasion wounds on the upper back, produced under anesthesia	N=70 14 days	Primary: Pigmentary composite score (PCS), textural composite score (TCS) Secondary: Overall ranking of pigmentary changes, overall ranking of textural changes, percentage area of the test site exhibiting scarring	Primary: The triple-antibiotic ointment treatment group had a statistically significant lower PCS (2.6) at 90 days after study onset, compared to the group receiving gauze alone (4.2) (P<0.001). PCS did not significantly differ between the double-antibiotic and the gauze-only group. The mean TCS 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 TCS 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. 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.[47]	RCT, DB	N=706	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1998) Mupirocin calcium topical cream 2% TID vs. cephalexin 250 mg QID	Patients with secondarily infected wounds (small lacerations, abrasions, or sutured wounds)	10 days	Clinical success rates at the end of therapy	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 = .89). The intention-to-treat success rate was 83% 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 = .22). The occurrence of adverse experiences related to study treatment was similar for the 2 groups, with fewer patients in the mupirocin cream group reporting diarrhea (1.1 % vs 2.3% for cephalexin).
Rist et al.[50] (2002) Mupirocin calcium topical cream 2% TID, in addition to oral placebo QID for 10 days vs. cephalexin 250 mg QID, in addition to cream placebo TID for 10 days	RCT, DB, DD, MC, PG Patients ≥8 years old, weighing >40 kg, with secondary eczema infection scored as >8, on the total skin infection rating scale (SIRS)	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).
Parish et al.[43] (2006) Retapamulin ointment 1% twice daily for 5 days vs	DB, DD, MC, NI, RCT Patients ≥9 months of age with underlying inflammatory skin disease (atopic dermatitis, psoriasis, or allergic contact	N=547 17-19 days	Primary: Clinical response at follow-up (total resolution of all signs and symptoms of infection such that no additional antibiotic	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 (–3.8% difference; 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 (–3.4% difference; 95% CI, –

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cephalexin 500 mg PO twice daily for 10 days	dermatitis) experiencing one or more signs or symptoms of secondarily infected dermatitis		necessary) Secondary: Clinical response at end of therapy, microbiologic response (elimination [verified via culture] or presumed elimination of the baseline pathogen, without infection with a new pathogen) at follow-up and end of therapy	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, –1.8% difference; no P value reported). 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, 0.5% difference; no P value reported). 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, –1.1% difference) and at follow-up (87.2% vs 91.8%, respectively, –4.6% difference). 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, 2.1% difference) and at follow-up (83.5% vs 87.8%, respectively, –4.3% difference).
Free et al.[44] (2006) Retapamulin ointment 1% twice daily for 5 days vs cephalexin 500 mg PO twice daily for 10 days	2 DB, DD, MC, NI, RCT Patients ≥9 months of age with a secondarily infected traumatic lesion (abrasion, small laceration, sutured wound) Study consisted of results from 2 identical clinical trials.	N=1,904 17-19 days	Primary: Clinical response (resolution or improvement of infection signs and symptoms) at follow-up in the PP clinical population for both studies Secondary: Microbiologic response (culture-confirmed or presumed eradication of baseline pathogen)	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 91.9% and 92.0% observed with oral cephalexin treatment (–3.2% difference; 95% CI, –7.4 to 0.9) and (–1.6% difference; 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 (–2.4% difference; 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 (–2.3% difference; no P value reported) and (0.6%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			at follow-up in the PP clinical population for both studies	difference; no P value reported) 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 (–1.0% difference; no P value reported).
Bacterial Vaginosis				
Fischbach et al.[37] (1992) Clindamycin phosphate vaginal cream 2%, 5 g intravaginally at bedtime for 7 days, in addition to two placebo capsules BID for 7 days vs. metronidazole 500 mg BID for 7 days and placebo vaginal cream intravaginally at bedtime for 7 days	RCT, DB, AC, MC Premenopausal, non-pregnant women ≥18 years of age diagnosed with bacterial vaginosis	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%. 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%).
Arredondo et al.[38] (1992) Metronidazole 500 mg capsules BID for 7 days in addition to placebo cream vs.	RCT, DB, MC Women with symptomatic bacterial vaginosis	N=184 50 days	Primary: Total healing rate, relapse rate, failure rate, adverse events	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. While clindamycin had a failure rate of 3%, 15% of patients in the metronidazole group failed treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clindamycin vaginal cream 2%, 5 g BID for 7 days in addition to placebo capsules				Both drugs were well tolerated, with the most serious side effect, generalized rash, reported by a patient on metronidazole therapy.
Andres et al.[39] (1992) Metronidazole 500 mg capsules BID for 7 days in addition to placebo cream vs. clindamycin vaginal cream 2%, 5 g BID for 7 days in addition to placebo capsules	RCT, DB, PC, PRO 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 1-week and 4-week follow-up visits, adverse events	Primary: There was no statistically significant difference between the metronidazole (82%) and clindamycin (97%) study groups at the 1-week follow-up visit in terms of patients who have either improved or were cured post-treatment. There was no statistically significant difference between the metronidazole (94.1%) and clindamycin (89.5%) study groups at the 4-week follow-up visit in terms of patients who had either improved or were cured post-treatment. There was no statistically significant difference in terms of clinical failure rate among patients randomized to receive either of the two study drugs. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs.
Schmitt et al.[40] (1993) Metronidazole 500 mg capsules BID for 7 days in addition to placebo cream vs. clindamycin vaginal cream 2% 5 g QD for 7 days	RCT, DB, PC 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 1-week and 4-week follow-up visits, adverse events, *Candida* infections	Primary: There was no statistically significant difference in the overall cure rate between the metronidazole (87%) and clindamycin (72%) study groups at the 1-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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in addition to placebo capsules				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.
Ferris et al.[36] (1993) Clindamycin vaginal cream 2%, 5 g QD for 7 days vs. metronidazole vaginal gel BID for 5 days vs. metronidazole 500 mg BID for 7 days	RCT, DB, AC Premenopausal, non-pregnant women ≥18 years of age diagnosed with bacterial vaginosis	N=101 14 days	Primary: Cure rate, post-treatment vulvovaginal candidiasis	Primary: There was no significant difference in cure rates for oral metronidazole (84.2%), metronidazole vaginal cream (75%), 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).
Austin et al.[35] (1995) Clindamycin vaginal ovules QD for 3 days vs. metronidazole vaginal gel QD for 5 days	RCT, DB, AC Premenopausal, non-pregnant women ≥18 years of age diagnosed with bacterial vaginosis	N=119 90 days	Primary: Overall clinical outcome, microbiologic response	Primary: The clinical response rate did not differ between the two treatment groups. At 7-12 days, cure rates were 79% and 88% for metronidazole and clindamycin, respectively (P=0.3). At 35-45 days, cure rates were 62% and 55%, respectively (P=0.5). The rates were 58% and 55%, respectively, at days 70-90 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). Women treated with metronidazole had a significant decrease in colonization by *Ureaplasma urealyticum* (P<0.001) compared with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 7-12 days after therapy even among patients initially colonized by clindamycin-susceptible strains.
McCormack et al.[33] (2000) Clindamycin phosphate 2% vaginal cream, 5 g applied intravaginally at bedtime and placebo, 5 g applied intravaginally in the morning vs. triple sulfonamide vaginal cream, 5 g applied intravaginally in the morning and at bedtime	RCT, DB, MC Patients were nonpregnant nonlactating women, aged 16 years and older, with symptomatic bacterial vaginosis	N=159 7 days, with follow-up visits at days 5-10 and 25-39	Primary: Clinical cure or improvement	Primary: Clinical cure or improvement was seen in 69.6% (55/79) of patients in the clindamycin treatment group compared to 41.8% (33/79) of patients in the triple sulfonamide group (P<0.0001). Among patients with a history of bacterial vaginosis, the cure rate at 5-10 days after treatment for clindamycin and sulfonamide was 25% and 51%, respectively (P<0.001); and, at 25-39 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 5-10 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 25-39 days post-treatment, the cure rates for clindamycin and sulfonamide were 44.2% and 46.4%, respectively (P=0.11). 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).
Faro et al.[32] (2001) Clindamycin	RCT, MC, SB, PG, AC Patients were non-	N=540 30 days	Primary: Investigator cure, clinical cure, therapeutic cure	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

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phosphate 2%, formulated in 5 g of sustained-release vaginal cream, for a total of 100 mg (Clindesse®), one intravaginal dose vs. clindamycin phosphate 2%, formulated in 5 g conventional vaginal cream (Cleocin®), applied once a day	pregnant women, 18 years of age or older, with bacterial vaginosis (BV) infections			0.702, 0.945, and 0.572, respectively.
Higuera et al.[41] (2002) Metronidazole 500 mg capsules BID for 7 days in addition to placebo cream vs. clindamycin vaginal cream 2% 5 g QD for 7 days in addition to placebo capsules	RCT, DB, PC Nonpregnant women 16 to ≤60 years of age diagnosed with bacterial vaginosis	N=82 50 days	Primary: Cure rate, improvement, clinical failure rate, relapse rate Secondary: microbiological cure rate, vaginal fluid description, patient's efficacy evaluation, adverse effects	Primary: There was no statistically significant difference between the metronidazole (82%) and clindamycin (86%) study groups at the 1-week follow-up visit in terms of patients who have either improved or were cured post-treatment. There was no statistically significant difference in cure rate between the metronidazole (88%) and the clindamycin (90%) groups at the 4-week follow-up visit. There was no statistically significant difference in failure rate between the metronidazole (17.9%) and clindamycin (14.3%) treatment groups at the 1-week and 4-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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 with 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
Paavonen et al.[34] (2005) Clindamycin 100 mg ovules administered intravaginally for 3 consecutive days, in addition to placebo capsules administered BID for 7 days vs. metronidazole 500 mg capsules administered BID for 7 days	RCT, DB, AC, MC 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, adverse effects	Primary: No statistically significant difference between the two treatment groups was observed regarding the primary endpoint (95% CI, –10.6-13.4; P=0.810). 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 between the proportion of patients in the metronidazole treatment group who rated their vaginal infection as cured (79.6%) vs. the proportion of patients randomized to clindamycin therapy who considered themselves cured (78.3%); P value not reported. 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nyirjesy et al.[31] (2006) Clindamycin 2% vaginal cream as a single dose vs. clindamycin 2% vaginal cream once daily for 7 days vs. metronidazole 0.75% vaginal gel twice daily for 5 days	RETRO Three studies similarly designed, which were multicenter, blinded, and controlled trials. Eligible patients were nonpregnant women at least 18 years of age with a clinical diagnosis of bacterial vaginosis.	N=408 21 – 30 days	Primary: Change in *Lactobacillus* scores from baseline to the test-of-cure visit	Primary: Lactobacillus scores were similar between the 3 treatment groups at the test-of-cure visit (P = .71). The percentages of patients with a score of 4 (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 0 (reflecting fully restored Lactobacillus). The 3 groups were comparable with respect 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 3 treatment groups (P = 0.50).
Nyirjesy et al.[59] (2007) Clindamycin 2% vaginal cream as a single dose vs. metronidazole 0.75% vaginal gel twice daily for 5 days	RETRO Three studies similarly designed, which were multicenter, blinded, and controlled trials. Eligible patients were nonpregnant women at least 18 years of age with a clinical diagnosis of bacterial vaginosis and *Mobiluncus* morphotypes present in Gram-stained vaginal fluid samples at baseline.	N=55 21-30 days	Primary: Microbiologic, clinical, and therapeutic cure of bacterial vaginosis.	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±0.05 and 0.33±0.19 in the clindamycin and metronidazole groups, respectively; P<0.0471), indicating a significantly greater decrease in the presence of Mobiluncus in the clindamycin group compared with the metronidazole group. Significantly more patients in the clindamycin group compared to the metronidazole group achieved microbiologic (57.5% vs. 26.7%, respectively; P=0.04) and clinical cure (57.5% vs. 26.7%, respectively 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Impetigo				
Goldfarb et al.[51] (1988) Mupirocin topical ointment 2% TID for 8 days vs. erythromycin ethylsuccinate 40 mg/kg/day QID for 8 days	RCT, AC Children ≥3 months of age with impetigo	N=62 15 days	Primary: Clinical response, bacteriologic response, adverse events	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.
Dagan et al.[52] (1992) Mupirocin topical ointment 2% TID administered in addition to a placebo suspension for 7 days vs. erythromycin ethylsuccinate suspension 50 mg/kg/day, up to maximum daily dose of 750 mg daily, in addition to placebo ointment, administered TID for 7 days	RCT, DB, AC Children ≤16 years of age with impetigo	N=102 8 days	Primary: Cure rate or improved lesion, worsening of lesion, appearance of new lesions	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 ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Koning et al.[53] (2003) Any program of topical or systemic treatment, including antibiotics, disinfectants or any other intervention for impetigo	SR Randomized controlled trials of treatments for non-bullous and bullous, primary and secondary impetigo	N=3533 57 trials	Primary: Cure as defined by clearance of crusts, blisters and redness as assessed by the investigator; relief of symptoms as assessed by participants Secondary: Adverse effects	Primary: <u>Non-bullous Impetigo</u> Topical antibiotics showed better cure rates or more improvement than placebo (odds ratio (OR) 6.49, 95% confidence interval (CI) 3.93 to 10.73). This result was consistent for mupirocin (OR 5.40, 95% CI 2.79 to 10.45). In one small study, bacitracin did not show a difference in cure rate compared with placebo (OR 3.97, 95% CI 0.15 to 104.18). No one topical antibiotic clearly showed greater efficacy over another. Pooling of 10 studies which compared mupirocin with oral erythromycin showed significantly better cure rates or more improvement with mupirocin (OR 1.76, 95% CI 1.05 to 2.97). No significant differences were seen between 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 erythromycin. <u>Bullous Impetigo:</u> Oral erythromycin was significantly more effective than neomycin/bacitracin (OR 0.06, 95% CI 0.01 to 0.68). Secondary: The reported number of side effects was low. Oral antibiotic treatment caused more side effects, especially gastrointestinal ones, than topical treatment.
Oranje et al.[42] (2007) Retapamulin ointment 1% twice daily for 5 days vs	MC, NI, RCT Patients ≥9 months of age with clinical diagnosis of primary bullous or nonbullous impetigo identified by presence of either	N=519 14 days	Primary: Clinical response (absence of treated lesions, or treated lesions had become dry without crusts with or without erythema compared	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%, respectively, 5.1% difference; 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sodium fusidate ointment 2% (not available in the US) three times daily for 7 days	≥1 lesion characterized by red spots, or blisters without crusts that progressed to those that ooze and form yellow or honey-colored crusts surrounded by an erythematous margin		to baseline, or had improved [defined as a decline in the size of the affected area, number of lesions or both] such that no further antimicrobial therapy was required) Secondary: Bacteriological responses (eradication of pathogen verified via culture) at end of therapy and at follow-up	90.1% observed with sodium fusidate treatment (4.7% difference; 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 (2.7% difference; 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 (2.6% difference; 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%, respectively, 6.2% difference; 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%, respectively, 6.5% difference; 95% 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 (4.1% difference; 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 (5.4% difference; 95% CI, –1.8 to 12.5; P=0.134).
Koning et al.[46] (2008)	RCT, DB, MC, PC Patients age ≥9	N=213 14 days	Primary: Clinical response rate at the end of	Primary: A clinical response of ‘success’ was achieved by 86% (119/139) of the intention-to-treat population at the end of therapy for the retapamulin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Retapamulin 1% ointment twice daily for 5 days vs. placebo ointment twice daily for 5 days	months (≥18 months in the Netherlands) with a clinical diagnosis of primary impetigo (bullous or nonbullous)		therapy (7 days)	group compared with 52% (37/71) of the placebo group (P<0.0001). The clinical success rate (intention to treat), 14 days after start of treatment, was 76% and 39% for retapamulin and placebo, respectively (P< 0.0001).
Catheter-Related Infections				
Lok et al.[54] (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 vs. placebo	RCT, DB, MC 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, catheter removal due to infections	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 5 patients would prevent one infection (95% CI, 3-11). 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). It was calculated that treating 7 patients would prevent one case of bacteremia (95% CI, 4-33). There were 13 deaths in the placebo group compared to 3 deaths in the treatment group during the study period (P=0.0041). It was calculated that treating 8 patients would prevent one death (95% CI, 5-27). More patients in the placebo group compared to the active treatment group 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).
Bernardini et al.[48] (2005) Mupirocin calcium 2% topical cream, applied to the	RCT, DB, MC Patients ≥18 years of age on peritoneal dialysis	N=133 12 months	Primary: *P. aeruginosa* and *S. aureus* catheter infection rates Secondary:	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
catheter exit site QD vs. gentamicin sulfate 0.1% topical cream, applied to the catheter exit site QD			Gram-negative and gram-positive peritonitis, overall catheter infection, peritonitis rate, causative organism, catheter removal, 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 in both groups (0.09/year with mupirocin vs. 0.15/year with gentamicin; P=0.45).
Chu et al.[45] (2008) Gentamicin cream vs. mupirocin ointment	PRO All adult peritoneal dialysis patients attending an outpatient clinic in Hong Kong.	N=95 475.6 patient-months (gentamicin) 538.7 patient-months (mupirocin)	Primary: Exit-site infection rates (ESI)	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 7 patients in the mupirocin group. The over-all rate was 0.20 episodes/patient-year. Six patients in the gentamicin group developed 13 peritonitis episodes, whereas 12 peritonitis episodes were reported in 10 patients in the mupirocin group. No statistically significant results were found.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, RR=relative risk, SR=systematic review

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
Bacitracin and polymyxin B‡	ointment, packet	N/A	N/A	$
Clindamycin	vaginal cream, vaginal suppository	Cleocin®*, Clindesse®	$$$	$$
Gentamicin	cream, ointment	N/A	N/A	$
Metronidazole	vaginal gel	MetroGel-Vaginal®*, Vandazole®*	$$	$$
Mupirocin	ointment	Bactroban®*, Centany®*	$$$	$$
Mupirocin calcium	cream	Bactroban®	$$	N/A
Neomycin, bacitracin, and polymyxin B‡	ointment, packet	N/A	N/A	$
Neomycin, bacitracin, polymyxin B, and hydrocortisone	ointment	Cortisporin®	$$$	N/A
Neomycin and polymyxin B	irrigation	Neosporin® G.U. Irrigant*	$$$$	$-$$$
Neomycin, polymyxin B, and hydrocortisone	cream	Cortisporin®	$$$	N/A
Retapamulin	ointment	Altabax®	$$$	N/A

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
N/A=Not available

X. Conclusions

The topical antibacterials are useful for preventing and treating a variety of skin infections.[16,43-44,49-50,55-58] Several studies have demonstrated that prophylactic administration of topical antibiotics decreases infection rates in minor wounds.[16,55-56] Treatment with bacitracin, neomycin, and polymyxin B prevented infections to a similar degree as mupirocin monotherapy and bacitracin monotherapy in patients who presented to the emergency department with an uncomplicated soft tissue wound.[55-56] Topical antibacterials are also effective for the treatment of secondarily infected wounds. Two studies conducted in healthy volunteers with administered wounds demonstrated no difference in wound healing rates between bacitracin, neomycin, and polymyxin B (triple-antibiotic) compared to bacitracin and polymyxin B (double-antibiotic).[57-58] Studies comparing topical mupirocin or retapamulin to oral antibiotics also demonstrated similar clinical response rates in patients with secondarily infected wounds.[43-44,47,50]

Due to the complications associated with bacterial vaginosis, all symptomatic women should be treated. Guidelines recommend initial treatment with either oral/vaginal metronidazole or clindamycin products.[12-14] The recommended metronidazole regimens are equally efficacious.[13] Cure rates do not differ between intravaginal clindamycin cream and ovules.[13] Several clinical trials have also demonstrated similar efficacy between metronidazole and clindamycin treatment regimens.[14,34-41]

The topical antibacterials have been shown to be effective for the treatment of impetigo in several clinical trials and a systematic review.[42,46,51-53] However, there are limited head-to-head clinical trials comparing the various agents. According to the IDSA guidelines on the management of skin and soft-tissue infections, the best topical agent for the treatment of impetigo is mupirocin, although resistance has been described.[15] Other agents, such as bacitracin and neomycin, are less effective treatments for impetigo.[15] The IDSA guidelines also state that topical therapy with mupirocin is equivalent to oral antimicrobials and may be used when lesions are limited in number.[15] Retapamulin is a newer topical antibacterial, which was not available when the IDSA guidelines were published in 2005. Therefore, there are no statements about the place in therapy for this agent. There are no published head-to-head trials comparing retapamulin to mupirocin.

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.[48,62] The ISPD guidelines recommend either mupirocin ointment/cream or gentamicin cream daily after cleansing in all patients.[17] Mupirocin ointment at the exit site, in contrast to mupirocin cream, should be avoided in patients with polyurethane catheters, as structural damage to the catheter has been reported.[17]

Therefore, all brand skin and mucous membrane antibacterials within the class reviewed are comparable to each other and to the generics and OTC 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antivirals
AHFS Class 840406
May 13, 2009

I. Overview

The skin and mucous membrane antivirals are used to treat herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), as well as external anogenital warts. Infection with HSV is associated with chronic, life-long viral infections.[5] 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.[2,5] 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.[1] Recurrent episodes are generally shorter and produce mainly localized vesicles which progress through ulcerated and crusted stages for up to 10 days.[1] Approximately 38% of patients with genital herpes experience six or more recurrences per year.[2]

Labial herpes typically results from infection with HSV-1.[4] Initial primary episodes can be widespread and associated with severe discomfort; however, recurrent episodes tend to be more localized.[2] Before skin lesions appear, there is often a prodrome phase consisting of pain, itching, tingling and burning.[2,4] Papules then present on the lip and infrequently on the palate, chin or the oral mucosa. This is then followed by progression through ulcerated, crusted, and healing stages within five days (for recurrent episodes).[4] Patients with recurrent labial herpes experience 1 to 6 episodes per year, on average.[2]

Treatment options for HSV infections include oral, intravenous, and topical antiviral agents. Oral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection.[5] Topical antivirals reduce the duration of viral shedding and the length of time before all lesions become crusted but this treatment is much less effective than oral or intravenous therapies. No antiviral agent will eradicate HSV; therefore, treatment is aimed at managing, rather than curing, the disease. Acyclovir and penciclovir are the only topical antiviral agents indicated for the treatment of genital and labial herpes.

Anogenital warts (condylomata acuminata) is caused by human papilloma virus (HPV) infection.[33] Patients with condylomata acuminata may present with papules on the vulva, cervix, vagina, penis, perineum, or anal region.[34] Anogenital warts are generally asymptomatic; however, localized burning, itching, and tenderness may occur.[34] Treatment involves either chemical destruction, immune modulation, or surgical excision.[33] There is no evidence that one treatment modality is more efficacious than another.[33] The primary goal of treating visible genital warts is the removal of the warts. If left untreated, visible genital warts might spontaneously resolve, remain unchanged or increase in size or number.[33] Recurrence rates of 30% to 70% have been reported within six months of treatment.[33]

Sinecatechins is the only topical antiviral agent indicated for the treatment of anogenital warts. 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.[30] The mechanism of action of sinecatechins for the treatment of genital and perianal warts is unknown.[30] Sinecatechins is approved for external use only and should not be used to treat warts caused by the human papilloma virus in the vagina, cervix or inside the anus.

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. No generic products are available in this class. This class was last reviewed in February 2007.

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Acyclovir	cream, ointment	Zovirax®	Zovirax®
Penciclovir	cream	Denavir®	none
Sinecatechins	ointment	Veregen®	none

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)
British Association for Sexual Health and HIV (BASHH) Clinical Effectiveness Group: **2007 National Guideline for the Management of Genital Herpes[29] (2007)**	Genital Herpes: • Oral antiviral drugs are indicated within 5 days of the start of the episode and while new lesions are still forming. • 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. Genital Herpes with HIV Infection: • 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 5–10 mg/kg body weight IV every 8 hours may necessary.
Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[3,5] (2006)**	Genital Herpes: • 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. • However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir. • Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is discouraged. Genital Herpes with HIV Infection: • Whereas antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV among HIV-positive persons. • Oral acyclovir, valacyclovir, and famciclovir are safe for use in immunocompromised patients in the doses recommended for treatment of genital herpes. • For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg body weight IV every 8 hours might be necessary. HPV Infection and Anogenital 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. • The majority of patients require a course of therapy rather than a single

Clinical Guideline	Recommendation(s)

	treatment.
	• The treatment modality should be changed if a patient has not improved substantially.
	• The majority of genital warts respond within 3 months of therapy.
	• Recommended regimens for external genital warts (patient-applied):
	  o Podofilox 0.5% solution or gel applied to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, for up to four cycles.
	  o Imiquimod 5% cream applied once daily at bedtime, three times a week for up to 16 weeks.

American College of Obstetricians and Gynecologists: **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Gynecologic Herpes Simplex Virus Infections**[7] **(2004)**	• 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 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.
The World Health Organization (WHO): **Guidelines for the Management of Sexually Transmitted Infections**[6] **(2003)**	<u>Genital Herpes:</u> • There is no known cure for genital herpes, but the course of symptoms can be modified if systemic therapy with acyclovir, or its analogues, 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. <u>Genital Herpes with HIV Infection:</u> • 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[8-11,30-31]

Generic Name(s)	Acyclovir	Penciclovir	Sinecatechins
Management of initial genital herpes	✔ [a]		
Treatment of recurrent herpes labialis	✔ [b]	✔	
Management of non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients	✔ [a]		
Treatment of external genital and perianal warts in immunocompetent patients			✔

[a] Ointment formulation only.
[b] Cream formulation only.

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[8-11,30-31]

Drug (s)	Systemic Absorption	Distribution	Renal Excretion (%)
Acyclovir cream	Minimal	No data	0.04
Acyclovir ointment	Minimal	No data	<0.02 - 9.4
Penciclovir cream	Minimal	No data	Not detected
Sinecatechins	Minimal	No data	No data

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane antivirals, no significant drug interactions have been reported.[11]

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[8-11,30-31]

Adverse Events	Acyclovir	Penciclovir	Sinecatechins
Cardiovascular			
Regional lymphadenopathy	-	-	3
Central Nervous System			
Headache	-	✔	-
Paresthesia	-	✔	-
Dermatological			
Aggravated condition	-	✔	-
Bleeding	-	-	1
Burning skin	<1	-	36
Cracked lips	<1	-	-

Adverse Events	Acyclovir	Penciclovir	Sinecatechins
Desquamation	<1	-	4
Discharge	-	-	2
Dryness of the lips	<1	-	-
Eczema	-	-	<1
Edema	✔	✔	34
Erythema	-	✔	38
Flakiness of the skin	<1	-	-
Induration	-	-	24
Inflammation	<1	-	-
Local anesthesia	-	<1	-
Pain at application site	✔	✔	42
Pruritus	<1	✔	24
Rash	✔	<1	1
Scar formation	-	-	1
Skin discoloration	-	✔	<1
Skin necrosis	-	-	<1
Stinging of the skin	<1	-	-
Ulceration/Erosion	-	-	39
Urticaria	-	✔	-
Vesicular rash	-	-	14
Genitourinary			
Cervical dysplasia	-	-	<1
Pelvic pain	-	-	<1
Phimosis	-	-	2
Urethritis	-	-	<1
Other			
Decreased therapeutic response	-	✔	-
Hypersensitivity reaction	-	-	2
Oral/pharyngeal edema	-	✔	-
Pain	-	✔	-
Parosmia	-	✔	-
Perianal infection	-	-	<1
Systemic infection	-	-	<1
Taste perversion	-	<1	-

✔ Percent not specified
\- Event not reported

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[8-11,30-31]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acyclovir	Cream: Recurrent herpes simplex labialis: Apply topically 5 times per day for 4 days Ointment: Genital herpes simplex initial therapy: Apply topically every 3 hours (6 times per day) for 7 days in sufficient	Safety and efficacy have not been established in children less than 12 years of age	Cream: 5% Ointment: 5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	quantities to adequately cover lesion Herpes simplex, non-life-threatening mucocutaneous immunocompromised-patient: Apply topically every 3 hours (6 times per day) for 7 days in sufficient quantities to adequately cover lesions		
Penciclovir	Recurrent herpes simplex labialis: Apply topically every 2 hours while awake for 4 days	Safety and efficacy have not been established in children less than 12 years of age	Cream: 1%
Sinecatechins	External genital/perianal warts in immunocompetent patients: Apply three times per day to all external genital and perianal warts	Safety and effectiveness in pediatric patients have not been established.	Ointment: 15%

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.[12] (1984) Acyclovir 5% ointment, applied after an occurrence of a prodrome; 6 times a day at 3 hour intervals vs. placebo, applied after an occurrence of a prodrome; 6 times a day at 3 hour intervals	RCT, MC, PC Male and female 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 days vs. 2 days; P=0.04). In male patients, there was no difference between the acyclovir and placebo groups (1.8 days; No P value reported). 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 days and 3.8 days, respectively. The mean duration of pain and itching in females treated with acyclovir compared to placebo was 5.4 days and 4.4 days, respectively (no P values were reported for males or females).
Reichman et al.[13] (1983) Acyclovir 5% ointment applied 6 times a day at 3 hour intervals vs. placebo applied 6 times a day at 3 hour intervals	RCT, DB, PC Male and female patients with culture-proven recurrent herpes simplex genitalis; patients entered study within 48 hours of the onset of lesions	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	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 days 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Corey et al.[14] (1982) Acyclovir 5% ointment applied 4 or 6 times a day vs. placebo applied 4 or 6 times a day	RCT, DB, PC Patients with initial or recurrent episodes of genital herpes	N=180 21 days	Primary: Mean duration of viral shedding from genital lesions, mean duration of local pain or itching, mean time to healing of lesions	Primary: Among acyclovir recipients with first episodes of genital herpes, the mean duration of viral shedding from genital lesions (2.0 days vs. 4.6 days), mean duration of local pain or itching (3.6 days vs. 6.7 days), and the mean time to healing of lesions (11.2 days 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 days and 7.5 days, respectively, in acyclovir recipients compared with 5.0 days (P=0.03) and 9.7 days (P=0.07), respectively, in placebo recipients.
Kinghorn et al.[15] (1983) Acyclovir 5% ointment applied topically 5 times a day vs. placebo cream applied topically 5 times a day	DB, PC, RCT Patients with a clinically diagnosed 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	Primary: For first episodes treated with acyclovir, the duration of pain (4 days vs. 8 days, P<0.05), time to healing (8 days vs. 14 days, P<0.001), duration of viral shedding (4 days vs. 11 days, P=0.001), and duration of new lesion formation (0 days 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 days vs. 6 days, P<0.001), for time to healing (4 days vs. 6 days, P<0.01), and for the formation of new lesions (5% vs. 29%, P<0.01) compared to placebo.
Kinghorn et al.[16] (1986) Acyclovir 5% cream applied topically 5 times a day for 7 days in combination with acyclovir 200 mg tablets taken 4 times a day vs.	RCT, DB, PC Men and women aged 16 years or older 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	Primary: Duration of viral shedding in the acyclovir cream group compared to placebo was not statistically significant (external lesions: 2.6 days vs. 2.0 days; urethra or cervix: 2.1 days 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 days vs. 2.8 days; cervix: 1.7 days vs. 1.8 days). The duration of symptoms of pain, dysuria, and discharge showed no statistical significance between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo applied topically 5 times a day for 7 days in combination with acyclovir 200 mg tablets taken 4 times a day				There was a decrease in the duration of itching with acyclovir cream compared to placebo (1.2 days vs. 2.2 days; P=0.08). The mean duration of time to healing of lesions was not significantly different.
Chen et al.[17] (2000) Penciclovir 1% cream applied topically 5 times a day vs. acyclovir 3% cream applied topically 5 times a day	RCT, DB, MC, PG Patients aged 18-65 years with clinical diagnosis of genital herpes, treatment 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	Primary: A decrease in crusting time was noted in patients with primary first episodes of genital herpes with penciclovir compared to acyclovir (2.0 days 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 7 indicated that there was no difference between penciclovir and acyclovir treatment (86/104 vs. 80/101; P=0.53).
Herpes Labialis				
Spruance et al.[22] (1984) Acyclovir 5% ointment, applied topically 4 times per day for 5 days vs. placebo, applied topically 4 times a day for 5 days	DB, PC Patients who had an episode of herpes simplex labialis	N=208 5 days	Primary: Decrease in median virus titers in lesions between the first and second clinic visit	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 0-8 hours after the onset of lesions. No differences were found in patients who began treatment 9-25 hours after lesion onset. The acyclovir group had a mean number of episodes per month of 0.38 compared with 0.45 in the placebo group (P=0.22).
Shaw et al.[21] (1985) Acyclovir 5% cream,	RCT, DB, PC Patients aged 18 years and older with at least 3	N=45 5 days	Primary: Healing time of original lesions, and original lesion	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
applied topically 5 times a day vs. placebo, applied topically 5 times a day	recurrences of herpes labialis a year		and fresh lesion combined; time to first crust on the original lesion and loss of crust from original lesion; duration of all symptoms	The median healing times for acyclovir and placebo were 9 and 10 days, respectively (P=0.82). The median duration of all symptoms was 5 days for the acyclovir group versus 6 days for the placebo group (P=0.33).
Gibson et al.[19] (1986) Acyclovir 5% cream, applied 4 times a day vs. placebo applied 4 times a day	RCT, DB, PC Patients aged 16 years and older with 6 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	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).
Raborn et al.[20] (1997) Acyclovir 5% cream applied topically 4 times a day at 4 hour intervals vs. placebo applied topically 4 times a day at 4 hour intervals	RCT, DB, MC, PC Patients 18 years or older who had experienced more than three episodes of sun-induced herpes labialis within the past year, first application was to be applied twelve hours before intensive sun exposure	N=191 8 days	Primary: Number of lesions formed during treatment, number of lesions formed during follow-up	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 versus placebo (P<0.01).
Spruance et al.[18] (2002) Acyclovir 5% cream	RCT, DB, PC, MC Two identical studies conducted in 45 centers	N=1,385 4 days	Primary: Clinician-assessed duration of herpes labialis episode	Primary: The mean clinician-assessed duration of herpes labialis episode was significantly shorter for the patients treated with acyclovir cream versus patients treated with placebo cream in each of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
initiated within 1 hour of first sign of symptoms and applied 5 times daily vs. placebo cream initiated within 1 hour of first sign of symptoms and applied 5 times a daily	in the United States Healthy adult patients 18 years of age and older with a clinical history of recurrent herpes labialis (at least 3 episodes in the past year)		Secondary: Patient-assessed duration of pain, proportion of patients developing classical lesions (ulcers, vesicles, and crust)	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).
Spruance et al.[25] (1997) Penciclovir 1% cream applied every two hours while awake vs. placebo applied every two hours while awake	RCT, DB, PC, PG, PRO, MC Healthy patients with a history of frequent episodes of herpes labialis, treatment was self initiated by the patient within 1 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 6-8 Secondary: Time to loss of lesion pain	Primary: Healing of classical lesions based on the investigator-assessed data was found to be 1 day faster in the patients who received penciclovir compared to the patients who received placebo (5 days 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 days vs. 5.5 days; P<0.001). Investigator-assessed proportion of patients who lost classical lesions by days 6, 7, and 8 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the patient-assessed data, the proportion of patients who lost classical lesions by days 6, 7, and 8 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 days vs. 4.1 days; P<0.001) resolved more quickly for penciclovir treated patients compared with patients who applied the placebo control.
Boon et al.[24] (2000) Penciclovir 1% cream initiated within 1 hour of first sign of symptoms and applied every two hours while awake vs. placebo initiated within 1 hour of first sign of symptoms and applied every two hours while awake	RCT, DB, PC, PG Patients between the ages of 18 and 81 years with a history of sun-induced herpes labialis, at least 3 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 2 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 7 days for penciclovir patients versus 8 days for patients using placebo. Fewer penciclovir treated patients rated their pain, itching, burning, and tenderness as moderate or severe due to lesions compared with the placebo group (P<0.027).
Raborn et al.[23] (2002) Penciclovir 1% cream initiated within 1 hour of first sign of symptoms and applied 6 times on day 1 then every two hours while awake	RCT, DB, PC, MC, PG, PRO Male and female patients 18 years of age and older, with a history of recurrent herpes simplex labialis, who had 3 or more episodes per year that typically manifested as classical	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 6 was significantly greater in the penciclovir group (70%) than in the placebo group (59%; P=0.001). The percentage of cases healed by day 8 was significantly greater in the penciclovir group (85%) than in the placebo group (78%) as determined by the investigator (P=0.012). A similar

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. placebo initiated within 1 hour of first sign of symptoms and applied 6 times on day 1 then every two hours while awake	lesions			finding was reported by the patient at day 8 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 days 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.[26] (2001) Penciclovir 1% cream applied every two hours while awake at onset of prodrome phase or at appearance of vesicles vs. acyclovir 5% cream applied every two hours while awake at onset of prodrome phase or at appearance of vesicles	RCT Individuals ranging from 12 to 47 years who had a history of frequent episodes of recurrent herpes labialis (at least 5 each year)	N=40 4 days	Primary: Clinicians' judgment of the appearance of vesiculation to crusting and patients' experience of pain	Primary: In the prodromal acyclovir group, labial lesions reached a crusting stage by 6 days, with pain ceasing at day 5. In the prodromal penciclovir group, both phases were reached earlier; the crusting phase was reached and pain ceased by day 4, a difference that was significant (P=0.002041). In the disease therapy (appearance of vesicles) group, the acyclovir patients' clinical evolution and symptomology 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).
Lin et al.[27] (2002) Penciclovir 1% cream applied up to 5 times a day	RCT, DB, MC, PG Patients 18-65 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. acyclovir 3% cream applied up to 5 times a day			blisters, crusting and loss of crust	significant reduction in scores relative to baseline (P<0.01). On days 5 and 7 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 7 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.
Herpes Simplex Virus in Immunocompromised Patients				
Whitley et al.[28] (1984) Acyclovir 5% ointment applied topically 6 times a day vs. placebo applied topically 6 times a day	DB, PC, RCT Immunocompromised patients with diagnosed herpes simplex virus regardless of type	N=63 28 days	Primary: Viral clearance, resolution of pain, total lesion healing	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.
Anogenital Warts (Condylomata Acuminata)				
Tatti et al.[32] (2008) Sinecatechins 15% ointment three times daily vs. sinecatechins 10% ointment three times daily vs.	RCT, DB, MC, PC, PG Male and female outpatients, aged 18 years or older, clinically diagnosed with 2 to 30 external genital and perianal warts with a total wart area of 12 mm^2 to 600 mm^2	N=502 16 weeks of treatment 12-week treatment-free follow-up	Primary: Clearance of warts	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 vehicle group (P<0.001). The numbers needed to treat were 4.3 and 4.4. Both genders in both the sinecatechins ointment 15% (women 64.6%; P<.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 with vehicle (women 45.8%; men 23.2%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				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 with 53 (51.5%) of the vehicle patients (P<0.001). 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 with 8.8% of vehicle-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.

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ration, OS=observational study, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SB=single-blind, TB=triple-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 8. Relative Cost of the Skin and Mucous Membrane Antivirals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Acyclovir	cream, ointment	Zovirax®	$$$$	N/A
Penciclovir	cream	Denavir®	$$	N/A
Sinecatechins	ointment	Veregen®	$$$$$	N/A

N/A=Not available

X. Conclusions

The skin and mucous membrane antivirals are approved for the treatment of herpes simplex virus (HSV) infections and external anogenital warts. Only acyclovir ointment is FDA-approved for the treatment of genital herpes; however, both topical acyclovir and penciclovir have been shown to be more effective than placebo for this indication.[12-16,18-25] Only one study directly compared acyclovir and penciclovir, which demonstrated similar efficacy among the agents.[17] Guidelines on the management of genital herpes state that topical antiviral agents are less effective than oral agents, offer minimal clinical benefits and do not recommend their use for this indication.[5-7,29]

Acyclovir and penciclovir creams are FDA-approved for the treatment of recurrent herpes labialis. Both acyclovir and penciclovir have been shown to decrease lesion healing time and duration of pain compared to placebo.[18-20,23-25] Although the results were statistically significant, the clinical significance is unknown. Healing times and duration of pain were only reduced by one day, or less, compared to placebo.[18,21,23-25] Two studies directly compared acyclovir and penciclovir for the 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.[26] In a second study, acyclovir and penciclovir demonstrated similar efficacy in clinical cure rates and time to healing.[27] There are no published guidelines on the management of labial herpes.

Sinecatechins is FDA-approved for the treatment of external genital and perianal warts. Only one published clinical trial with sinecatechins was found in the medical literature. This study demonstrated that 57% of patients treated with sinecatechins had complete clearance of their warts compared to 33% of placebo-treated patients ($p<0.001$).[32] There are no published head-to-head clinical trials comparing this antiviral agent to other treatment options for anogenital warts. Guidelines state that there is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.[3]

Therefore, all brand skin and mucous membrane antivirals within the class reviewed are comparable to each other and to the generics and OTC 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antifungals
AHFS Class 840408
May 13, 2009

I. Overview

The skin and mucous membrane antifungals are used to treat a variety of fungal infections, including cutaneous candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, seborrheic dermatitis, onychomycosis and dermatophyte infections. Local cutaneous and mucous membrane infections with *Candida* species are generally benign and are the result of changes in the normal flora.[3] 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.[4] 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*.[4] Onychomycosis is an infection of the nails and can be caused by any fungus, including dermatophytes, yeasts, and non-dermatophyte molds. Dermatophyte infections are known by the names "tinea" and "ringworm" and are named by location (e.g., tinea corporis, tinea pedis, tinea unguium, tinea capitis, tinea cruris, and tinea barbae).[5] *Epidermophyton*, *Trichophyton*, and *Microsporum* are the three dermatophytes which lead to the majority of infections.[5]

The antifungal agents are classified based upon their chemical structures: allylamines (naftifine, terbinafine); imidazoles (butoconazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole, terconazole, tioconazole); benzylamines (butenafine); hydroxypyridones (ciclopirox); polyenes (nystatin), and thiocarbamates (tolnaftate).[1] Most of these agents share similar mechanisms 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.[1] Mycological and clinical cure is often achieved with topical therapy alone.

There are several combination antifungal products available, which include benzoic acid/salicylic acid, clotrimazole/betamethasone, nystatin/triamcinolone, ketoconazole/pyrithione zinc, miconazole/zinc oxide, and sodium thiosulfate/salicylic acid. The mechanism of action varies with each product. Benzoic acid and sodium thiosulfate have antifungal properties.[2] Salicylic acid acts as a keratolytic agent to help soften/shed the outer layer of the skin.[2,11] Products containing betamethasone and triamcinolone help to control host inflammation, which increases infection cure rates.[40-41,44-45] Zinc oxide acts as a skin protectant and mild astringent with weak antiseptic properties.[43]

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. Clotrimazole, miconazole, terbinafine, tioconazole and tolnaftate are also available over-the-counter. This class was last reviewed in February 2007.

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Benzoic acid and salicylic acid	ointment	Bensal HP®	none
Butenafine	cream	Mentax®	none
Butoconazole	vaginal cream	Gynazole-1®	none
Ciclopirox	cream, gel, shampoo, solution, suspension, kit	Loprox®*, Penlac®*	ciclopirox
Clotrimazole‡	cream, solution, troche, vaginal cream, vaginal tablet	Clotrim Antifungal®*, Cruex®*, Desenex®*, Femcare®*, Gyne-Lotrimin®*, Lotrimin AF®*, Mycelex®*	clotrimazole
Clotrimazole and	cream, lotion	Lotrisone®*	clotrimazole and

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
betamethasone			betamethasone dipropionate
Econazole	cream	N/A	econazole
Ketoconazole	cream, gel, shampoo	Kuric®*, Xolegel®	ketoconazole
Ketoconazole and pyrithione zinc	kit	Xolegel Duo®	none
Miconazole‡	cream, vaginal cream, vaginal suppository	Baza Antifungal®*, Micatin®*, Micro-Guard®*, Monistat 7®*	miconazole
Miconazole and zinc oxide	ointment	Vusion®	none
Naftifine	cream, gel	Naftin®	none
Nystatin	cream, ointment, powder, vaginal tablet	Mycostatin®*	nystatin
Nystatin and triamcinolone	cream, ointment	N/A	nystatin and triamcinolone
Oxiconazole	cream, lotion	Oxistat®	none
Sertaconazole	cream	Ertaczo®	none
Sodium thiosulfate and salicylic acid	lotion	N/A	sodium thiosulfate and salicylic acid
Sulconazole	cream, solution	Exelderm®	none
Terbinafine‡	cream, spray	Lamisil®, Lamisil AT®*	terbinafine
Terconazole	vaginal cream, vaginal suppository	Terazol 3®*, Terazol 7®*, Zazole®*	terconazole
Tioconazole‡	vaginal ointment	Vagistat-1®*	tioconazole
Tolnaftate‡	aerosol powder, cream	Tinactin®*	tolnaftate

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
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 antifungals are summarized in Table 2.

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

Clinical Guideline	Recommendation(s)

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[8] (2006)**	<u>Uncomplicated Vulvovaginal Candidiasis</u>
	• Short-course topical formulations (i.e., single dose and regimens of 1-3 days) effectively treat uncomplicated vulvovaginal candidiasis (VVC).
	• The topically applied azole drugs are more effective than nystatin.
	• Treatment with azoles results in relief of symptoms and negative cultures in 80%-90% of patients who complete therapy.
	• Recommended regimens include:
	  o Butoconazole 2% cream 5 g intravaginally for 3 days
	  o Butoconazole 2% cream 5 g single intravaginal application
	  o Clotrimazole 1% cream 5 g intravaginally for 7-14 days
	  o Clotrimazole 100 mg vaginal tablet for 7 days
	  o Clotrimazole 100 mg vaginal tablet, two tablets for 3 days
	  o Miconazole 2% cream 5 g intravaginally for 7 days
	  o Miconazole 100 mg vaginal suppository for 7 days
	  o Miconazole 200 mg vaginal suppository for 3 days

Clinical Guideline	Recommendation(s)
	○ Miconazole 1,200 mg vaginal suppository, for 1 day ○ Nystatin 100,000-unit vaginal tablet, one tablet for 14 days ○ Tioconazole 6.5% ointment 5 g intravaginally once ○ Terconazole 0.4% cream 5 g intravaginally for 7 days ○ Terconazole 0.8% cream 5 g intravaginally for 3 days ○ Terconazole 80 mg vaginal suppository for 3 days ○ Fluconazole 150 mg oral tablet, one tablet in single dose <u>Complicated Vulvovaginal Candidiasis (>4 episodes/year)</u> • Treatment: Each individual episode of recurrent VVC caused by *C. 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., 7–14 days of topical therapy or a 100 mg, 150 mg, or 200 mg oral dose of fluconazole every third day for a total of 3 doses (day 1, 4, and 7) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Maintenance regimens: Oral fluconazole weekly for 6 months is the first line of treatment. If this regimen is not feasible, some specialists recommend topical clotrimazole 200 mg twice a week, clotrimazole (500-mg dose vaginal suppositories once weekly), or other topical treatments used intermittently. <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 7–14 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 VVC remains unknown. Options include longer duration of therapy (7–14 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 2 weeks. This regimen has clinical and myco-logic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.
The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: **Clinical Management Guidelines for Obstetrician-Gynecologists: Vaginitis[9] (2006)**	<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 1 day ○ Clotrimazole 1% cream 5 g daily for 7 days ○ Clotrimazole 2% cream 5 g daily for 3 days ○ Clotrimazole 100-mg vaginal suppository daily for 7 days ○ Clotrimazole 200-mg vaginal suppository daily for 3 days ○ Clotrimazole 500-mg vaginal suppository daily for 1 day ○ Fluconazole 150-mg oral tablet daily for 1 day ○ Miconazole 2% cream 5 g daily for 7 days ○ Miconazole 100-mg vaginal suppository daily for 7 days ○ Miconazole 200-mg vaginal suppository for 3 days ○ Miconazole 1,200-mg vaginal suppository daily for 1 day ○ Nystatin 100,000 units vaginal tablets daily for 14 days ○ Terconazole 0.4% cream 5 g daily for 7 days ○ Terconazole 0.8% cream 5 g daily for 3 days ○ Tioconazole 2% cream 5 g daily for 3 days ○ Tioconazole 6.5% cream 5 g daily for 1 day • Because all listed antifungal treatments seem to have comparable

Clinical Guideline	Recommendation(s)
	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 7–14 days to achieve mycologic remission, prolonged antifungal treatment with fluconazole, 150 mg weekly for 6 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.
Finnish Medical Society Duodecim. **Seborrheic Dermatitis**[6] **(2007)**	Treatment: • The treatment does not cure the disease permanently. 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 sulphur (but not Vaseline) or by wetting and washing. • Seborrhoeic skin should be washed more often than usual. Decreasing Fungal Growth: • Washing the scalp with ketoconazole shampoo or selenium sulphide 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.
Infectious Diseases Society of America (IDSA): **Guidelines for the Treatment of Candidiasis**[7] **(2004)**	Oropharyngeal Candidiasis • Topical azoles (clotrimazole troches), oral azoles (fluconazole, ketoconazole, or itraconazole), or oral polyenes (such as nystatin or oral amphotericin B) are usually effective treatments for oropharyngeal candidiasis. • Initial episodes of oropharyngeal candidiasis can be treated with clotrimazole troches. • Oral fluconazole is as effective as—and, in some studies, superior to—topical therapy. Itraconazole solution is as efficacious as fluconazole. Ketoconazole and itraconazole capsules are less effective than

Clinical Guideline	Recommendation(s)
	fluconazole, because of variable absorption. • For refractory or recurrent infections, orally administered and absorbed azoles (ketoconazole, fluconazole, or itraconazole solution), amphotericin B suspension, intravenous caspofungin, or intravenous amphotericin B (only for otherwise unresponsive infections) may be used. Candidal Onychomycosis • Topical agents are usually ineffective. • Oral griseofulvin has largely been replaced by more-effective agents, including oral terbinafine or itraconazole. • Terbinafine has not demonstrated consistently good activity in trials. • Although the number of reported cases is small, therapy with itraconazole does appear to be effective. Itraconazole appears to be the most appropriate treatment. Candidal Skin Infection • Topical azoles and polyenes, including clotrimazole, miconazole, and nystatin, are effective. Keeping the infected area dry is important. Genital Candidiasis • Topical agents including azoles (all are used for 1–7 days depending on risk classification), nystatin, and oral azoles. Boric acid administered vaginally is also effective. • Uncomplicated vaginitis is seen in 90% of patients and responds readily to short-course oral or topical therapy. • The complicated vaginitis seen in ~10% of patients requires antimycotic therapy for ≥7 days, either daily as topical therapy or as two 150-mg doses of fluconazole administered 72 h apart. • Azole therapy is unreliable for non-*albicans* species of *Candida.* • Recurrent vaginitis is usually due to azole-susceptible *C. albicans*. Induction therapy with 2 weeks of a topical or oral azole should be followed by a maintenance regimen for 6 months. Suitable maintenance regimens include fluconazole, ketoconazole, itraconazole or daily therapy with any topical azole.
British Association of Dermatologists: **Guidelines for Treatment of Onychomycosis[10] (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. Currently, topical therapy can only be recommended for the treatment of superficial white onychomycosis (SWO) and in very early cases of distal and lateral subungual onychomycosis (DLSO) where the infection is confined to the distal edge of the nail. • A combination of topical and systemic therapy may improve cure rates still further or possibly shorten the duration of therapy with the systemic agent. • Terbinafine is superior to itraconazole for dermatophyte onychomycosis, and should be considered first-line treatment, with itraconazole as the next best alternative.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antifungals 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 Antifungals[1-2,11-47]

Generic Name(s)	Tinea Corporis	Tinea Cruris	Tinea Pedis	Tinea Versicolor	Onychomycosis	Cutaneous Candidiasis	Oropharyngeal Candidiasis	Vulvovaginal Candidiasis	Seborrheic Dermatitis	Dermatitis
Benzoic acid and salicylic acid										✔ *
Butenafine	✔	✔	✔	✔						
Butoconazole								✔		
Ciclopirox (cream)	✔	✔	✔	✔		✔				
Ciclopirox (gel)	✔		✔						✔	
Ciclopirox (shampoo)									✔	
Ciclopirox (solution)					✔					
Ciclopirox (suspension)	✔	✔	✔	✔		✔				
Clotrimazole (cream, solution)	✔	✔	✔	✔		✔				
Clotrimazole (troche)							✔			
Clotrimazole (vaginal cream/ suppository)								✔		
Clotrimazole and betamethasone	✔	✔	✔							
Econazole	✔	✔	✔	✔		✔				
Ketoconazole (cream)	✔	✔	✔	✔		✔			✔	
Ketoconazole (gel)									✔	
Ketoconazole (shampoo)				✔					✔	
Ketoconazole and pyrithione zinc									✔	
Miconazole (cream)	✔	✔	✔							
Miconazole (vaginal suppository)								✔		
Miconazole and zinc oxide						✔				
Naftifine	✔	✔	✔							
Nystatin (cream, ointment, powder)						✔				
Nystatin (vaginal tablet)								✔		

Generic Name(s)	Tinea Corporis	Tinea Cruris	Tinea Pedis	Tinea Versicolor	Onychomycosis	Cutaneous Candidiasis	Oropharyngeal Candidiasis	Vulvovaginal Candidiasis	Seborrheic Dermatitis	Dermatitis
Nystatin and triamcinolone						✔				
Oxiconazole (cream)	✔	✔	✔	✔						
Oxiconazole (lotion)	✔	✔	✔							
Sertaconazole			✔							
Sodium thiosulfate and salicylic acid				✔						
Sulconazole (cream)	✔	✔	✔	✔		✔				
Sulconazole (solution)	✔	✔		✔		✔				
Terbinafine	✔	✔	✔							
Terconazole								✔		
Tioconazole								✔		
Tolnaftate	✔	✔	✔	✔						

*FDA-approved for the treatment of nonspecific dermatitis/eczema/ fungal infections, insect bites, and burns

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antifungals[1-2,11-47]

Generic Name(s)	Systemic Absorption (%)	Distribution	Protein Binding (%)	Renal Excretion (%)	Metabolites
Benzoic acid	Not appreciably absorbed	No data	No data	Yes	Benzoyl-glucuronic acid, hippuric acid
Betamethasone	12-14	No data	64	<5	Yes
Butenafine	Minimal	Trans-epidermal/ transfollicular penetration	No data	Minimal	Yes (Hydroxylation at terminal t-butyl side chain)
Butoconazole	5.5	No data	No data	2.7	No data
Ciclopirox	Cream: No data Gel/shampoo: No data Solution: 1.3	0.8-1.6 in stratum corneum at 1.5-6h post-application	94-98	0.5-10	Yes (Glucuronide conjugates)
Clotrimazole	Cream/solution: <0.5 Troche: Poor, erratic Vaginal: 3-10	Cream/solution: Penetrates epidermal layers Troche: No data Vaginal: No data	No data	Cream/solution: 0.05-0.5 Troche: No data Vaginal: No data	Yes (multiple metabolites identified)
Econazole	Minimal	No data	98	<1	Yes (>20 urinary metabolites separated)
Ketoconazole	Negligible	No data	No data	No data	No data
Miconazole	<0.013-1.4	No data	90-93	<1	Yes (2,4-dichlorophenyl-1 H imidazole ethanol, 2-4-dichloromandelic acid)
Naftifine	2.5-6	No data	No data	64	Yes (multiple metabolites identified)
Nystatin	Minimal	No data	No data	No data	No data
Oxiconazole	Minimal	No data	No data	<0.3	No data
Pyrithione zinc	No data	No data	No data	No data	No data
Salicylic acid	9-25	No data	50-80	95%	Salicylate glucuronide, salicyluric acid, ether

Generic Name(s)	Systemic Absorption (%)	Distribution	Protein Binding (%)	Renal Excretion (%)	Metabolites
					glucuronide, phenolic glucuronide, ester glucuronide, acyl glucuronide
Sertaconazole	Minimal	Penetrates epidermal layers	No data	No data	No data
Sodium thiosulfate	No data	No data	No data	28.5	No
Sulconazole	Cream: 8.7 Solution: No data	No data	No data	Cream: 6.7 Solution: No data	No data
Terbinafine	<5	No data	>99	75	N-demethyl terbinafine, monohydroxy metabolite
Terconazole	5-16	No data	95	32-56	Yes
Tioconazole	Negligible	No data	No data	2.9	Yes (Glucuronide conjugates)
Tolnaftate	No data	No data	No data	No data	No data
Triamcinolone	1 - 36	No data	No data	Extensive	6-β-hydroxytriamcinolone acetonide, 21-carboxy-6-β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane antifungals, no significant drug interactions have been reported.[2]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antifungals are listed in Tables 5 – 6.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antifungals (Drugs A-O)[1-2,11-47]

Adverse Events	Benzoic Acid	Betameth-asone	Buten-afine	Butocon-azole	Ciclo-pirox	Clotrim-azole	Econ-azole	Ketocon-azole	Micon-azole	Nafti-fine	Ny-statin	Oxi-conazole
Central Nervous System												
Dizziness	-	-	-	-	-	-	-	<1	-	-	-	-
Headache	-	-	-	-	1-10	-	-	<1	-	-	-	-
Paresthesia	-	-	-	-	-	-	-	<1	-	-	-	-
Dermatological												
Abnormal hair texture	-	-	-	-	-	-	-	<1	-	-	-	-
Acne	-	✔	-	-	<1	-	-	<1	-	-	-	-
Alopecia	-	-	-	-	<1	-	-	<1	-	-	-	-
Burning	-	✔	>1	-	<1	-	3	-	✔	>10	-	-
Dermatitis	-	✔	<1	-	-	-	-	<1	✔	-	✔	-
Discharge	-	-	-	-	-	-	-	<1	-	-	-	-
Dry skin	-	✔	-	-	< 1	-	-	<1	-	1-10	-	1-10
Erythema	-	✔	>1	-	1-10	-	3	<1	-	1-10	-	1-10
Facial edema	-	-	-	-	<1	-	-	<1	-	-	-	-
Folliculitis	-	✔	-	-	-	-	-	-	-	-	-	-
Hypertrichosis	-	✔	-	-	-	-	-	-	-	-	-	-
Impetigo	-	-	-	-	-	-	-	<1	-	-	-	-
Irritation	✔	✔	>1	-	-	✔	-	1-5	-	1-10	-	1-10
Maceration	-	-	-	-	-	-	-	-	✔	-	-	-
Miliaria	-	✔	-	-	-	-	-	-	-	-	-	-
Nail disorder	-	-	-	-	1-10	-	-	<1	-	-	-	-
Oily skin	-	-	-	-	-	-	-	<1	-	-	-	-
Pain (local)	-	-	-	-	-	-	-	<1	-	-	-	-
Pruritus	-	✔	>1	-	1-10	✔	3	1-5	-	1-10	-	1-10
Pustules	-	-	-	-	-	-	-	<1	-	-	-	-
Pyogenic granuloma	-	-	-	-	-	-	-	<1	-	-	-	-
Rash	-	-	-	-	1-10	-	-	-	-	-	-	-
Scalp pustules	-	-	-	-	-	-	-	<1	-	-	-	-
Skin atrophy	-	✔	-	-	-	-	-	-	-	-	-	-
Stinging	-	-	>1	-	-	-	3	5	-	>10	-	1-10
Stevens-Johnson syndrome	-	-	-	-	-	-	-	-	-	-	✔	-
Striae	-	✔	-	-	-	-	-	-	-	-	-	-
Urticaria	✔	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Benzoic Acid	Betameth-asone	Buten-afine	Butocon-azole	Ciclo-pirox	Clotrim-azole	Econ-azole	Ketocon-azole	Micon-azole	Nafti-fine	Ny-statin	Oxi-conazole
Vesiculation	-	✔	-	-	-	-	-	-	-	-	-	-
Gastrointestinal												
Abdominal cramping	-	-	-	✔	-	-	-	-	✔	-	-	-
Abdominal pain	-	-	-	✔	-	-	-	-	-	-	-	-
Pelvic pain	-	-	-	✔	-	-	-	-	-	-	-	-
Genitourinary												
Dysmenorrhea	-	-	-	-	-	-	-	-	-	-	-	-
Itching	-	-	-	✔	-	-	-	-	-	-	-	-
Penile discomfort	-	-	-	-	-	<1	<1	-	-	-	-	-
Polyuria	-	-	-	-	-	<1	-	-	-	-	-	-
Soreness	-	-	-	✔	-	-	-	-	-	-	-	-
Swelling	-	-	-	✔	-	-	-	-	-	-	-	-
Vulvar/vaginal burning	-	-	-	✔	-	1-10	1-10	-	✔	-	-	-
Vulvar discomfort	-	-	-	-	-	<1	<1	-	✔	-	-	-
Other												
Eye irritation	-	-	-	-	-	-	-	<1	-	-	-	-
Eye swelling	-	-	-	-	-	-	-	<1	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	-	-	-	-	<1	-	-	-	-

✔ Percent not specified
\- Event not reported

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antifungals (Drugs P-Z)[1-2,11-47]

Adverse Events	Pyrithione Zinc	Salicylic Acid	Sertacon-azole	Sodium Thiosulfate	Sulcon-azole	Terbin-afine	Tercon-azole	Tiocon-azole	Tolnaf-tate	Triamcin-olone	Zinc Oxide
Central Nervous System											
Headache	-	-	-	-	-	-	5-10	✔	-	-	-
Dermatological											
Acne	-	-	-	-	-	-	-	-	-	✔	-
Burning	-	✔	1-10	-	1-10	1-10	1-4	-	-	✔	-
Dermatitis	-	-	1-10	✔	-	1-10	-	-	✔	✔	-
Desquamation	-	-	✔	-	-	-	-	-	-	-	-
Dry skin	-	-	1-10	-	-	1-10	-	-	-	✔	-
Erythema	-	-	✔	-	1-10	-	-	-	-	-	-
Folliculitis	-	-	-	-	-	-	-	-	-	✔	-
Hyperpigmentation	-	-	✔	-	-	-	-	-	-	-	-
Hypertrichosis	-	-	-	-	-	-	-	-	-	✔	-
Hypopigmentation	-	-	-	-	-	-	-	-	-	✔	-
Irritation	✔	✔	-	✔	-	1-10	-	-	✔	✔	1-10
Maceration	-	-	-	-	-	-	-	-	-	✔	-

Adverse Events	Pyrithione Zinc	Salicylic Acid	Sertacon-azole	Sodium Thiosulfate	Sulcon-azole	Terbin-afine	Tercon-azole	Tiocon-azole	Tolnaf-tate	Triamcin-olone	Zinc Oxide
Miliaria	-	-	-	-	-	-	-	-	-	✔	-
Oral mucosa atrophy	-	-	-	-	-	-	-	-	-	✔	-
Pain (local)	-	-	-	-	-	-	2-3	-	-	-	-
Peeling	-	✔	-	-	-	-	-	-	-	-	-
Perioral dermatitis	-	-	-	-	-	-	-	-	-	✔	-
Pruritus	-	-	✔	-	1-10	1-10	-	-	✔	✔	-
Scaling	-	✔	-	-	-	-	-	-	-	-	-
Sensitization	-	-	-	-	-	-	-	-	-	-	✔
Skin atrophy	-	-	-	-	-	-	-	-	-	✔	-
Skin infection (secondary)	-	-	-	-	-	-	-	-	-	✔	-
Stinging	-	-	-	-	1-10	1-10	-	-	✔	-	-
Striae	-	-	-	-	-	-	-	-	-	✔	-
Tenderness	-	-	1-10	-	-	-	-	-	-	-	-
Vesiculation	-	-	✔	-	-	-	-	-	-	-	-
Gastrointestinal											
Abdominal cramping	-	-	-	-	-	-	1-10	✔	-	-	-
Abdominal pain	-	-	-	-	-	-	-	✔	-	-	-
Genitourinary											
Dysmenorrhea	-	-	-	-	-	-	1-10	-	-	-	-
Penile discomfort	-	-	-	-	-	-	<1	-	-	-	-
Polyuria	-	-	-	-	-	-	<1	-	-	-	-
Vulvar/vaginal burning	-	-	-	-	-	-	1-10	✔	-	-	-
Vulvar discomfort	-	-	-	-	-	-	<1	✔	-	-	-
Other											
Chills	-	-	-	-	-	-	1-10	-	-	-	-
Fever	-	-	-	-	-	-	1-10	-	-	-	-
Flu-like syndrome	-	-	-	-	-	-	<1	-	-	-	-

✔ Percent not specified
\- Event not reported

VII. Dosing and Administration

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

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Antifungals[1-2,11-47]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Benzoic acid and salicylic acid	Dermatitis/eczema: Apply to affected area(s) of skin twice daily	Safety and efficacy in children have not been established.	Ointment: 6%-3%
Butenafine	Interdigital tinea pedis: Cream: apply to affected area(s) twice daily for 7 days or once daily for 4 weeks Tinea versicolor, tinea corporis, tinea pedis, tinea cruris: Cream: apply to affected area(s) once daily for 2 weeks	For children >12 years old: Tinea corporis, tinea cruris, tinea versicolor: Cream: apply to affected area(s) once daily for 2 weeks Tinea pedis: Cream: apply to affected area(s) twice daily for 7 days or once daily for 4 weeks	Cream: 1%
Butoconazole	Vulvovaginal candidiasis: Cream: insert 1 applicatorful vaginally once daily at bedtime for 1 day	Safety and efficacy in children have not been established	Vaginal cream: 2%
Ciclopirox	Cutaneous candidiasis: Suspension: gently massage into affected skin area(s) twice daily for 4 weeks Onychomycosis: Solution: apply to affected nail plate(s) once daily Seborrheic dermatitis, Gel: gently massage into affected skin area(s) twice daily for 4 weeks Shampoo: initial, wet hair and apply 1 to 2 teaspoonfuls to scalp for 3 minutes then rinse; maintenance, repeat twice weekly for 4 weeks with a minimum of 3 days between applications Tinea cruris, tinea versicolor: Cream, suspension: gently massage into affected skin area(s) twice daily for 2 weeks Tinea corporis, tinea pedis: Cream, gel, suspension: gently massage into affected skin area(s) twice daily for 4 weeks	For children >16 years old: Seborrheic dermatitis: Gel: gently massage into affected skin area(s) twice daily for 4 weeks Shampoo: initial, wet hair and apply 1 to 2 teaspoonfuls to scalp for 3 minutes then rinse; maintenance, repeat twice weekly for 4 weeks with a minimum of 3 days between applications Tinea cruris, tinea versicolor: Cream, suspension: gently massage into affected skin area(s) twice daily for 2 weeks Tinea corporis, tinea pedis: Cream, gel, suspension: gently massage into affected skin area(s) twice daily for 4 weeks	Cream: 0.77% Gel: 0.77% Shampoo: 1% Solution: 8% Suspension: 0.77% Kit: ciclopirox solution 8% and non-acetone nail lacquer remover

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Clotrimazole	Cutaneous candidiasis: Cream, solution (Rx dosage forms): apply to affected area(s) twice daily for 4 weeks Oropharyngeal candidiasis: Troche: initial treatment, dissolve 1 troche in mouth five times daily for 2 weeks; maintenance (prophylaxis), dissolve 1 troche in mouth three times daily Tinea corporis, tinea pedis: Cream, solution (OTC dosage forms): apply to affected area(s) twice daily for 4 weeks Tinea cruris: Cream, solution (OTC dosage forms): apply to affected area(s) twice daily for 2 weeks Tinea versicolor: Cream, solution (Rx dosage forms): apply to affected area(s) twice daily for 4 weeks Vulvovaginal candidiasis: Vaginal cream (1%): initial, insert 1 applicatorful vaginally at bedtime for 7 to 14 days Vaginal cream (2%): insert 1 applicatorful vaginally at bedtime for 3 days Vaginal suppository (100 mg): insert 1 suppository vaginally at bedtime for 7 days	For children >3 years old: Oropharyngeal candidiasis: Troche: dissolve 1 troche in mouth five times daily for 2 weeks For children >2 years old: Tinea corporis, tinea cruris, tinea pedis, tinea versicolor: Cream, solution (OTC dosage forms): apply to affected area(s) twice daily for 2 to 4 weeks For children >12 years old: Vulvovaginal candidiasis: Vaginal cream (1%): initial, insert 1 applicatorful vaginally at bedtime for 7 to 14 days Vaginal cream (2%): insert 1 applicatorful vaginally at bedtime for 3 days Vaginal suppository (100 mg): insert 1 suppository vaginally at bedtime for 7 days	Cream: 1% Solution: 1% Troche: 10 mg Vaginal cream: 1%, 2% Vaginal suppository: 100 mg
Clotrimazole and betamethasone	Tinea corporis, tinea cruris: Cream, lotion: initial, apply to affected area(s) of skin twice daily for one to two weeks; maximum, 45 g/week. Tinea pedis: Cream, lotion: initial, apply to affected area(s) of skin twice daily for two to four weeks; maximum, 45 g/week	Safety and efficacy in patients less than 17 years of age have not been established.	Cream: 1%-0.05% Lotion: 1%-0.05%
Econazole	Cutaneous candidiasis: Apply to affected area(s) twice daily for 2 weeks Tinea corporis, tinea cruris, tinea versicolor:	Safety and efficacy in children have not been established	Cream: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Apply to affected area(s) once daily for 2 weeks Tinea pedis: Apply to affected area(s) once daily for 1 month		
Ketoconazole	Dandruff: Shampoo: initial, shampoo twice weekly for up to 8 weeks with 3 days between each application; maintenance, shampoo intermittently as needed Seborrheic dermatitis: Cream: apply to affected area(s) twice daily for 4 weeks Gel: apply to affected area(s) once daily for 2 weeks Tinea corporis, tinea cruris, tinea versicolor, cutaneous candidiasis: Cream: apply to affected area(s) once daily for 2 weeks Tinea pedis, Cream: apply to affected area(s) once daily for 6 weeks	For children > 12 years old: Dandruff: Shampoo (1%): shampoo twice weekly for 4 weeks with 3 days between each application	Cream: 2% Gel: 2% Shampoo: 2%
Ketoconazole and pyrithione zinc	Seborrheic dermatitis: Ketoconazole 2% gel: apply thick layer once daily for 2 weeks; wash hands well both before and after application. Pyrithione zinc 1% shampoo: Wet hair, apply shampoo and work into lather; apply at least 2 times a week, but not more often than once daily.	Safety and efficacy in patients less than 12 years of age have not been established.	Kit: ketoconazole 2% gel and pyrithione zinc 1% shampoo
Miconazole	Tinea cruris (OTC and Rx dosage forms): Cream: apply to affected area(s) twice daily for 2 weeks Tinea corporis, tinea pedis (OTC and Rx dosage forms): Cream: apply to affected area(s) twice daily for 4 weeks Vulvovaginal candidiasis: Vaginal suppository (100 mg): insert 1 suppository vaginally at bedtime for 7 days Vaginal suppository (200 mg): insert 1 suppository vaginally at	For children > 2 years old: Tinea corporis, tinea cruris, tinea pedis (OTC and Rx dosage forms): Cream: apply to affected area(s) twice daily For children > 12 years old: Vulvovaginal candidiasis: Vaginal suppository (100 mg): insert 1 suppository vaginally at bedtime for 7 days	Cream: 2% Vaginal cream: 2% Vaginal suppository: 100 mg, 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	bedtime for 3 days	Vaginal suppository (200 mg): insert 1 suppository vaginally at bedtime for 3 days	
Miconazole and zinc oxide	Diaper dermatitis: Apply to affected area(s) of skin at each diaper change for seven days	For infants aged 4 weeks and older: Diaper dermatitis: Apply to affected area(s) of skin at each diaper change for 7 days	Ointment: 0.25%
Naftifine	Tinea corporis, tinea cruris, tinea pedis: Cream: apply to affected area(s) once daily for 4 weeks Gel: apply to affected area(s) twice daily for 4 weeks	Safety and efficacy in children have not been established	Cream: 1% Gel: 1%
Nystatin	Cutaneous candidiasis: Cream, ointment, powder: apply to affected area(s) two to three times daily until healing is complete Vulvovaginal candidiasis: Vaginal tablet: insert 1 tablet vaginally once daily for 2 weeks	Cutaneous candidiasis: Cream, ointment, powder: apply to affected area(s) two to three times daily until healing is complete	Cream: 100,000 units/g Ointment: 100,000 units/g Powder: 100,000 units/g Vaginal tablet: 100,000 units
Nystatin and triamcinolone	Cutaneous candidiasis: Apply to affected area(s) of skin twice daily up to 25 days	Cutaneous candidiasis: Apply to affected area(s) of skin once to twice daily up to 25 days	Cream: 100,000 u/g-0.1% Ointment: 100,000 u/g-1%
Oxiconazole	Tinea corporis, tinea cruris: Apply to affected area(s) twice daily for 2 weeks Tinea pedis: Apply to affected area(s) twice daily for 4 weeks Tinea versicolor: Cream: apply to affected area(s) once daily for 2 weeks	Tinea corporis, tinea cruris: Apply to affected area(s) twice daily for 2 weeks Tinea pedis: Apply to affected area(s) twice daily for 4 weeks Tinea versicolor: Apply to affected area(s) once daily for 2 weeks	Cream: 1% Lotion: 1%
Sertaconazole	Tinea pedis: Apply to affected area(s) twice daily for 4 weeks	For children > 12 years old: Tinea pedis: Apply to affected area(s) twice daily for 4 weeks	Cream: 2%
Sodium thiosulfate and salicylic acid	Tinea versicolor: Apply to affected area(s) of skin twice daily	Safety and efficacy in children have not been established.	Lotion: 25%-1%
Sulconazole	Cutaneous candidiasis: Apply to affected area once or	Safety and efficacy in children have not been	Cream: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	twice daily for 3 to 4 weeks Tinea corporis, tinea cruris, tinea versicolor: Apply to affected area(s) once or twice daily for at least 3 weeks Tinea pedis: Cream: apply to affected area(s) twice daily for 4 weeks	established	Solution: 1%
Terbinafine	Tinea corporis, tinea cruris: Cream: apply to affected area(s) once daily for 1 week Tinea pedis: Apply to affected area(s) twice daily for 1 week	For children > 12 years old: Tinea corporis, tinea cruris: Cream: apply to affected area(s) once daily for 1 week Tinea pedis: Apply to affected area(s) twice daily for 1 week	Cream: 1% Spray: 1%
Terconazole	Vulvovaginal candidiasis: Vaginal cream (0.4%): insert 1 applicatorful at bedtime for 7 days Vaginal cream (0.8%): insert 1 applicatorful at bedtime for 3 days Vaginal suppository: insert 1 suppository vaginally at bedtime for 3 days	Safety and efficacy in children have not been established	Vaginal cream: 0.4%, 0.8% Vaginal suppository: 80 mg
Tioconazole	Vulvovaginal candidiasis: Insert 1 applicatorful vaginally once at bedtime	Safety and efficacy in children have not been established	Vaginal ointment: 6.5%
Tolnaftate	Tinea corporis, tinea cruris, tinea pedis, tinea versicolor: Apply to affected area(s) twice daily for 2 to 3 weeks	For children >2 years old: Tinea corporis, tinea cruris, tinea pedis, tinea versicolor: Apply to affected area(s) twice daily for 2 to 3 weeks	Aerosol powder: 1% Cream: 1% Spray: 1%

VIII. Effectiveness

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

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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cutaneous Candidiasis				
Bagatell et al.[51] (1985) Ciclopirox 1% cream applied to affected area(s) BID vs. clotrimazole 1% cream applied to affected area(s) BID vs. cream vehicle applied to affected area(s) BID In study A, participants received either ciclopirox or vehicle. In study B, participants received either ciclopirox or clotrimazole	2 DB, MC, PG, RCT Patients aged 12 to 75 years old 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, statistically 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 2-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 2 weeks of therapy in study B, 17% and 0% of patients treated with ciclopirox and clotrimazole, respectively, achieved clinical cure (P≤0.05). At 3 weeks, 38% and 21% of patients treated with ciclopirox and clotrimazole, respectively, achieved clinical cure (P≤0.05). After 4 weeks of treatment, both treatment groups showed similar results. At 2 weeks of therapy, a greater number 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 statistically significant difference between treatment groups relative to mycological cure. Secondary: No adverse events were reported.
Clayton et al.[52] (1973)	DB, AC, RCT	N=103	Primary: Clinical cure,	Primary: Relative to patients with confirmed tinea corporis, there was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clotrimazole 1% cream applied to affected area(s) of skin BID vs. nystatin 100,000 U/g ointment applied to affected area(s) of skin BID vs. Whitfield's Ointment® (3% salicylic acid, 6% benzoic acid) applied to affected area(s) of skin BID	Patients aged 13 to 63 years old with confirmed tinea corporis, tinea pityriasis, erythrasma, or *Candida* infections.	4 weeks	mycological cure	statistically significant difference in efficacy between patients treated with clotrimazole or Whitfield's Ointment®. Relative to patients with confirmed tinea pityriasis, there was no statistically significant difference in efficacy between patients treated with clotrimazole or Whitfield's ointment. Relative to patients with confirmed erythrasma, there was no statistically significant difference in efficacy between patients treated with clotrimazole or Whitfield's ointment. Relative to patients with Candida infections, there was no statistically significant difference in efficacy between patients treated with clotrimazole or nystatin.
Beveridge et al.[116] (1977) Nystatin cream applied to affected area(s) of skin on right/left arm vs. nystatin/triamcinolone acetonide combination cream applied to affected area(s) of skin on the other arm	DB, MC, PG, RCT Patients aged 6 months to 71 years with confirmed bilateral Candidal lesions of the flexures	N=31 14 days	Primary: Eradication of *Candida*, clinical progress of lesions, patient preference for agent, physician preference for agent Secondary: Adverse events	Primary: There was little difference between clinical (12/31 [38.7%] vs. 14/31 [45%], respectively) and mycological cure (27/31 [87.1%] vs. 26/31 [83.8%], respectively) between nystatin and nystatin/triamcinolone therapies. There was no statistically 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tanenbaum et al.[53] (1983) Miconazole 2% cream applied to affected area(s) on skin BID vs. sulconazole 1% cream applied to affected area(s) on skin QD vs. sulconazole 1% cream applied to affected area(s) on skin BID vs. cream vehicle applied to affected area(s) BID In study A, participants received either sulconazole or vehicle given BID. In study B, participants received either sulconazole given	2 DB, PG, RCT Patients with cutaneous candidiasis	N=96 3 weeks	Primary: Mycological cure rate, signs of inflammation (erythema, scaling, pustules, maceration, vesiculation, fissuring), itching, clinician rated overall clinical status Secondary: Adverse effects	Primary: At the end of 3 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 3 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 3 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 3 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: One patient receiving the vehicle experienced itching. Erythema and/or pruritus was reported by 6 patients treated with sulconazole and 3 patients treated with miconazole.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD or miconazole given BID.				
Oropharyngeal Candidiasis				
Kirkpatrick et al.[54] (1978) Clotrimazole 10 mg buccal troche dissolve 1 troche five times daily vs. troche vehicle dissolve 1 troche five times daily	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 (6 vs. 1, respectively; P<0.001). Secondary: No adverse events were reported with either study group.
Owens et al.[55] (1984) Clotrimazole 10 mg troche dissolve 1 troche TID vs. troche vehicle dissolve 1 troche TID	DB, PRO, RCT Patients with either leukemia or solid malignant neoplasms treated with chemotherapy or renal transplant patients treated with immunosuppressives taken to prevent graft rejection	N=84 27 to 81 days	Primary: Signs and symptoms of oral candidiasis, culture Secondary: Adverse events	Primary: Oral thrush was observed after 9 days in leukemic patients, and 3 weeks in renal transplant patients and patients with solid malignant neoplasms who were treated prophylactically (P<0.05). Oral candidiasis occurred in 13% and 57% of patients treated with clotrimazole and placebo, respectively (P<0.0005). Of the renal transplant patients, 8% 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 statistically 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Vulvovaginal Candidiasis				
Drogemueller et al.[56] (1984) Butoconazole 2% cream insert 1 applicatorful (6 mL) 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 8 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 statistically significant. At 8 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 statistically significant. 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/vaginal irritation and burning.
Hajman et al.[57] (1988) Butoconazole 2% vaginal cream insert 1 applicatorful intravaginally QHS (for 3 days) vs. clotrimazole 1% vaginal cream insert	PG, RCT, SB Female patients aged 19 to 63 years old with laboratory confirmed vulvovaginal candidiasis	N=63 3 to 6 days	Primary: Clinical cure, microbiological cure, therapeutic cure (combines clinical and microbiological cure) Secondary: Adverse events	Primary: The difference between the clinical response of patients treated with butoconazole at the initial vs. final visit was statistically 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 7 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1 applicatorful intravaginally QHS (for 6 days)				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 statistically significant difference between treatment groups in terms of clinical, microbiological, and therapeutic cure rates. Secondary: No adverse events were reported.
Brown et al.[58] (1999) Butoconazole 2% vaginal cream insert 1 applicatorful intravaginally at bedtime (for 1 day) vs. miconazole 2% vaginal cream insert 1 applicatorful intravaginally at bedtime (for 7 days)	MC, PG, RCT Female, nonpregnant 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 1 to day 7 since treatment initiation. At 8 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 8 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 statistically different with the exception of the difference in the rapidity of severe symptom relief after the first dose of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				butoconazole compared to miconazole (P=0.01). Secondary: No systemic events were reported. Vulvovaginal irritation (e.g., burning, itching) was reported.
Kaufman et al.[59] (1989) Butoconazole 2% vaginal cream insert 1 applicatorful (5 g) intravaginally QHS (for 3 days) vs. miconazole 2% vaginal cream insert 1 applicatorful intravaginally QHS (for 7 days)	MC, PG, RCT Female patients aged 18 to 61 years old who are nonpregnant and confirmed for vulvovaginal candidiasis	N=225 3 to 7 days	Primary: Microbiological cure, clinical cure Secondary: Adverse events	Primary: At days 8 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 statistically different. Secondary: Minimal side effects were reported from both butoconazole- and miconazole-treated patients including vaginal irritation.
Higton et al.[60] (1974) Clotrimazole 100 mg vaginal tablet insert 1 intravaginally QHS vs. nystatin 100,000 unit vaginal suppository insert 2	PG, RCT Obstetrical and gynecological patients with mycologically confirmed vaginal candidiasis	N=50 6 days	Primary: Relapse rate, overall cure rate Secondary: Adverse event	Primary: After 6 days of therapy, initial cure rates were 96% and 76% for patients treated with clotrimazole and nystatin, respectively. After 4 weeks post treatment, infection relapse rates were 12.5% and 42% for patients treated with clotrimazole and nystatin, respectively. At this time, overall cure rates were higher for patients treated with clotrimazole compared to patients treated with nystatin (84% vs. 58%; difference was not statistically significant). Both clotrimazole and nystatin reduced symptoms at 5 days post treatment (P<0.05) and, again, at 4 weeks (P<0.05) post treatment and complaints of discharge at 6 days (P<0.05). There was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
intravaginally QHS				statistically significant difference between study groups though trends favored clotrimazole over nystatin. Secondary: No local or general adverse event was reported for either treatment group.
Stein et al.[61] (1986) Clotrimazole 100 mg vaginal tablets insert intravaginally QD (for 3 days) vs. tioconazole 6.5% ointment insert 1 applicatorful (5 g) intravaginally QHS (for 1 day)	RCT Nonpregnant, female patients aged 18 to 65 years old with confirmed vulvovaginal candidiasis (clinical signs and symptoms and microscopic test)	N=80 1 to 3 days	Primary: Symptomatic response, mycological response Secondary: Adverse events	Primary: Based on follow-up examinations at 4 weeks post treatment, 84% and 85% of patients treated with tioconazole and clotrimazole, respectively, remained asymptomatic. The overall clinical success rate was similar between treatment groups. After 4 weeks post treatment, 59% and 62% of patients treated with tioconazole and clotrimazole, respectively, remained culture negative. The mycological response was similar between treatment groups. Secondary: Of the patients treated with tioconazole, 30% reported local irritation or itching. Of the patients treated with clotrimazole, 5% reported either vaginal burning or sensitive clitoris. The difference in adverse reactions was significant between the two treatment groups (P=0.006).
Davis et al.[62] (1974) Miconazole 2% cream insert 1 applicatorful intravaginally QHS (for 14 days) vs. nystatin 100,000 unit vaginal tablets insert, using an	PG, RCT Pregnant and nonpregnant patients with mycologically confirmed vulvovaginal candidiasis	N=116 14 to 15 days	Primary: Overall cure rates, cure rates in sub-groups (i.e., pregnant patients, nonpregnant patients, nonpregnant patients taking oral contraceptives) Secondary: Adverse events	Primary: Cure rates were higher in patients treated with miconazole compared to patients treated with nystatin (91.1% vs. 76.6%, respectively; P=0.05). In pregnant patients, 100% and 82.6% of patients treated with miconazole and nystatin, respectively achieved cure. In nonpregnant patients, 84.8% and 73% of patients treated with miconazole and nystatin, respectively, achieved cure. In nonpregnant patients taking oral contraceptives, 82.4% and 63.2% of patients treated with miconazole and nystatin, respectively, achieved cure. P values not reported for these three comparisons. Secondary: Patients treated with nystatin reported adverse events, such as condyloma acuminata of the labia, severe burning and vulvar edema,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applicator, 1 vaginal tablet intravaginally QAM and QPM (for 15 days)				and pelvic pain. Patients treated with miconazole reported adverse events, such as mild headache, vaginal burning, and moderate irritation.
Cohen et al.[63] (1985) Clotrimazole 10% vaginal cream 5 g QD for one dose vs. clotrimazole 2% vaginal cream 5 g BID for 3 days	OS, PRO Patients aged 16 years and older who presented clinical signs and symptoms of acute vaginal candidiasis (female) or candidal balanitis (male) in the past 3 months	N=111 1 to 3 days	Primary: Cultures Secondary: Adverse effects	Primary: At 1 week after treatment, the 1-dose treatment and 3-day treatment demonstrated equal efficacy shown by negative cultures in vulvovaginal candidiasis at day 7 (90.9% vs. 96.4%) and day 35 (84% vs. 81%) Secondary: No adverse events were reported for either agent in female patients. Of the male patients, 45% reported signs and symptoms of balanitis.
Fluery et al.[64] (1985) Clotrimazole 100 mg vaginal tablet insert 2 tablets intravaginally QD (for 3 days) vs. clotrimazole 500 mg vaginal tablet insert 1 tablet intravaginally QD (for 1 day)	DB, PG, MC, RCT Patients aged 17 to 51 years old with clinically and mycologically confirmed vulvovaginal candidiasis	N=103 1 to 3 days	Primary: Clinical cure, mycological cure Secondary: Adverse events	Primary: Between 5 to 10 days post treatment, 90% and 89% of patients treated with clotrimazole 500 mg and clotrimazole 200 mg, respectively, achieved both clinical and mycological cure. At 27 days post treatment, 75% and 72% of patients treated with clotrimazole 500 mg and clotrimazole 200 mg, respectively, achieved treatment success. There was no statistically significant difference in efficacy between either treatment group in all study parameters. Secondary: One patient taking clotrimazole 200 mg reported moderate edema of the vulva.
Lebherz et al.[65] (1985) Clotrimazole 100 mg vaginal tablet	DB, PG, RCT Patients aged 19 to 71 years old with mycologically and	N=101 1 to 3 days	Primary: Mycological cure, clinical cure Secondary:	Primary: Between 5 to 10 days post treatment, 77% and 89% of patients treated with single-dose and three-day regimens of clotrimazole, respectively, achieved mycological and clinical cure.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
insert 2 tablets intravaginally QD (for 3 days) vs. clotrimazole 500 mg vaginal tablet insert 1 tablet intravaginally QD (for 1 day)	clinically active vulvovaginal candidiasis		Adverse events	At 27 days post treatment, 65% and 74% of patients treated with single-dose and three-day regimens of clotrimazole, respectively, achieved mycological and clinical cure. There was no statistically significant difference in efficacy between either treatment group in all study parameters. Secondary: Two patients treated with either the one- or three-day therapy of clotrimazole reported a vulvar lesion. One patient treated with 3-day therapy of clotrimazole complained of a perianal rash.
Thomason et al.[66] (1990) Miconazole 100 mg vaginal suppositories insert 1 intravaginally QHS vs. terconazole 80 mg vaginal suppositories insert 1 intravaginally QHS (for 3 days), then suppository vehicle insert 1 intravaginally (for 4 days) vs. suppository vehicle insert 1 intravaginally QHS	DB, RCT Nonpregnant patients with at least one clinical vulvovaginal sign or symptom and culture-confirmed vulvovaginal candidiasis	N=29 7 days	Primary: Microbiologic cure, clinical cure, therapeutic cure Secondary: Adverse events	Primary: At 8-10 days, 100% of patients (N=5) 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 statistically significant improvements in clinical, microbiologic, and therapeutic cure compared to placebo ($P<0.05$). There was no statistically significant difference in cure rates between miconazole and terconazole treatment groups. Secondary: No adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jacobson et al.[67] (1985) Butoconazole 1% vaginal cream insert 1 applicatorful (5 g) QD vs. butoconazole 2% vaginal cream insert 1 applicatorful (5 g) QD vs. miconazole 2% vaginal cream insert 1 applicatorful (5 g) QD	DB, MC, PG, RCT Patients aged 13 to 39 years old with confirmed vulvovaginal candidiasis by clinical signs and symptoms of vaginal yeast infection (e.g., swelling, redness, itching, burning, and/or characteristic discharge) or presence of Candida albicans confirmed by potassium hydroxide test and culture	N=130 6 days	Primary: Microbiological cure, clinical cure, relapse rate Secondary: Adverse effects	Primary: On day 8, 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 statistically significant. Secondary: Two patients in each treatment group reported side effects (i.e., headache, vaginal burning, leakage of cream, and bleeding).
Corson et al.[68] (1991) Miconazole 2% cream insert 1 applicatorful (5 g) intravaginally QD vs. terconazole 0.4% cream insert 1 applicatorful (5 g) intravaginally QD vs.	DB, MC, RCT Nonpregnant, female patients aged 17 to 61 years old 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, 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 8 to 10 days post treatment (visit 1), 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 statistically significant difference for other comparisons. After 7 days of treatment, patients treated with terconazole 0.4%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
terconazole 0.8% cream insert 1 applicatorful (5 g) intravaginally QD				terconazole 0.8%, and miconazole 2% had complete symptom relief rates of 83.3%, 77.0%, and 79.5%, respectively. There was no statistically significant difference between treatment groups. After 7 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 statistically significant difference between treatment groups. Between 30 to 35 days post treatment (visit 2), there were no statistically significant differences in microbiologic, clinical, or therapeutic cure rates in the treatment groups. Secondary: There was no statistically 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.
Hirsch et al.[69] (1989) Clotrimazole 200 mg tablets (for 3 days) vs.	MA Patients with confirmed vulvovaginal candidiasis in mostly DB, MC, PC, RCT trials, pregnant patients were included in most of the trials	N=1,800 1 to 7 days 16 trials	Primary: Clinical cure rate Secondary: Adverse effects	Primary: According to the meta-analysis, the most effective regimens of terconazole were the 80 mg suppository for 3 days, 240 mg suppositories for 1 day, and the 0.4% cream for 7 days. The 240 mg suppository for 1 day was more effective than the 80 mg suppository for 3 days. The clinical efficacies of the 0.4% and 0.8% cream for 7 days were comparable.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clotrimazole 1% cream insert 1 applicatorful (5 g) intravaginally QHS (for 7 days) vs. econazole 150 mg suppositories* (for 3 days); dosing not specified vs. miconazole 2% cream insert 1 applicatorful (5 g) intravaginally QHS (for 7 days) vs. terconazole (40 mg, 80 mg, 240 mg) vaginal suppositories, (0.2%, 0.4%, 0.8%) cream, or other formulations				At 4 weeks from the start of treatment, 92% patients receiving terconazole 80 mg suppositories achieved clinical cure; 88% for terconazole 240 mg suppository for 1 day, 94% for terconazole 0.8% cream for 5 days, 90% for terconazole 0.4% cream for 7 days. After 4 weeks, mycological cure rates with terconazole 0.2% cream were similar to miconazole 2% cream but less compared to terconazole 0.4% cream. After 4 weeks, mycological cure rates were 100% and 80% for terconazole 0.4% cream and clotrimazole 1% cream, respectively, for nonpregnant patients. After 4 weeks, mycological cure rates were 92% and 89% for terconazole 0.4% cream and clotrimazole 1% cream, respectively, for pregnant patients. After 4 weeks, mycological cure rates were similar between terconazole 80 mg suppositories and econazole 150 mg suppositories for pregnant and nonpregnant patients. After 4 weeks, mycological cure rates were similar between terconazole 80 mg and 240 mg suppositories and clotrimazole 240 mg tablets. Note: Statistical significance was not addressed in the study results; P values were not reported. 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.
Brown et al.[70] (1986) Butoconazole 1%	DB, MC, PG, RCT Patients aged 17 to 67 years old with confirmed	N=580 3 to 6 days	Primary: Microbiological cure, clinical cure, therapeutic cure	Primary: Clinical and microbiological cure rates were greater in all butoconazole- and miconazole-treated patients compared to placebo (P<0.003 for each comparison).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vaginal cream (for 3 days), then cream vehicle (for 3 days) vs. butoconazole 1% vaginal cream (for 6 days) vs. butoconazole 2% vaginal cream (for 3 days); then cream vehicle (for 3 days) vs. butoconazole 2% vaginal cream (for 6 days) vs. miconazole 2% vaginal cream (for 6 days) vs. vehicle from the butoconazole cream	vulvovaginal candidiasis		Secondary: Adverse events	There was no statistically significant difference in microbiologic and clinical cure rate between different butoconazole regimens and butoconazole compared to miconazole. There was no statistically significance difference in therapeutic cure rates in patients treated with butoconazole 1% for 6 days and placebo. All other treatment 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.
Young et al.[71] (2001) Clotrimazole	MA (all RCTs) Pregnant patients receiving any topical	Sample size not reported 10 trials	Primary:	Primary: According to data from 5 trials, patients treated with topical azoles achieved greater cure compared to patients treated with nystatin (odds ratio 0.21, 95% CI 0.06 to 0.29).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(specific agent and dosing not reported) vs. econazole* (specific agent and dosing not reported) vs. hydrargaphen* (specific agent and dosing not reported) vs. miconazole (specific agent and dosing not reported) vs. nystatin (specific agent and dosing not reported) vs. terconazole (specific agent and dosing not reported) vs. placebo	treatment for vaginal candidiasis			According to data from 1 trial, there was no statistically significant difference between patients treated with nystatin compared to hydrargaphen* (odds ratio 0.14, 95% CI 0.05 to 1.84). According to data from trials with clotrimazole, the following results were reported: (1) clotrimazole is more effective than placebo (odds ratio 0.14, 95% CI 0.06 to 0.31), (2) clotrimazole treatment was similar regardless of single or multiple (i.e., 3 to 4 days) dosing, (3) clotrimazole treatment for 7 days was more efficacious compared to treatment for 4 days (odds ratio 11.7, 95% CI 4.21 to 29.15), (4) clotrimazole treatment was similar regardless of 7-day or 14-day treatment duration (odds ration 0.41, 95% CI 0.16 to 1.05), (5) clotrimazole and terconazole had similar efficacy (odds ratio 1.41, 95% CI 0.28 to 7.10).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Thomason et al.[72] (1989) Miconazole 2% vaginal cream (for 7 days; dosing regimen not specified) vs. miconazole 100 mg vaginal suppositories (for 7 days; dosing regimen not specified) vs. terconazole 0.4% vaginal cream (for 7 days; dosing regimen not specified) vs. terconazole 80 mg vaginal suppositories (for 3 days; dosing regimen not specified) vs.	MA (DB, PG, RCT; AC, PC, or both) Patients greater than 18 years old, nonpregnant, with signs and symptoms of vulvovaginal candidiasis (i.e., itching, burning, irritation, erythema, edema, excoriation) and confirmed vulvovaginal candidiasis	N=1,259 3 to 7 days Number of trials not reported	Primary: Clinical cure rate, mycological cure rate, relapse rate Secondary: Adverse events	Primary: Terconazole cream and suppository formulations were more efficacious compared to placebo (P<0.001, P<0.001, respectively). 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 7 days. Secondary: 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
terconazole 80 mg vaginal suppositories (for 3 days) and suppository vehicle (for 4 days); dosing regimens not specified) vs. cream vehicle (for 7 days; dosing regimen not specified) vs. suppository vehicle (for 7 days; dosing regimen not specified)				
Seborrheic Dermatitis				
Aly at el.[73] (2003) Ciclopirox 0.77% gel applied to affected area(s) BID vs. gel vehicle applied to affected area(s) BID	DB, MC, PC, RCT Patients aged 19 to 85 years old 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 >75% improvement in global evaluation scores compared to those treated with the vehicle (P=0.01). At days 15 (P=0.01), days 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 vehicle. Twenty-nine percent of patients treated with ciclopirox rated the medication as cosmetically acceptable. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A burning sensation was reported in 13% and 9% in ciclopirox and vehicle-treated patients, respectively.
Vardy et al.[74] (2000) Ciclopirox 1% shampoo twice weekly vs. shampoo vehicle twice weekly	DB, PC, PRO, RCT Patients aged 15 years and older with mild to moderate seborrheic dermatitis of the scalp	N=82 4 weeks	Primary: Symptom scores, clinical cure, clinical assessments	Primary: At the end of 4 weeks of treatment, 93% and 41% of patients treated with ciclopirox and placebo, respectively, had improvement or clearing of infections (P<0.00001). No recurrence was observed at 2 weeks post treatment. At the 2-week checkup, 4-week checkup, and at 2 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, P=0.014, respectively). After 4 weeks of treatment, both patient and physician assessment scores showed a statistically significant difference in clinical response favoring ciclopirox at weeks 4 (P=0.00001, P<0.00001, respectively) and 6 (P=0.00059, P<0.00023, respectively).
Lebwohl et al.[115] (2004) Ciclopirox 1% shampoo twice weekly vs. shampoo vehicle twice weekly	RCT, DB, PC Patients with a mild to pronounced expression of stable or exacerbating seborrheic dermatitis of the scalp	N=499 4 weeks	Primary: Effective treatment (defined as a score of 0 or 1, if baseline score ≥3) for status, scaling, and erythema Secondary: Clearance (score = 0 for status, scaling, erythema and itching) and improvement (status score = 0 or 1, or improvement by ≥3 points), sum scores of scaling, itching and erythema	Primary: Effective treatment was noted in 65 subjects (26.0%) in the ciclopirox group, compared with 32 patients (12.9%) in the vehicle group (P=0.0001; OR: 2.383, 95% CI: 1.494– 3.799). 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 4. Reductions of means in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vehicle group were from 8.7 to 6.1 at week 4 (2.6-point reduction). This difference between groups was statistically significant in favor of ciclopirox at both week 2 (P=0.0003) and week 4 (P<0.0001).
Shuster et al.[123] (2005) Study Segment A Ciclopirox 1% shampoo once or twice weekly for 4 weeks vs. shampoo vehicle once or twice weekly for 4 weeks Study Segment B Ciclopirox 1% shampoo prophylactically once weekly or every 2 weeks for 12 weeks vs. shampoo vehicle once weekly or every 2 weeks for 12 weeks	RCT, MC, DB, PC Patients aged 18-88 years 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	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). Secondary: Higher response rates were demonstrated with ciclopirox than with vehicle (ciclopirox twice weekly, 23.1% [P<0.001)]; ciclopirox once weekly, 17% [P=0.4]; vehicle, 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 2 weeks, and 35.5% in the vehicle group (P<0.001 and P<0.001, respectively).
Green et al.[75] (1987) Ketoconazole 2% cream applied to	DB, PC, RCT Patients aged 16 to 78 years old with seborrheic dermatitis of the face	N=20 4 weeks	Primary: Degree of seborrheic dermatitis (ranging from 0=no scaling	Primary: After 4 weeks, patients treated with ketoconazole experienced a statistically 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
affected area(s) on skin and wash hair with ketoconazole 2% shampoo two to three times weekly vs. cream vehicle applied to affected area(s) on skin and wash hair with shampoo vehicle two to three times weekly	and possible seborrheic dermatitis of the scalp and/or chest/back		to 3=severe), patient assessment of facial rash, scalp itching and scalp scaling (ranging from none to worse ever)	ketoconazole showed improved visual analogue scores for facial rash at 3 weeks (P<0.05) and 4 weeks (P<0.01). Six out of ten patients receiving ketoconazole experienced statistically significant reduction in scalp scaling (P<0.05). Patients receiving the placebo experienced no change or improvement in clinical or visual analogue scores.
Cauwenbergh et al.[76] (1986) Ketoconazole 2% scalp gel wash hair twice weekly by massaging in gel for 3-5 minutes prior to rinsing with warm water vs. gel vehicle wash hair twice weekly by massaging in gel for 3-5 minutes prior to rinsing with warm water	DB, PC, RCT Patients aged between 15 to 59 years old with dandruff for periods between 1 month to 25 years	N=43 4 weeks	Primary: Clinical response, global evaluation Secondary: Adverse events	Primary: After 4 weeks of therapy, the response rate of patients treated with ketoconazole was greater than that of patients receiving placebo (88% vs. 23%, respectively; P≤0.001). Based on global evaluation by the patients, ketoconazole was given a higher score than placebo (88% vs. 32%, respectively; P≤0.001). Secondary: Adverse events were mostly cosmetic in nature. One patient who received placebo reported hair loss, and one patient treated with ketoconazole reported dry hair.
Elewski et al.[77] (2006)	PC, PRO, RCT	N=459	Primary: Successful	Primary: At day 28, successful treatment was reported in more patients treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ketoconazole 2% gel applied QD vs. gel vehicle applied QD	Patients aged 13 to 91 years old with moderate to severe seborrheic dermatitis (baseline signs and symptoms scored greater than 2 for erythema and scaling and greater than 1 for pruritus; investigator's global assessment score of 3 or greater)	14 days	treatment at day 28 Secondary: Change from baseline in signs and symptoms scores for erythema, scaling, and pruritus at day 14, adverse events	with ketoconazole compared to placebo (27.2% v 13.9%, respectively; P=0.0005). With the intent-to-treat analysis, ketoconazole treatment shower greater efficacy compared to placebo (P=0.0014). Secondary: Scaling was reduced by ketoconazole as compared to placebo (-1.55 vs. -1.31, respectively; P=0.0022). Mean overall symptom severity was reduced by ketoconazole and placebo (53% vs. 39%, respectively). With the intent-to-treat analysis, ketoconazole treatment was associated with a lower overall mean score compared to placebo at day 7 (2.92 vs. 3.32, respectively; P=0.048) and at day 28 (2.76 vs. 3.56, respectively; P<0.001). Medication-induced adverse events were reported by 6.6% and 7.4% of patients treated with ketoconazole and placebo, respectively. Common adverse events reported were application site burning (2.6%), application erythema (1.5%), and application-site reaction (1.1%) regardless of study group.
Carr et al.[78] (1987) Ketoconazole 2% shampoo wash hair QD for 4 weeks, then wash hair QD with Johnson's Baby Shampoo for 4 weeks, then wash hair QD with shampoo vehicle for 4 weeks vs. Shampoo vehicle wash hair QD for 4	DB, PC, RCT, XO Patients aged 25 to 65 years old with seborrheic dermatitis on the scalp	N=20 12 weeks	Primary: Degree of scalp scaling (ranging from 0=no scaling to 3=severe), patient assessment of scalp itching and scaling (ranging from none to worse ever)	Primary: Seventy-four percent of patients treated with ketoconazole 2% shampoo experienced a statistically significant improvement in clinical scores characterizing the degree of scalp scaling compared to patients receiving the placebo shampoo (P<0.01). Patients treated with ketoconazole 2% shampoo experienced a statistically 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, then wash with Johnson's Baby Shampoo for 4 weeks, then wash hair with ketoconazole 2% QD for 4 weeks				
Piérard-Franchimont et al.[79] (2001) Ketoconazole 1% shampoo wash hair twice weekly vs. ketoconazole 2% shampoo wash hair twice weekly	OL, PG, RCT Patients aged 20 to 69 years old with severe dandruff and seborrheic dermatitis	N=66 4 weeks	Primary: Squamometry *Malassezia* spp. counts, clinical assessment Secondary: Adverse events, relapse rate	Primary: After 2 and 4 weeks of treatment, ketoconazole 2% was more effective than ketoconazole 1% relative to decreasing flakiness and Malassezia spp. counts (P<0.001). On week 2, 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, P=0.001, respectively). On 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%.
Pierard-Franchimont et al.[49] (2002) Ketoconazole 2% shampoo twice weekly for 4 weeks vs.	RCT, OL, MC, PG 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; total dandruff severity score (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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
zinc pyrithione 1% shampoo at least twice weekly and when hair was shampooed for 4 weeks				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) and at the end of the follow-up period (P<0.04).
Onychomycosis				
Gupta et al.[50] (2000) Ciclopirox nail lacquer 8% topical solution applied to affected fingernail(s) and toenail(s) QD vs. topical solution vehicle applied to affected fingernail(s) and toenail(s) QD Both study A and study B participants received either ciclopirox nail lacquer 8% topical solution or vehicle given QD	2 DB, MC, PC, PG Patients aged 18 to 70 years old with mild to moderate toenail onychomycosis caused by dermatophytes	N=560 48 weeks	Primary: Mycological cure rate, treatment success, treatment cure, negative culture Secondary: Adverse effects	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; 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 statistically 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 statistically significant difference between ciclopirox and the vehicle in terms treatment cure (5.5% vs. 0.9%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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), P values not reported. 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), P values not reported.
Gupta et al.[50] (2000) Ciclopirox nail lacquer topical solution therapies vs. topical solution vehicle therapies	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 6 months 13 trials	Primary: Mycological cure, clinical cure, clinical response for ciclopirox therapies Secondary: Adverse effects	Primary: Mycological cure rates ranged from 46.7% to 85.7%, clinical cure ranged from 0% to 56.9%, and clinical response ranged from 36.7% to 86% when ciclopirox was used according to dosing regimens ranging from once daily 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 once-daily regimens. P values not reported in the MA. Average relapse rate was 20.7% at up to 6 months of treatment. P values not reported in the MA. Secondary: Minimal local side effects were associated with ciclopirox therapy. Reported side effects included nail changes, burning, stinging, erythema, pain, and skin reactions. P values not reported in the MA.
Brenner et al.[48] (2007)	OL, MC Diabetic patients with	N=49 48 weeks	Primary: Clinical improvement as	Primary: After 48 weeks of treatment, 63.4% of patients experienced clinical improvement, success, or cure with ciclopirox.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ciclopirox 8% nail lacquer topical solution applied once daily	distal subungual onychomycosis		determined by involved area, severity, subungual hyperkeratosis, and signs/symptoms (color, surface, thickness of target nail)	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.
Tinea Infections				
Wu et al.[80] (1991) Ciclopirox 1% cream applied to affected area(s) 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 (N=42) 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 (N=33) 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.
Kagawa et al.[81] (1989) Terbinafine 1% cream applied to affected area(s) BID	MC Patients with tinea pedis, tinea corporis, tinea cruris, interdigital and intertriginous candidiasis and pityriasis	N=614 4 weeks for tinea pedis; 2 weeks for other tinea infections	Primary: Mycological efficacy, improvement of clinical signs and symptoms (e.g., erythema, scaling,	Primary: Mycological efficacy was demonstrated in 74% of 218 patients treated for tinea pedis and 93% of 85 patients treated for Candida intertrigo. Approximately 78% to 94% of patients found the treatment acceptable. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			itching, papule formations, vesiculation, erosion, maceration) Secondary Adverse effects	Adverse reactions, such as acute irritant contact dermatitis and pruritus, were reported in 1% of patients treated with terbinafine. These reactions were reversible upon discontinuing treatment and initiating corticosteroid or imidazole treatment.
Reyes et al.[82] (1997) Butenafine 1% cream in vehicle applied to tinea pedis lesions QD vs. cream vehicle applied to tinea pedis lesions QD	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, effective treatment Secondary: Adverse effects	Primary: Patients who received butenafine were more likely to experience mycological cure at 4 weeks compared to the vehicle (91% vs. 63%, respectively; P<0.01). Mycological cure persisted in patients receiving butenafine 4 weeks after the end of the 4-week treatment period compared to the vehicle (83% vs. 38%, respectively; P<0.001). According to the investigator global response, patients receiving butenafine had significantly better clinical response to compared to the vehicle at 4 (P=0.03) and 8 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 the vehicle (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 the vehicle at 4 (58% vs. 31%, respectively; P<0.01) and 8 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 (no P value reported).
Tschen et al.[83] (1997)	DB, PC, RCT	N=80	Primary: Mycological cure,	Primary: Patients who received butenafine were more likely to experience

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Butenafine 1% cream applied to tinea pedis lesions QD vs. cream vehicle applied to tinea pedis lesions QD	Patients with interdigital tinea pedis with a minimum erythema score of 2 and a minimum score of 2 for either pruritus and scaling	4 weeks	investigator global assessment of clinical response, patient's assessment of change, effective treatment Secondary: Safety, tolerability	mycological cure at 4 weeks compared to the vehicle (88% vs. 33%). According to the investigator global response, patients receiving butenafine had significantly better clinical response as compared with those treated with the vehicle at 4 weeks (P<0.01) and at 8 weeks (P=0.001). Effective clinical response persisted in patients receiving butenafine compared to the vehicle at 8weeks (clinical response at 4 weeks was 68% vs. 40%, respectively [P<0.01]; at 8 weeks was 78% vs. 35% respectively [P<0.001]). 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 the vehicle at 4 weeks (P=0.003) and 8 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 the vehicle at 2 weeks (55% vs. 23%, respectively; P=0.001) and 8 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 the vehicle experienced burning, itching, stinging, a red streak, and/or a high serum lactate dehydrogenase concentration.
Aly et al.[84] (2003) Ciclopirox 0.77% gel applied to affected area(s) of skin BID vs.	2 DB, MC, RCT Patients aged 16 to 80 years old with clinically diagnosed, stable or exacerbating interdigital tinea pedis with or without plantar involvement with positive culture and	N=317 28 days	Primary: Treatment success (mycological and clinical cure) Secondary: Global clinical response, signs and symptoms severity scores,	Primary: At the end of the study, 60% and 6% of patients treated with ciclopirox and vehicle, respectively, achieved treatment success, >75% clinical improvement (P=0.05). This statistically significant difference in treatment success between ciclopirox and vehicle 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
gel vehicle applied to affected area(s) of skin BID	potassium hydroxide test		mycological evaluation, mycological cure, treatment cure	ciclopirox and vehicle, respectively, had complete clinical cure. This statistically significant difference in clinical cure between ciclopirox and vehicle 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 vehicle, respectively, had either cleared or excellent improvement relative to the infection (P=0.05). At 2 weeks post treatment, 85% and 16% of patients treated with ciclopirox and vehicle, respectively, were mycologically cured (P=0.05). At the end of the treatment, 46% and 24% of patients treated with ciclopirox and vehicle, respectively, described treatment as cosmetically acceptable.
Mandy et al.[85] (1974) Miconazole 2% cream applied to affected area(s) of skin sparingly BID vs. cream vehicle applied to affected area(s) of skin sparingly BID	DB, RCT Male patients between 17 and 39 years of age with confirmed dermatophyte infections (primarily tinea cruris, but inclusive of tinea corporis and tinea pedis)	N=62 4 weeks	Primary: Clinical evaluation, symptomatic evaluation Secondary: Adverse events	Primary: After 4 weeks of therapy, 93.3% of patients treated with miconazole and 18.8% of patients receiving the placebo cream experienced resolution of infection; P values not reported. After 4 weeks of therapy, 6.7% of patients treated with miconazole tested positive on the potassium hydroxide test and 10% of patients tested positive upon culturing. After 4 weeks of therapy, 66% of patients receiving placebo tested positive on the potassium hydroxide test and 72% of patients tested positive upon culturing. Secondary: No adverse events were reported.
Jordon at el.[86] (1990) Naftifine 1% cream applied to affected area(s) of skin QD	DB, RCT Patients aged 14 to 67 years old with confirmed tinea cruris or tinea corporis	N=70 4 weeks	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: After 2 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 statistically significant trend favoring naftifine persisted throughout the treatment period (86% vs. 30%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. cream vehicle applied to affected area(s) of skin QD				respectively; P<0.001) and 2 weeks post treatment (66% vs. 26%, respectively; P=0.002). Secondary: Two patients treated with vehicle reported adverse effects including severe edema and erythema. No side effects were reported by patients treated with naftifine.
Van Esso et al.[87] (1995) Sertaconazole 2% cream applied to affected area(s) on skin QD vs. cream vehicle applied to affected area(s) on skin QD	MC, OL Patients aged 2 to 16 years old with either tinea corporis, tinea cruris, or tinea pedis (primarily tinea corporis)	N=16 2 weeks	Primary: Symptoms (erythema, desquamation, vesicles, pruritus), clinical cure Secondary: Adverse effects	Primary: The number of patients experiencing symptoms of tinea infections decreased throughout the treatment duration of 2 weeks; exact percentages were not provided. All of the patients treated with sertaconazole achieved clinical cure after 4 weeks since start of treatment; 31% achieved cure at week 1 and 75% achieved cure at week 2. Secondary: No local or systemic adverse effects were observed.
Villars et al.[88] (1989) Terbinafine 1% cream applied to affected area(s) as directed vs. cream vehicle applied to affected area(s) as directed	MA Patients with tinea infections (i.e., tinea corporis, tinea pedis, cutaneous candidiasis, onychomycosis, pityriasis versicolor)	N=1,258 Duration not reported 27 trials	Primary: Complete cure, mycological cure, clinical signs and symptoms for terbinafine 1% cream therapies Secondary: Adverse effects for terbinafine 1% cream therapies	Primary: In the topical treatment of dermatomycoses, terbinafine demonstrated clinical efficacy between 70% and 90%; relative to tinea versicolor, topical terbinafine showed a cure rate of 70% to 80%. No P values reported. Secondary: In 2.2% of patients receiving topical terbinafine 1% cream experienced adverse effects such as burning, itching, and redness of the site of application.
Singal et al.[122] (2005) Butenafine 1%	RCT, DB Patients over 14 years of age with localized tinea	N=80 8 weeks	Primary: Clinical and mycological cure	Primary: The clinical assessment score, clinical cure rates, and mycological cure rates were similar for the butenafine and clotrimazole treatment groups at 4 and 8 weeks of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cream applied once daily for 2 weeks vs. clotrimazole 1% cream applied twice daily for 4 weeks	cruris and localized tinea corporis			In the butenafine group, relapse was not observed in any patient, while two patients in the clotrimazole group became KOH-positive again at 8 weeks and one of them also had evidence of clinical relapse.
Kamalam et al.[89] (1980) Clotrimazole (dosing regimen not reported) vs. econazole (dosing regimen not reported)	DB, OS Patients aged 45 days to 36 years old with confirmed tinea infections	N=45 3 to 60 days	Primary: Clinical cure, microscopically negative results Secondary: Adverse events	Primary: At 6 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: 5-29 days) and microscopically negative results were seen in 1 to 2 weeks. At 6 weeks post treatment, all cases were cured. For clotrimazole-treated patients, clinical cure was observed in approximately 16.5 days (range: 3-44 days) and microscopically negative results were seen in 1 to 6 weeks. At 6 weeks post treatment, there was 1 case not cured. Secondary: No adverse effects were reported. There was 1 report of a recurrence after 2 weeks of stopping therapy.
Clayton et al.[119] (1973) Clotrimazole 1% cream applied to affected area(s) of skin BID vs.	DB, AC, RCT Patients aged 13 to 63 years old with either confirmed tinea corporis, tinea pityriasis, erythrasma, or *Candida* infections	N=103 4 weeks	Primary: Clinical cure, mycological cure	Primary: Relative to patients with confirmed tinea corporis, there was no statistically significant difference in efficacy in patients treated with clotrimazole or Whitfield's Ointment. Relative to patients with confirmed tinea pityriasis, there was no statistically significant difference in efficacy in patients treated with clotrimazole or Whitfield's ointment. Relative to patients with confirmed erythrasma, there was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nystatin 100,000 U/g ointment applied to affected area(s) of skin BID vs. Whitfield's Ointment® (3% salicylic acid, 6% benzoic acid) applied to affected area(s) of skin BID				statistically significant difference in efficacy in patients treated with clotrimazole or Whitfield's ointment. Relative to patients with Candida infections, there was no statistically significant difference in efficacy in patients treated with clotrimazole or nystatin.
Lassus et al.[90] (1983) Clotrimazole 1% cream applied to affected area(s) on skin BID vs. sulconazole 1% cream applied to affected area(s) on skin BID	DB, PG Patients with microbiologically confirmed dermatomycosis (primarily tinea pedis)	N=40 4 weeks	Primary: Clinical signs and symptoms (erythema, itching, scaling, maceration, fissuring, vesiculation), overall clinical improvement, cosmetic acceptability Secondary: Adverse events	Primary: Patients with signs and symptoms of scaling and erythema responded better to sulconazole than clotrimazole at weeks 2 ($P<0.05$), 3 ($P<0.01$), and 4 ($P<0.05$) of treatment. There was no statistically significant difference in the other signs and symptoms regardless of therapy. Overall clinical improvement at weeks 2, 3, and 4 was greater with sulconazole (94.8%, 100%, 100%, respectively) compared to clotrimazole (73.7%, 78.9%, 83.4%, respectively). Secondary: One patient from each treatment group experienced an allergic reaction during the first week of therapy.
Rajan et al.[91] (1983) Clotrimazole 1% cream applied to affected area(s) of skin BID	DB, PG, RCT Patients (mean age 41 years) with clinically proven cutaneous candidiasis (interdigital or intertriginous candidiasis or perlèche)	N=41 3 weeks	Primary: Efficacy parameters (fungal culture/ microscopic preparation, physician's assessment of	Primary: At week 2, 62.5% and 85.7% of patients treated with sulconazole and clotrimazole, respectively, had negative fungal cultures. At week 3, 62.5% and 33.3% of patients treated with sulconazole and clotrimazole, respectively, had negative fungal cultures. At this time, 7 and 3 patients treated with sulconazole and clotrimazole, respectively, failed treatment. Although both treatment groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. sulconazole 1% cream applied to affected area(s) of skin QAM and cream vehicle applied to affected area(s) QHS			overall improvement) Secondary: Adverse events	experienced improvement in certain symptoms of infection, there was no statistically significant difference between the two treatment groups (erythema, P=0.45; scaling, P=0.69; itching, P=0.88). At week 3, 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.
Tham et al.[92] (1987) Clotrimazole 1% solution applied to affected area(s) on skin BID vs. sulconazole 1% solution applied to affected area(s) on skin QAM and lotion vehicle applied to affected area(s) QHS	Study design not reported Patients aged 14 to 62 years old with microscopically confirmed pityriasis versicolor	N=84 3 weeks	Primary: Clinical assessment (itching, scaling, erythema), investigator assessment, patient assessment, negative microscopy Secondary: Adverse effects	Primary: Reduced rates of itching, scaling, and erythema did not differ between treatment groups at weeks 2 and 3 (P>0.05). Potassium hydroxide results did not differ (P>0.05) between patients treated with sulconazole or clotrimazole at weeks 2 (67% vs. 72%, respectively) and 3 (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 6 weeks post treatment, negative microscopy was maintained by 79% and 92% of patients taking sulconazole and clotrimazole, respectively. This difference was not statistically 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.[93] (1999) Clotrimazole 1%	DB, MC, PG, PRO, RCT Patients with clinically	N=104 4 weeks	Primary: Mycological cure Secondary:	Primary: After 1 week of treatment, 84.6% and 55.8% of patients treated with terbinafine and clotrimazole, respectively, were culture negative (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cream applied to affected area(s) of skin BID for 4 weeks vs. terbinafine 1% cream applied to affected area(s) of skin BID (for 1 week), then cream vehicle applied to affected area(s) BID (for 3 weeks)	diagnosed and mycologically confirmed interdigital tinea pedis		Effective treatment, complete cure, perceived efficacy, relapse rate, adverse events	There was no statistically significant difference between study groups with regards to mycological cure at weeks 4, 8, 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 clotrimazole, respectively. Most commonly reported adverse effects included burning, hypersensitivity, stinging, and exacerbation of pruritus.
Wortzel et al.[120] (1982) Betamethasone dipropionate applied to affected area(s) of skin QAM and QPM vs. clotrimazole applied to affected area(s) of skin QAM and QPM vs. betamethasone dipropionate/	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 2 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 2 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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clotrimazole (strength unspecified) combination applied to affected area(s) of skin QAM and QPM				One patient treated with betamethasone reported severe burning and tingling.
Katz et al.[121] (1984) Betamethasone dipropionate 0.05% cream applied to affected area(s) of skin BID vs. clotrimazole 1% cream applied to affected area(s) of skin BID vs. betamethasone dipropionate 0.05%/clotrimazole 1% combination cream applied to affected area(s) of skin BID	DB, MC, PG, RCT Patients with a microscopically confirmed clinical diagnosis of moderate to severe tinea cruris or tinea corporis	N=331 2 weeks	Primary: Total signs and symptoms severity score/clinical response ratings, mycologic findings Secondary: Adverse events	Primary: Patients treated with clotrimazole had higher total signs and symptoms scores at baseline (P<0.05). At days 7, 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 7 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 combination product had better total signs and symptoms scores compared to patients treated with betamethasone dipropionate (P<0.05). According to mycologic responses (e.g., negative cultures), the combination product and clotrimazole were more effective than betamethasone dipropionate (63% vs. 51% vs. 32%, respectively; P<0.05). Secondary: Adverse events were not common and were of minimal clinical significance. Two patients treated with the combination product reported mild macular papular eruption and/or mild paresthesia. Eight patients treated with betamethasone dipropionate reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				paresthesia and/or severe pain followed by a papular eruption. Three patients treated with clotrimazole reported paresthesia.
Petres et al.[94] (1984) Econazole 1% cream applied to affected area(s) of skin BID vs. sulconazole 1% cream applied to affected area(s) of skin BID	DB, PG, RCT Patients with culture and microscopy confirmed dermatophytoses (primarily tinea pedis)	N=38 4 weeks	Primary: Microbiological cure, clinical cure (itching, erythema, scaling, fissuring, maceration, vesiculation, pustulation), overall clinical improvement, relapse, cosmetic acceptability Secondary: Adverse effects	Primary: By week 2, every patient achieved microbiological cure with the exception of one patient treated with sulconazole. By week 4, all patients achieved microbiological cure. Both treatment groups responded well to treatment leading to significant reductions in itching, scaling, and erythema. However, by week 4, 2 and 3 patients treated with sulconazole and econazole, respectively, were still mildly symptomatic. There was no statistically significant difference between treatment groups in terms of overall clinical improvement. The diagnosis of tinea pedis in 80% of the study participants did not influence the study results. At week 10, all patients treated with sulconazole remained symptom- and microbiologically-free of infection, whereas 3 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 statistically 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.
Grigoriu et al.[95] (1983) Econazole 1% cream applied to affected area(s) of skin BID vs.	DB, RCT Patients (average age was 30 years old) with confirmed fungal skin infection or erythrasma	N=61 average of 38 to 40 days	Primary: Clinical response, mycological response, combined clinical and mycological cure	Primary: There was one case of non-antifungal infection in each study group. 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tioconazole 1% cream applied to affected area(s) of skin BID				There was no statistically 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.
Bonifaz et al.[96] (2000) Ketoconazole 2% cream applied to affected area(s) QD (for 14 days) vs. terbinafine 1% emulsion gel applied to affected area(s) of skin QD (for 7 days)	OL, PG, PRO, RCT Patients aged 12 to 79 years old with clinically and mycologically 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 statistically 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 (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 3 patients treated with ketoconazole reported dermatitis-like side effects. Terbinafine was better tolerated than ketoconazole (P=0.003)
Tanenbaum et al.[97] (1984) Miconazole 2% cream applied to affected area(s) of skin 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: Patients treated with miconazole reported stinging, itching, dermatitis, or irritation. Patients treated with sulconazole reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sulconazole 1% cream applied to affected area(s) of skin BID				itching, stinging/burning, dryness/scaling, and fissure/cracking.
Tanenbaum et al.[98] (1982) Miconazole 2% cream applied to affected area(s) BID vs. sulconazole 1% cream applied to affected area(s) BID	DB, PG, RCT Patients aged 18 to 65 years old with cutaneous dermatomycosis (tinea pedis and tinea cruris/corporis)	N=96 3 weeks (tinea cruris/ corporis); 4 weeks (tinea pedis)	Primary: Mycological cure, clinical cure, relapse rate Secondary: Adverse events	Primary: At the end of 4 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 3 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 3 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.
Vander Ploeg et al.[99] (1984) Miconazole 2% cream applied to affected area(s) on skin BID vs. tioconazole 1%	Study design not reported Patients aged 18 to 72 years old with mycologically proven infection with one of the following fungi: *Trichophyton* sp, *Microsporum* sp, *Epidermophyton* sp, *Candida* sp, and	N=77 4 weeks	Primary: Mycological cure, clinical cure, relapse rates Secondary: Adverse effects	Primary: After 4 weeks of treatment, 91.4% and 85.3% of patients taking tioconazole and miconazole, respectively, achieved both clinical and mycological cures. After 4 weeks from the end of the treatment period, 93.5% and 89.3% of patients taking tioconazole and miconazole remained cured. There was no statistically significant difference between clinical or mycological cure rates between tioconazole and miconazole therapies.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cream applied to affected area(s) on skin BID	*Pityrosporum orbiculare*			Secondary: Four patients treated with tioconazole reported side effects (e.g., burning) and one patient treated with miconazole reported side effects (e.g., papular rash on the chest)
Fredriksson et al.[100] (1983) Miconazole 2% cream applied to affected area(s) BID vs. tioconazole 1% cream applied to affected area(s) BID	SB, PG Patients with microscopically and culture-confirmed fungal skin infections	N=60 14 days (tinea pityriasis); 28 days (dermatophyte and yeast infections)	Primary: Clinical cure, mycological cure Secondary: Adverse events	Primary: At the end of the treatment, 77% and 63% of patients treated with tioconazole and miconazole, respectively, were both clinically and mycologically cured. Relative to the most common infection (by Trichophyton rubrum), tioconazole and miconazole cured 80% and 38%, respectively. The difference was not statistically significant. Approximately 6 weeks later, patients treated with tioconazole and miconazole remained infection-free at rates of 87% and 95%, respectively. Secondary: No adverse events were recorded during the study.
Ramelet et al.[101] (1987) Oxiconazole cream applied to affected area(s) of skin QAM and placebo applied to affected area(s) of skin QPM vs. oxiconazole cream applied to affected area(s) of skin QAM and QPM	DB, MC, RCT Patients aged 8 to 80 years old with one or more clinically and mycologically confirmed dermatomycoses (tinea pedis, tinea cruris, tinea corporis) 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 once daily and twice daily, respectively, achieved cure. The cure rates were 92% and 93.3% for patients treated with oxiconazole once daily and twice daily, respectively; no statistically 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.
Bogaert et al.[102] (1986)	2 DB, MC, PG, RCT Patients with tinea	N=229 28 weeks	Primary: Clinical evaluation (scores ranging	Primary: In study A, patients treated with ciclopirox demonstrated statistically significant improvement in clinical and mycological cure rate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ciclopirox 1% cream applied to affected area(s) on skin BID vs. clotrimazole 1% cream applied to affected area(s) on skin BID vs. cream vehicle applied to affected area(s) on skin BID In study A, patients received either ciclopirox 1% cream BID or vehicle BID. In study B, patients received either ciclopirox 1 % cream BID or clotrimazole 1 % cream BID.	corporis or tinea cruris		from 1=none to 4-severe), assessment of treatment response Secondary: Safety, tolerance	compared to the patients receiving the vehicle at 6 weeks (61% vs. 15%; P<0.001). In study B, there was no statistically significant difference in clinical and mycological cure rate between treatment groups receiving ciclopirox or clotrimazole creams (64% vs. 69%). Secondary: In study A, no side effects associated with ciclopirox were reported; one patient receiving the vehicle reported transient burning. In study B, one patient receiving ciclopirox reported pruritus and one patient receiving clotrimazole reported burning, pruritus, and worsening of lesions.
Fuerst et al.[103] (1980) Tolnaftate 1% cream applied to affected area(s) of skin QAM and QPM	DB, PG, PRO Male patients with symptomatic and clinically evident tinea pedis	N=103 4 weeks	Primary: Clinical cure, mycological cure	Primary: At 2 weeks, 34.2%, 28.1%, and 15.2% of patients treated with undecylenic acid, tolnaftate, and placebo, respectively had negative potassium hydroxide test results. At 4 weeks, 65.8%, 46.9%, and 30.3% of patients treated with undecylenic acid, tolnaftate, and placebo, respectively had negative potassium hydroxide test results. At this time, 84.2%, 80.7%, and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. undecylenic acid 5% ointment applied to affected area(s) of skin QAM and QPM vs. vehicle (dosage form not reported) applied to affected area(s) of skin QAM and QPM				26.9% of patients treated with these agents, respectively, achieved negative cultures. At 6 weeks, 65.6%, 59.2%, and 41.9% of patients treated with undecylenic acid, tolnaftate, and placebo, respectively, had negative potassium hydroxide test results. At this time, 68.7%, 66.6%, and 25.0% of patients treated with these agents, respectively, achieved negative cultures. Relative to negative potassium hydroxide results, undecylenic was more efficacious than placebo at weeks 2 (P=0.05), 4 (P<0.05), and 6 (P=0.05). Tolnaftate was not more efficacious than placebo at any point (P>0.05). Both tolnaftate and undecylenic acid were not significantly different from each other in terms of negative cultures (P>0.05). Tolnaftate and undecylenic acid were not statistically different from each other in terms of negative cultures or potassium hydroxide tests (P>0.05). Patients treated with undecylenic acid and tolnaftate improved more rapidly compared to placebo in regards to symptoms of erythema, scaling, fissuring, vesiculation, and itching/burning.
Tschen et al.[105] (1979) Tolnaftate cream applied to affected area(s) of skin on feet BID vs. undecylenic acid ointment applied to affected area(s) of skin on feet BID vs.	DB, PC, PG, RCT Patients aged 18 to 62 years old with clinically and mycologically proven tinea pedis	N=90 4 weeks	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: At four weeks of treatment, patients treated with undecylenic acid had a greater improvement compared to placebo (P<0.002). At four weeks of treatment, patients treated with tolnaftate had a greater improvement compared to placebo (P<0.05). There was no statistically significant difference relative to efficacy between undecylenic acid and tolnaftate. Secondary: No adverse effects noted in either treatment group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ointment vehicle applied to affected area(s) of skin on feet BID				
Gupta et al.[106] (2005) Ciclopirox 0.77% gel applied to affected area(s) QD vs. ciclopirox 0.77% gel applied to affected area(s) BID vs. gel vehicle applied to affected area(s) BID	DB, PC, PRO, RCT Patients aged 18 to 70 years old 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, complete cure; clinical evaluation scores range from 1 excellent to 7 worse Secondary: Adverse effects	Primary: There was no statistically significant difference in improved evaluation scores between once daily or twice daily applications of ciclopirox. However, both once and twice daily ciclopirox treatment groups showed significant improvement in evaluation scores compared to the vehicle at week 8 (2.06 vs. 6.17, P=0.0003 and 2.41 vs. 6.17, P=0.0036, respectively). There was no statistically significant difference in improved mycological cure rates between once daily or twice daily applications of ciclopirox; P values not reported. However both once and twice daily ciclopirox treatment groups showed significant improvement in mycological cure rate compared to the vehicle at week 8 (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 the vehicle (50.0% vs. 12.5%, respectively, P=0.014). Other comparisons were not statistically significant. Secondary: The most common reported adverse effects were local site reactions of burning or itching. There was no statistically significant difference in the incidence of adverse effects between treatment groups.
Pariser et al.[107] (1994) Oxiconazole 1% lotion applied to affected area(s) BID	DB, MC, PC, PG, RCT Patients aged 12 to 82 years old with confirmed tinea pedis	N=332 6 weeks	Primary: Mycological cure, clinical cure, overall cure (i.e., combined mycological and clinical cure),	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 and placebo, respectively, experienced good to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. lotion vehicle applied to affected area(s) of skin QAM, then oxiconazole 1% lotion applied to affected area(s) QPM vs. lotion vehicle applied to affected area(s) BID			global response score Secondary: Adverse events	excellent improvement in clinical signs and symptoms of tinea pedis as well as global response. A statistically 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.
Tanenbaum et al.[108] (1989) Clotrimazole cream applied to affected area(s) of skin BID vs. sulconazole 1% cream applied to affected area(s) of skin QAM, then cream vehicle applied to affected area(s) of skin QPM vs. sulconazole 1% cream applied to	2 DB, PG, RCT Male patient with tinea cruris/tinea corporis	N=117 3 weeks	Primary: Microbiological cure, culture conversion, overall clinical evaluation Secondary: Adverse events	Primary: In study A, there was no statistically significant difference between treatment groups throughout the study relative to microbiological cure or culture conversion. In study B, there was a statistically significant improvement in culture conversion and microbiological cure for patients treated with sulconazole compared to vehicle at week 2 (P=0.0001) and week 3 (P=0.0001). By week 3, 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 statistically significant improvement in overall clinical evaluation compared to placebo (P=0.0001). Secondary: In study A, 4 patients receiving clotrimazole cream reported moderate to severe side effects, including erosive primary irritation, fissuring, and erythema. In study B, 6 patients receiving the vehicle

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
affected area(s) of skin BID vs. cream vehicle applied to affected area(s) of skin BID In study A, participants received either sulconazole applied QAM with cream vehicle QPM or clotrimazole applied BID. In study B, participants received either sulconazole applied BID or a cream vehicle applied BID.				experienced primary irritant reactions (erosions, burning).
Sivayathorn et al.[109] (1978) Clotrimazole 1% cream applied to affected area(s) of skin TID vs. miconazole 2% cream	DB, RCT Patients aged 2 to 72 years old 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 statistically significant difference between clotrimazole, miconazole, and tolnaftate treatment groups (P>0.05). Clotrimazole, miconazole, and tolnaftate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied to affected area(s) of skin TID vs. tolnaftate 2% cream applied to affected area(s) of skin TID vs. Whitfield's Ointment® (3% salicylic acid, 6% benzoic acid) applied to affected area(s) of skin TID				therapies were more efficacious compared to Whitfield's Ointment® (P<0.05). Secondary: There were no reported adverse reactions.
Aly et al.[110] (1989) Ciclopirox 1% cream applied to affected area(s) on skin BID vs. ciclopirox 1% lotion applied to affected area(s) on skin BID vs. cream vehicle applied to affected area(s) on skin BID	DB, MC, PG, RCT Patients with clinically and mycologically confirmed plantar, interdigital, or vesicular tinea pedis	N=134 28 days	Primary: Clinical cure, mycological cure Secondary: Adverse events	Primary: On day 29, patients treated with ciclopirox lotion experienced greater mycological response compared to patients receiving the placebo (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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. lotion vehicle applied to affected area(s) on skin BID				
Hart et al.[111] (1999) Allylamines (specific agents and dosing not reported) vs. azoles (specific agents and dosing not reported) vs. ciclopirox (specific agent and dosing not reported) vs. tolnaftate (specific agent and dosing not reported) vs. undecenoic acid† (specific agent and dosing not reported) vs.	MA (RCT, AC or PC) Patients with culture- and/or microscopy-confirmed superficial fungal infection of the skin and nails of the feet	Sample size not reported 72 trials	Primary: Relative risk of failure to cure for topical antifungal agents	Primary: According to a meta-analysis of 17 trials comparing topical azoles to vehicle, the pooled relative risk of failure to cure was 0.54 (95% CI, 0.42 to 0.68). According to a meta-analysis of 12 trials comparing allylamines to vehicle, the pooled relative risk of failure to cure was 0.30 (95% CI, 0.24 to 0.38). According to a meta-analysis of 12 trials comparing azoles (i.e., bifonazole*, clotrimazole, miconazole) to allylamines (i.e., naftifine, terbinafine) given QD or BID for ≥4 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 statistically significance difference in (1) the clinical efficacy of the azoles and duration of use and (2) relative risk estimates reported by English and foreign language papers. No difference was detected between individual azoles and allylamines. According to a meta-analysis of 3 trials comparing tolnaftate to vehicle, the pooled risk for failure to cure was 0.46 (95% confidence interval 0.17 to 1.22). Data showed that tolnaftate was not as effective as haloprogin or clotrimazole. According to a meta-analysis of 4 trials comparing undecenoic acid to vehicle or active control, the pooled risk for failure to cure was 0.28 (95% confidence interval 0.11 to 0.74). In nail trials, ciclopirox was shown to be statistically better than vehicle (0.14, 0.06 to 0.32) and better than, though not significantly, clotrimazole (0.89, 0.72 to 1.10). Study data was limited.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tea tree oil (specific agent and dosing not reported) vs. placebo vehicles (specific dosing not reported)				Relative to trials of fungal nail infections, a larger trial showed clotrimazole solution and tea tree oil both achieving a cure rate of 10% after 6 months.
Crawford et al.[112] (2006) Allylamines (specific agents and dosing not reported; includes amorolfine 0.5% cream*) vs. azoles (specific agents and dosing not reported; includes bifonazole 1% cream*, neticonazole cream*) vs. griseofulvin topical agent* (specific agent and dosing not reported)	MA (all RCTs) Patients with mycologically diagnosed fungal infections of the skin and nails of the foot	Sample size not reported 72 trials	Primary: Pooled relative risks of failure to cure for topical antifungal agents	Primary: Among the placebo-controlled trials, the pooled relative risks of failure to cure for skin infections were as follows for the topical antifungal agents: allylamines 0.30 (95% CI 0.23 to 0.37), azoles 0.53 (95% CI 0.42 to 0.68), undecenoic acid 0.28 (0.11 to 0.74), and tolnaftate 0.46 (0.17 to 1.22). Relative to 11 meta-analysis trials comparing allylamines and azoles, the pooled relative risks of failure to cure for skin infections was 0.88 (0.78 to 0.99) in favor of allylamines; of note, there appears to be language bias in the reported results, where the 7 English language studies favored allylamines and the 4 foreign language studies reported no statistical difference.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. haloprogin* (specific agent and dosing not reported) vs. tea tree oil (specific agent and dosing not reported) vs. tolnaftate (specific agent and dosing not reported; includes tolciclate solution*) vs. undecenoic acid† (specific agent and dosing not reported) vs. placebo vehicles (specific dosing not reported)				
Other				
Concannon et al.[117] (2001) Miconazole 0.25% in zinc oxide/petrolatum	DB, PC, PG, RCT Patients aged 2 to 13 months with acute diaper dermatitis	N=188 7 days	Primary: Number of rash sites, mean total rash score Secondary:	Primary: On days 5 and 7, 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 7, patients treated with miconazole/zinc oxide/petrolatum

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
base applied to rash at each diaper change and after infant's bath vs. zinc oxide/petrolatum base applied to rash at each diaper change and after infant's bath			Adverse events	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 statistically significant difference between treatment groups in mean total rash scores favoring the miconazole/zinc oxide/petrolatum study group (0.78 vs. 1.65, respectively; P=0.031) on day 7. For patients with moderate diaper dermatitis at baseline, there was a statistically significant difference between treatment groups in mean total rash scores favoring the miconazole/zinc oxide/petrolatum study group on days 3 (P=0.006), 5 (P<0.001), and 7 (P<0.001). For patients with severe diaper dermatitis at baseline, there was no statistically 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 statistically significant difference between treatment groups in mean total rash scores favoring the miconazole/zinc oxide/petrolatum study group on days 3, 5, and 7 (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 or discontinuations were noted with either treatment groups
Spraker et al.[118] (2006) Miconazole 0.25% in zinc oxide/petrolatum ointment applied to rash at each diaper change and after infant's bath	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, 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. zinc oxide/petrolatum ointment applied to rash at each diaper change and after infant's bath				had a higher overall rate of cure compared to patients treated with zinc oxide/petrolatum (23% vs. 20%, respectively; P=0.005). From days 3 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). Secondary: There was no statistical difference in the percentage of patients with adverse events between the study groups (P=0.585).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily, QAM=every morning, QHS=at bedtime, QPM=every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single blinded, XO=crossover
*Agent not available in the United States
†Undecenoic acid= undecylenic acid.

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
In 1990, clotrimazole became the first product available over-the-counter (OTC) for the treatment of uncomplicated candidal vaginitis. 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 ($P<0.05$).[113] Gurwitz et al. evaluated the impact of switching from prescription to OTC vaginal antifungal products on utilization of health care services within a health maintenance organization.[114] There was a decrease in the number of physician visits for vaginitis (0.66 per 100 patients) during the one-year period after the OTC availability of vaginal products.[114]

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 Antifungals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Benzoic acid and salicylic acid	ointment	Bensal HP®	$$$-$$$$$	N/A
Butenafine	cream	Mentax®	$$-$$$	N/A
Butoconazole	vaginal cream	Gynazole-1®	$$$	N/A
Ciclopirox	cream, gel, shampoo, solution, suspension, kit	Loprox®*, Penlac®*	$$$$	$-$$$$
Clotrimazole‡	cream, solution, troche, vaginal cream, vaginal tablet	Clotrim Antifungal®*, Cruex®*, Desenex®*, Femcare®*, Gyne-Lotrimin®*, Lotrimin AF®*, Mycelex®*	$-$$$	$-$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Clotrimazole and betamethasone	cream, lotion	Lotrisone®*	$-$$$	$-$$
Econazole	cream	N/A	N/A	$
Ketoconazole	cream, gel, shampoo	Kuric®*, Xolegel®	$$-$$$$$	$
Ketoconazole and pyrithione zinc	kit	Xolegel Duo®	$$$$$	N/A
Miconazole‡	cream, vaginal cream, vaginal suppository	Baza Antifungal®*, Micatin®*, Micro-Guard®*, Monistat 7®*	$	$-$$
Miconazole and zinc oxide	ointment	Vusion®	$$$$	N/A
Naftifine	cream, gel	Naftin®	$$$-$$$$	N/A
Nystatin	cream, ointment, powder, vaginal tablet	Mycostatin®*	$-$$$	$-$$$
Nystatin and triamcinolone	cream, ointment	N/A	N/A	$
Oxiconazole	cream, lotion	Oxistat®	$$$	N/A
Sertaconazole	cream	Ertaczo®	$$$-$$$$	N/A
Sodium thiosulfate and salicylic acid	lotion	N/A	N/A	$
Sulconazole	cream, solution	Exelderm®	$-$$	N/A
Terbinafine‡	cream, spray	Lamisil®, Lamisil AT®*	$	$
Terconazole	vaginal cream, vaginal suppository	Terazol 3®*, Terazol 7®*, Zazole®*	$$-$$$	$$
Tioconazole‡	vaginal ointment	Vagistat-1®*	$	$
Tolnaftate‡	aerosol powder, cream	Tinactin®*	$	$

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
N/A=Not available

X. Conclusions

The skin and mucous membrane antifungal agents are effective treatments for a variety of fungal infections, including cutaneous candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, seborrheic dermatitis, onychomycosis and dermatophyte infections.

Guidelines for the treatment of candidal skin infections state that topical imidazoles and polyenes are effective treatment options.[7] Clinical studies have reported no significant differences in efficacy between clotrimazole cream and nystatin ointment, nystatin cream and nystatin/triamcinolone cream, or sulconazole cream and miconazole cream.[52-53,116]

Guidelines for the treatment of oropharyngeal candidiasis state that topical/oral imidazoles or oral polyenes are effective treatment options.[7] Initial episodes can be treated with clotrimazole troches or oral nystatin. In refractory or recurrent cases, oral and intravenous antifungal agents are recommended.[7] Two clinical trials reported that clotrimazole troches were associated with significantly greater improvement in both clinical and mycological response in oropharyngeal candidiasis compared to placebo.[54-55] The clotrimazole troche is the only skin and mucous membrane antifungal indicated for the treatment of oropharyngeal candidiasis.

Several guidelines on the management of vulvovaginal candidiasis (VVC) have been published. For the treatment of uncomplicated VVC, short-course topical formulations (i.e., single dose and regimens of 1-3 days) are effective.[7-8] Patients with complicated VVC require a longer duration of initial therapy (7-14 days of topical

therapy or 3 doses of oral fluconazole).[7-9] Prolonged maintenance therapy with oral fluconazole is the first-line treatment option for recurrent VVC; however, intermittent topical antifungals are also acceptable.[7-9] Guidelines do not give preference to one vaginal antifungal agent over another.[7-9] Numerous clinical trials have demonstrated similar efficacy among various topical imidazole antifungal agents.[56-72] However, studies have shown that the imidazoles are more effective than nystatin.[8,62,71]

Ciclopirox, ketoconazole, and ketoconazole/pyrithione zinc are the only topical antifungal agents indicated for the treatment of seborrheic dermatitis. Guidelines for the treatment of seborrheic dermatitis are limited; however, one organization recommends ketoconazole shampoo and topical imidazole creams to decrease fungal growth.[6] Based on limited published data, ciclopirox demonstrated significant improvements in clinical cure rates compared to placebo.[73-74,115,123] In addition, a low relapse rate was maintained by once-weekly shampooing or shampooing once every 2 weeks over a 12-week period.[123] Ketoconazole demonstrated significant improvements in clinical cure rates compared to placebo and zinc pyrithione.[49,75-78] There were no published head-to-head studies directly comparing ciclopirox and ketoconazole. There were also no published studies found evaluating the dual use of ketoconazole gel and pyrithione zinc shampoo.

Ciclopirox 8% nail lacquer solution is the only topical antifungal agent approved for the treatment of onychomycosis. Guidelines for the treatment of onychomycosis state that systemic therapy is almost always more successful than topical treatment.[7,10] In addition, while it is possible to achieve clinical and mycological cure with topical nail preparations, these cure rates do not compare favorably with those obtained with systemic drugs.[10] Treatment with ciclopirox has led to improvements in clinical and mycological cure rates in clinical trials.[48,50] Data from a meta-analysis demonstrated that mycological cure rates ranged from 46.7% to 85.7%, clinical cure ranged from 0% to 56.9%, and clinical response ranged from 36.7% to 86% when ciclopirox was used in various dosing regimens.[50]

There are no current treatment guidelines that specifically address the management of tinea infections. Numerous studies have demonstrated similar efficacy among the various topical antifungal agents.[89,91-95,97-102,108-109,119,122] Relatively few published studies have demonstrated greater efficacy with one agent over another.[90,96,104,109] Two studies found that clotrimazole/betamethasone was more effective than monotherapy with either clotrimazole or betamethasone.[120-121] However, there were no published studies directly comparing clotrimazole/betamethasone combination product to dual therapy with clotrimazole and betamethasone as separate formulations.

No published clinical trials were found in the medical literature evaluating the safety and efficacy of sodium thiosulfate/salicylic acid combination product. Two studies demonstrated greater clinical cure of diaper dermatitis in patients treated with miconazole/zinc oxide compared to treatment with zinc oxide alone.[117-118] However, there were no published studies directly comparing miconazole/zinc oxide ointment to dual therapy with miconazole and zinc oxide as separate formulations.

Therefore, all brand skin and mucous membrane antifungals within the class reviewed are comparable to each other and to the generics and OTC 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Scabicides and Pediculicides
AHFS Class 840412
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I. Overview

The skin and mucous membrane scabicides and pediculicides are used to treat scabies and pediculosis (head lice). Scabies is a transmissible skin infection caused by the mite *Sarcoptes scabiei.*[1] 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.[1] Pediculosis is also 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*).[2] Pediculosis is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[2]

The goal of therapy is to eradicate the parasite. Several topical agents are approved for the treatment of scabies and pediculosis. Crotamiton has scabicidal and antipruritic actions; however, the exact mechanism of action is unknown.[9,16] Lindane is a central nervous system stimulant which causes convulsions and death of the arthropod.[9,12] Malathion is an organophosphate agent which inhibits cholinesterase activity.[17] Permethrin disrupts the sodium channel current, which leads to delayed repolarization and paralysis of the arthropod.[9,14] Pyrethrins stimulate the central nervous system and block nerve impulse transmissions, which results in paralysis and death of the arthropod.[9,15] Piperonyl butoxide is usually added to pyrethrins to enhance the efficacy of the product. Although it does not have any direct parasiticidal activity, piperonyl butoxide decreases the metabolism of pyrethrins in arthropods.[9,15]

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. Crotamiton and malathion are not available in a generic formulation. Permethrin and piperonyl butoxide/pyrethrins are both available over-the-counter. This class was last reviewed in February 2007.

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)
Crotamiton	cream, lotion	Eurax®	Eurax®
Lindane	lotion, shampoo	N/A	none
Malathion	lotion	Ovide®	none
Permethrin‡	cream, liquid	Acticin®*, Elimite®*	permethrin
Piperonyl butoxide and pyrethrins‡	foam, liquid, shampoo	Rid®*	piperonyl butoxide and pyrethrins
Piperonyl butoxide, pyrethrins, and permethrin‡	kit	Rid®	Rid®

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
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)
British Association of Sexual Health and HIV: **United Kingdom National Guideline on the Management of Scabies Infestation**[7] **(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.
British Association of Sexual Health and HIV: **United Kingdom National Guideline on the Management of *Phthirus pubis* Infestation**[8] **(2007)**	• 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 3-7 days is advised. <u>Recommended regimens:</u> • Malathion 0.5%: Apply to dry hair and wash out after at least 2, 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.
Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines**[5] **(2006)**	<u>Pediculosis pubis (pubic lice infestation)</u> Recommended regimens: • Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes (OR) • Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. Alternative regimens: • Malathion 0.5% lotion applied for 8-12 hours and washed off (OR) • Ivermectin 250 mcg/kg orally repeated in 2 weeks. <u>Scabies</u> Recommended regimens: • Permethrin 5% cream applied to all areas of the body from the neck down and washed off after 8-14 hours (OR) • Ivermectin 200 mcg/kg orally, repeated in 2 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 8 hours.

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[9-17]

Generic Name(s)	Scabies	Head Lice	Head and Pubic Lice	Head, Body, and Pubic Lice
Crotamiton	✔			
Lindane*	✔		✔	
Malathion		✔		
Permethrin	✔	✔		
Piperonyl butoxide and pyrethrins				✔
Piperonyl butoxide, pyrethrins, and permethrin				✔

*Lindane should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications.

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[9-17]

Generic Name(s)	Peak Concentration (hours)	Absorption (%)	Half-Life (hours)
Crotamiton	No data	No data	No data
Lindane	6	10	18
Malathion	No data	<10	No data
Permethrin	No data	≤ 2	No data
piperonyl butoxide and pyrethrins	0.5	No data	No data
Piperonyl butoxide, pyrethrins, and permethrin	0.5	No data	No data

V. Drug Interactions

There are no significant drug interactions with the skin and mucous membrane scabicides and pediculicides.[9-17] However, 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.[12]

VI. Adverse Drug Events

Malathion is an organophosphate agent. Inadvertent transdermal absorption has occurred from agricultural use.[17] Acute toxicity was manifested by excessive cholinergic activity (i.e., increased sweating, salivary and gastric secretion, gastrointestinal and uterine motility, and bradycardia).[17] 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.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Scabicides and Pediculicides[9-17]

Adverse Events	Crotamiton	Lindane	Malathion	Permethrin	Piperonyl Butoxide, Pyrethrins	Piperonyl Butoxide, Pyrethrins, Permethrin
Central Nervous System						
Ataxia	-	✔	-	-	-	-
Dizziness	-	✔	-	-	-	-
Headache	-	✔	-	-	-	-
Pain	-	✔	-	-	-	-
Seizures	-	✔	-	-	-	-
Dermatological						
Alopecia	-	✔	-	-	-	-
Dermatitis	✔	✔	-	-	-	-
Erythema	-	-	-	1-10	-	-
Irritation of skin and scalp	✔	-	✔	-	✔	✔
Mild transient burning/stinging	-	✔	-	1-10	✔	✔
Numbness	-	-	-	1-10	-	-
Pruritus	✔	✔	-	1-10	✔	✔
Rash	✔	-	-	1-10	-	-
Urticaria	-	✔	-	-	-	-
Gastrointestinal						
Nausea	-	✔	-	-	-	-
Vomiting	-	✔	-	-	-	-
Other						
Aplastic anemia	-	✔	-	-	-	-
Cardiac arrhythmia	-	✔	-	-	-	-
Conjunctivitis (if eye contact)	-	-	✔	-	-	-
Edema	-	-	-	1-10	-	-
Hematuria	-	✔	-	-	-	-
Hepatitis	-	✔	-	-	-	-
Paresthesia	-	✔	-	-	-	-
Pulmonary edema	-	✔	-	-	-	-

✔ Percent not specified
\- Event not reported

Table 6. Boxed Warning for Lindane[18]

WARNING
Lindane Shampoo should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of lice. (See INDICATIONS AND USAGE.) **Neurologic Toxicity** Seizures and deaths have been reported following Lindane Shampoo use with repeat or prolonged application, but also in rare cases following a single application according to directions. Lindane Shampoo should be used with caution in infants, children, the elderly, and individuals with other skin conditions, and those who weigh <110 lbs (50 kg) as they may be at risk of serious neurotoxicity. **Contraindications** Lindane Shampoo is contraindicated in premature infants and individuals with known uncontrolled seizure disorders. **Proper Use** Instruct patients on proper use of Lindane Shampoo, the amount to apply, how long to leave it on, and avoiding re-treatment. Inform patients that itching occurs after the successful killing of lice and is not necessarily an indication for retreatment with Lindane Shampoo. (See DOSAGE AND ADMINISTRATION.)

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[9-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Crotamiton	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 7 days if live mites appear or if no clinical improvement is observed.	Safety and effectiveness in children have not been established.	Cream: 10% Lotion: 10%
Lindane	<u>Lice</u> Apply shampoo directly to dry hair without adding water. Work thoroughly into the hair and allow to remain in place for 4 minutes only. Special attention should be given to the fine hairs along the neck. After 4 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 prescribe more than 2 ounces for	Pediatric patients have a higher surface to volume ratio and may be at risk of greater systemic exposure when lindane is applied. Infants and children may be at an even higher risk due to immaturity of organ systems such as skin and liver. Lindane Shampoo should be used with extreme caution in patients who weigh less than ~110 pounds and especially in infants.	Lotion: 1% Shampoo: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	larger adults. Do not retreat. Scabies 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 2 ounces for larger adults. Apply only once. Wash off in 8 to 12 hours. Do not retreat.	Lice Apply shampoo directly to dry hair without adding water. Work thoroughly into the hair and allow it to remain in place for 4 minutes only. Special attention should be given to the fine hairs along the neck. After 4 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 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 8 to 12 hours. Do not retreat.	
Malathion	Apply lotion 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 8 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 7-9 days, repeat with a second application of lotion. Malathion lotion is flammable. The lotion and hair wet with lotion should not be exposed to open flames or electric heat sources, including hair dryers and electric curlers. Do not smoke while applying lotion or while hair is wet. The person applying malathion lotion should wash hands after application. Allow hair to dry naturally and to remain uncovered after application.	Malathion is contraindicated in neonates and infants because their scalps are more permeable and may have increased absorption of malathion. The safety and effectiveness of malathion in children less than 6 years of age has not been established via well-controlled trials. Children >6 years of age: Malathion should only be used on children under the direct supervision of an adult. Apply lotion 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 8 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 7-9 days, repeat with a second application of lotion. Malathion lotion is flammable. The lotion and hair wet with	Lotion: 0.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		lotion should not be exposed to open flames or electric heat sources, including hair dryers and electric curlers. Do not smoke while applying lotion or while hair is wet. The person applying malathion lotion should wash hands after application. Allow hair to dry naturally and to remain uncovered after application.	
Permethrin	Lice Initial: A sufficient volume (25 to 50 ml) applied to saturate the hair and scalp, and left on hair no longer than 10 minutes. A second application may be indicated if live lice are present 7 days or more after the initial application. Scabies Initial: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Leave on 6-14 hours, then remove by washing off. Repeat dose 14 days later if demonstrable living mites.	Children >2 months of age: Lice Initial: A sufficient volume (25 to 50 ml) applied to saturate the hair and scalp, and left on hair no longer than 10 minutes. A second application may be indicated if live lice are present 7 days or more after the initial application. Scabies Initial: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Leave on 6-14 hours, and then remove by washing off. Repeat dose 14 days later if demonstrable living mites.	Cream: 5% Liquid: 1%
Piperonyl butoxide and pyrethrins	Apply to dry hair or other affected area until entirely wet. Allow product to remain on the hair (or other affected area) for 10 minutes, but no longer. Wash and rinse with large amounts of warm water. A second treatment must be done in 7 to 10 days to kill any newly hatched lice.	Children >2 years of age: Apply to dry hair or other affected area until entirely wet. Allow product to remain on the hair (or other affected area) for 10 minutes, but no longer. Wash and rinse with large amounts of warm water. A second treatment must be done in 7 to 10 days to kill any newly hatched lice.	Foam: 4%-0.33% Liquid: 3%-0.3%, 4%-0.33% Shampoo: 4%-0.33%
Piperonyl butoxide, pyrethrins, and permethrin	Shampoo: Apply to dry hair or other affected area until entirely wet. Allow product to remain on the hair (or other affected area) for 10 minutes, but no longer. Wash and rinse with large amounts of warm water. A second treatment must be done in 7 to 10 days to kill any newly hatched lice. Gel: Apply gel to one section of hair. Massage thoroughly until all strands	Children >2 years of age: Shampoo: Apply to dry hair or other affected area until entirely wet. Allow product to remain on the hair (or other affected area) for 10 minutes, but no longer. Wash and rinse with large amounts of warm water. A second treatment must be done in 7 to 10 days to kill any newly hatched lice.	Kit Shampoo: Piperonyl butoxide 4% and pyrethrins 0.33% Spray: Permethrin 0.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	of hair in this section are covered with the gel. Comb out eggs and nits for that section of hair; repeat until all hair has been combed. Spray: Use the spray to kill lice and their eggs on mattresses, furniture, car interiors and other non-washable items. Not for use on humans or animals.	Gel: Apply gel to one section of hair. Massage thoroughly until all strands of hair in this section are covered with the gel. Comb out eggs and nits for that section of hair; repeat until all hair has been combed. Spray: Use the spray to kill lice and their eggs on mattresses, furniture, car interiors and other non-washable items. Not for use on humans or animals.	

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
Scabies				
Haustein et al.[19] (1989) Lindane (1% and 0.3%) vs. permethrin (5% and 2.5%) vs. benzyl benzoate (20% and 10%)	OL Adults and children with scabies	N=194 3 weeks	Primary: Efficacy Secondary: Side effects	Primary: Efficacy: lindane 92% (treatment failures in three adults and two children), permethrin 100%, benzyl benzoate 100%. Lindane was shown to be less effective (P<0.025). Secondary: Benzyl benzoate had more immediate (22%) and late (42%) adverse effects.
Schultz et al.[20] (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 181 (91%) of 199 patients treated with permethrin (P=0.18) and in 177 (86%) of 205 patients given lindane (P=0.30). Secondary: The most frequent adverse effects were new or increased pruritus and mild, transient burning or stinging. 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 – 0.86).
Zargari et al.[21] (2006) Lindane 1% cream	RCT, DB Patients with scabies older than 5	N=99 4 weeks	Primary: Efficacy and pruritus	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. permethrin 5% cream	years of age		Secondary: Adverse events	At the 4-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.
Taplin et al.[22] (1986) Lindane 1% lotion vs. permethrin 5% cream	RCT Patients with microscopically confirmed scabies	N=23 1 month	Primary: Efficacy	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 1 month. Forty-eight percent of patients treated with permethrin cream were cured in 2 weeks and 91% were cured at 1 month (P<0.025).
Amer et al.[24] (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 4 weeks of observation, the cure rates for the 3 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.
Taplin et al.[23] (1990)	DB, RCT Treatment of	N=47 28 days	Primary: Clinical cure	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Permethrin 5% cream vs. crotamiton 10% cream	scabies in children 2 months to 5 years of age		Secondary: Pruritus	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 infants age 12 months or less were not completely cured at 28 days. In the corresponding age group treated with crotamiton, 56% of subjects were treatment failures. In children age 1 to 5 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 with 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 9 were only marginally improved.
Chouela et al.[25] (1999) Lindane 1% solution vs. ivermectin, oral dose, 150-200 mcg/kg of body weight	RCT, PRO, DB, DD, PG 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%-90.8%) compared to 54% of patients in the group treated with lindane (95% CI, 32.8%-74.4%). At 29 days, both treatments resulted in equivalent therapeutic efficacy. Ninety-five percent were healed with ivermectin (95% CI, 74.0%-99.9%) and 96% were healed with lindane (95% CI, 78.9%, and 99.9%). Secondary: Adverse effects from the treatments were few, mild, and transient.
Madan et al.[26] (2001) Lindane 1% lotion vs.	RCT Patients with scabies	N=200 1 month	Primary: Efficacy Secondary: Adverse effects	Primary: After a period of 4 weeks, 82.6% of the patients in the ivermectin group showed marked improvement; only 44.44% of the patients in the lindane group showed a similar response.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ivermectin in a single oral dose of 200 mcg/kg body weight.				Secondary: One severe headache from ivermectin was noted.
Usha et al.[27] (2000) Permethrin 5% cream vs. ivermectin in a single oral dose of 200 mcg/kg body weight.	RCT Patients with scabies and their family contacts older than 5 years of age	N=85 2 months	Primary: Efficacy	Primary: A single dose of ivermectin provided a cure rate of 70%, which increased to 95% with 2 doses at a 2-week interval. A single application of permethrin was effective in 97.8% of patients. One patient responded to 2 applications at a 2-week interval. Permethrin-treated patients recovered earlier.
Head, Body, or Pubic Lice				
Brandenberg et al.[28] (1986) Lindane 1% shampoo vs. permethrin 1% cream rinse	RCT Patients with the 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.
Taplin et al.[29] (1986) Permethrin 1% creme rinse vs. lindane 1%	DB, 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 subjects were not included in the pre-study blinded randomization of treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
shampoo vs. placebo				Secondary: No adverse experiences were noted during this study.
Bowerman et al.[30] (1987) Lindane shampoo vs. permethrin 1% creme rinse	RCT Patients with head lice in the Netzahualcoyotl community of Mexico city representing 296 family groups	N=1040 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.[31] (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 subjects were infested at the final assessment. In the permethrin group, 12 (43%) of 28 subjects were infested at the final assessment. The difference was not statistically significant. Secondary: Both treatments were well tolerated.
Carson et al.[32] (1988) Permethrin 1% vs. pyrethrins and piperonyl butoxide	RCT Patients with head lice	N=58 2 weeks	Primary: Efficacy 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 subjects receiving permethrin, 26 were lice free vs. 14 of the 31 piperonyl butoxide and pyrethrin-treated subjects (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 subjects were lice free). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both treatments were well tolerated, and no subject experienced adverse reactions.
DiNapoli et al.[33] (1988) Permethrin 1% creme rinse vs. pyrethrins and piperonyl butoxide	RCT Patients with head lice infestation	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.
Roberts et al.[34] (2000) Malathion lotion vs. wet combing	RCT Children aged 3 to 14 years with head lice	N=81 2 weeks	Primary: Efficacy	Primary: 74 children completed the study and 72 were included in the analysis. The cure rate was 38% (12 of 32) for wet combing and 78% (31 of 40) for malathion. Children assigned wet combing were 2.8 (95% CI 1.5-5.2) times more likely than those assigned malathion to have lice at the end of treatment (*P*=0.0006).
Meinking et al.[36] (2004) Malathion 0.5% lotion applied for 20 minutes vs. permethrin 1% creme rinse applied for 10 minutes	RCT, SB Patients between 6 and 70 years of age with head lice	N=66 15 days	Primary: Efficacy	Primary: On day 8, live lice were found on 8of the 41 malathion subjects (19.5%) and 9 of the 22 permethrin subjects (40.9%) (p = 0.08). For patients who required re-treatment on day 8, 88% (n=7) in the malathion group and 33% (n=3) 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). A 20-minute treatment with malathion, instead of the approved 8- to 12-hour application, cured 40 of 41 subjects (98%), demonstrating greater efficacy than permethrin.
Meinking et al.[37] (2007)	SB, PG, AC Patients with	N=172 23 days	Primary: Treatment success	Primary: In the intent-to-treat population, the treatment success rates were 98% for the 30-minute malathion gel (P < 0.0001), 93% for the 60-minute

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Malathion 0.5% gel for 30, 60 and 90 minute application period vs. malathion 0.5% lotion for an 8 to 12 hour application period vs. permethrin 1% creme rinse for a 10-minute application period	clinically diagnosed head lice		Secondary: Retreatment requirements and adverse events	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 per-protocol population, there were no significant differences in treatment success rates between the malathion gel groups and the malathion lotion group. Secondary: The proportions of subjects requiring retreatment on day 8 ± 1 were similar. The proportions of subjects requiring retreatment on day 8 ± 1was much greater for those treated with permethrin than for those treated with malathion gels or malathion lotion. The incidence of adverse events between treatment groups were not significantly different.
Hipolito et al.[35] (2001) Permethrin 1% creme rinse vs. trimethoprim and sulfamethoxazole vs. permethrin 1% creme rinse 1% plus trimethoprim and sulfamethoxazole	RCT Children with head lice ranging in age from 2 to 13 years	N=115 1 month	Primary: Efficacy Secondary: Adverse effects	Primary: At the 2-week follow-up visit, successful treatment for groups 1, 2, and 3 was 79.5%, 83%, and 95%, respectively. At the 4-week follow-up, successful treatment was 72%, 78%, and 92.5% for groups 1, 2, and 3, respectively. The absolute risk reduction for recurrence comparing group 1 versus group 2 was 6%, group 2 versus group 3 was 14%, and group 1 versus group 3 was 20%. Secondary: No major adverse complications were seen in any treatment group. There were 3 trimethoprim/sulfamethoxazole-related rashes. Of the 115 participants, 8 had minor adverse reactions to the treatment.

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial

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
Crotamiton	cream, lotion	Eurax®	$	N/A
Lindane	lotion, shampoo	N/A	N/A	$$$$
Malathion	lotion	Ovide®	$$$$	N/A
Permethrin‡	cream, liquid	Acticin®*, Elimite®*	$	$-$$
Piperonyl butoxide and pyrethrins‡	foam, liquid, shampoo	Rid®*	$	$
Piperonyl butoxide, pyrethrins, and permethrin‡	kit	Rid®	$	$

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
N/A=Not available

X. Conclusions

The skin and mucous membrane scabicides and pediculicides are effective treatment options for scabies and pediculosis of the head, body, and pubic region. The Centers for Disease Control guidelines on the management of scabies recommend initial treatment with either permethrin 5% cream or oral ivermectin.[5] Lindane is considered an alternative treatment option.[5] Several clinical trials have demonstrated greater efficacy with permethrin compared to lindane or crotamiton.[7,19,21-24,38] Permethrin was also found to be more effective than lindane or crotamiton at reducing pruritus, which can persist for several weeks in patients with scabies.[20,23,38]

The Centers for Disease Control guidelines for the treatment of pediculosis pubis recommend permethrin 1% creme rinse or piperonyl butoxide/pyrethrins.[5] Alternative treatments include malathion or oral ivermectin.[5] Malathion may be used when treatment failure is believed to have occurred because of resistance.[5] Only one published study evaluated the use of topical pediculicides for the treatment of pediculosis pubis. Kalter et al. demonstrated similar efficacy with the use of lindane and permethrin.[31]

There were no national or international guidelines found discussing the management of head lice. The American Academy of Pediatrics recommends permethrin as the initial treatment.[6] None of the available pediculicides are 100% ovicidal and resistance has been reported with lindane, pyrethrins and permethrin.[6] Several clinical trials have demonstrated greater efficacy with permethrin compared to lindane and pyrethrins/piperonyl butoxide.[28-30,32-33] Malathion was shown to be more effective than permethrin in two clinical trials.[36-37] It should be noted that both studies were conducted in the same study population in South Florida. The authors noted that observations from over 12 years suggests the presence of pesticide-resistant lice in this population.[36-37]

Potential adverse events limit the use of some of these agents. Seizures and deaths have been reported following lindane use with repeat or prolonged application, but also in rare cases following a single application.[18] Lindane should be used with caution in infants, children, the elderly, individuals with other skin conditions and those who weigh <110 pounds (50 kg) as they may be at risk of serious neurotoxicity.[18] Lindane is not recommended as first-line therapy because of toxicity. It should only be used as an alternative if the patient cannot tolerate other therapies or if other therapies have failed.[18] Malathion is an organophosphate agent and is flammable; the lotion and hair wet with lotion should not be exposed to open flames or electric heat sources, including hair dryers and electric curlers. Patients should not smoke while applying the lotion or while the hair is wet.[17]

Therefore, all brand skin and mucous membrane products within the class reviewed are comparable to each other and to the generics and OTC 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, generics and OTC products 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Local Anti-infectives, Miscellaneous
AHFS Class 840492
May 13, 2009

I. Overview

The skin and mucous membrane miscellaneous local anti-infectives have a variety of uses, including treatment of vaginal infections, antiseptic cleansing, and prevention/treatment of burn wounds. Vulvovaginal candidiasis is a common infection in females and is most often caused by *Candida albicans*.[1] Sulfanilamide has been used for decades for the treatment of vulvovaginal candidiasis. It blocks certain metabolic processes essential for the growth of susceptible organisms.[13] 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.[17] Acetic acid and oxyquinoline (with or without ricinoleic acid) is used as an adjunctive therapy when restoration and maintenance of vaginal acidity is desired, such as in bacterial vaginosis.[11-12]

Hexachlorophene is a bacteriostatic cleansing agent.[14,19] It exhibits good activity against *S. aureus* and relatively weak activity against gram-negative bacteria, fungi, and mycobacteria.[19] It is indicated for use as a surgical scrub and a bacteriostatic skin cleanser.[14] Hexachlorophene may also be used to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. It cleanses the skin thoroughly and has bacteriostatic action against *Staphylococci* and other gram-positive bacteria.[14]

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.[2-3] Complications secondary to infections are a major cause of morbidity and mortality in patients with severe burns. 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. *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.[2-3]

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.[5,15] Silver nitrate inhibits the growth of bacteria, which is due to the precipitation of bacterial proteins by liberated silver ions.[5] It also coagulates cellular protein to form an eschar, which is why it has been used for the destruction of exuberant granulations.[5] Silver sulfadiazine is formed by combining sulfadiazine with silver nitrate, which exhibits both bactericidal and bacteriostatic actions.[5]

The skin and mucous membrane miscellaneous local anti-infectives 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. This class was last reviewed in February 2007.

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)
Acetic acid and oxyquinoline	vaginal jelly	Relagard®*	acetic acid and oxyquinoline
Acetic acid, ricinoleic acid, and oxyquinoline	vaginal jelly	N/A	acetic acid, ricinoleic acid, and oxyquinoline
Hexachlorophene	liquid	pHisoHex®	Phisohex®
Mafenide	cream, packet	Sulfamylon®	none
Silver nitrate	solution	N/A	silver nitrate
Silver sulfadiazine	cream	Silvadene®*, SSD®*	silver sulfadiazine
Sulfanilamide	vaginal cream	AVC®	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 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 (CDC): **Sexually Transmitted Diseases Treatment Guidelines**[17] **(2006)**	Bacterial Vaginosis • Recommended regimens for the treatment of bacterial vaginosis in nonpregnant women include oral metronidazole, vaginal metronidazole or vaginal clindamycin. • The miscellaneous local anti-infectives were not mentioned in these recommendations. Uncomplicated Vulvovaginal Candidiasis • Short-course topical antifungals (i.e., single dose and regimens of 1-3 days) effectively treat uncomplicated vulvovaginal candidiasis (VVC). • The miscellaneous local anti-infectives were not mentioned in these recommendations. Complicated Vulvovaginal Candidiasis (>4 episodes/year) • Each episode of recurrent VVC caused by *C. 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., 7–14 days of topical therapy or a 100 mg, 150 mg, or 200 mg oral dose of fluconazole every third day for a total of 3 doses (day 1, 4, and 7) to attempt mycologic remission before initiating a maintenance antifungal regimen. • The miscellaneous local anti-infectives were not mentioned in these recommendations. Severe Vulvovaginal Candidiasis • Either 7–14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. • The miscellaneous local anti-infectives were not mentioned in these recommendations.
American College of Obstetricians and Gynecologists (ACOG): **Clinical Management Guidelines for Obstetrician-Gynecologists**[16] **(2006)**	Bacterial Vaginosis • Nonpregnant women with bacterial vaginosis can be treated with vaginal clindamycin, oral clindamycin, vaginal metronidazole, or oral metronidazole products. • The miscellaneous local anti-infectives were not mentioned in these recommendations. Uncomplicated Vulvovaginal Candidiasis • Women with uncomplicated vulvovaginal candidiasis can be treated successfully with any of the following options: butoconazole, clotrimazole, fluconazole, miconazole, nystatin, terconazole, or tioconazole. • The miscellaneous local anti-infectives were not mentioned in these recommendations. Complicated Vulvovaginal Candidiasis • After initial intensive therapy for 7–14 days to achieve mycologic remission, prolonged antifungal treatment with fluconazole, 150 mg weekly for 6 months, will successfully control more than 90% of symptomatic episodes and will lead to a prolonged protective effect in approximately 50% of women. • 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

Clinical Guideline	Recommendation(s)
	acceptable options. • The miscellaneous local anti-infectives were not mentioned in these recommendations.
British Association for Sexual Health and HIV, Clinical Effectiveness Group: **National Guideline for the Management of Bacterial Vaginosis[18] (2006)**	Bacterial Vaginosis • Recommended regimens for bacterial vaginosis include oral metronidazole. • The miscellaneous local anti-infectives were not mentioned in these recommendations.
Centers for Disease Control and Prevention. **Guideline for Hand Hygiene in Health-Care Settings[20] (2002)**	• Alcohol-based products are more effective for standard handwashing or hand antisepsis by health care workers 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 nonalcohol-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 FDA 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.

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[4-15]

Indication	Acetic Acid, Oxyquinoline	Acetic Acid, Ricinoleic Acid, Oxyquinoline	Hexachlorophene	Mafenide	Silver Nitrate	Silver Sulfadiazine	Sulfanilamide
Restoration and maintenance of vaginal acidity; adjunct	✔	✔					
Treatment of vulvovaginitis caused by *Candida albicans*							✔
Bacteriostatic skin cleanser			✔				
Surgical scrub			✔				
Control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful			✔				
Adjunct therapy in the treatment of second- and third-degree burns				✔ *		✔	
Adjunct therapy in the prevention of burn wound infections				✔ †	✔	✔	
Wound care, for reduction of exuberant granulations					✔		

*Cream formulation only.
†Solution formulation only.

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[4-15]

Generic Name(s)	Absorption	Excretion (%)	Half-Life (hours)
Acetic acid and oxyquinoline	No data	No data	No data
Acetic acid, ricinoleic acid, and oxyquinoline	No data	No data	No data
Hexachlorophene	Well absorbed	No data	6.1-44.2
Mafenide	No data	Renal	No data
Silver nitrate	Minimal	No data	No data
Silver sulfadiazine	Yes (amount not specified)	Renal (60)	10
Sulfanilamide	No data	No data	No data

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.[4]

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[4-15]

Adverse Events	Acetic Acid, Oxyquinoline	Acetic Acid, Ricinoleic Acid, Oxyquinoline	Hexa-chlorophene	Mafenide	Silver Nitrate	Silver Sulfadiazine	Sulfanil-amide
Central Nervous System							
CNS injury	-	-	<1	-	-	-	-
Delirium	-	-	✔	-	-	-	-
Diplopia	-	-	✔	-	-	-	-
Irritability	-	-	<1	-	-	-	-
Organic brain syndrome	-	-	✔	-	-	-	-
Seizure	-	-	<1	-	-	-	-
Dermatologic							
Pain	-	-	-	✔	-	-	✔
Burning	✔	✔	-	✔	✔	-	✔
Contact dermatitis	-	-	<1	✔	-	-	-
Dryness	-	-	<1	-	-	-	-
Edema	-	-	-	✔	-	-	-
Erythema	-	-	-	✔	-	-	-
Excoriation	-	-	-	✔	-	-	-
Erythema	-	-	<1	✔	-	✔	-
Hives	-	-	-	✔	-	-	-
Irritation	-	-	-	✔	✔	-	-
Pruritus	-	-	-	✔	-	✔	-
Rash	-	-	-	✔	-	✔	✔
Sensitivity reaction	-	-	-	✔	-	-	0.2

Adverse Events	Acetic Acid, Oxyquinoline	Acetic Acid, Ricinoleic Acid, Oxyquinoline	Hexa-chlorophene	Mafenide	Silver Nitrate	Silver Sulfadiazine	Sulfanil-amide
Staining	-	-	-	-	✔	✔	-
Stinging	✔	✔	-	-	-	-	-
Endocrine and Metabolic							
Hyperchloremia	-	-	-	✔	-	-	-
Hyponatremia	-	-	-	-	✔	-	-
Metabolic acidosis	-	-	-	✔	-	-	-
Gastrointestinal							
Diarrhea	-	-	-	-	-	-	-
Vomiting	-	-	✔	-	-	-	-
Genitourinary							
Interstitial nephritis	-	-	-	-	-	✔	-
Hematologic							
Agranulocytosis	-	-	-	-	-	✔	-
Aplastic anemia	-	-	-	-	-	✔	-
Bleeding	-	-	-	✔	-		-
Bone marrow suppression	-	-	-	✔	-	-	-
Hemolytic anemia	-	-	-	✔	-	✔	-
Leukopenia	-	-	-	-	-	✔	-
Methemo-globinemia	-	-	-	✔	✔	-	-
Porphyria	-	-	-	✔	-	-	-
Respiratory							
Dyspnea	-	-	-	✔	-	-	-
Hyperventilation	-	-	-	✔	-	-	-
Tachypnea	-	-	-	✔	-	-	-
Miscellaneous							
Anaphylaxis	-	-	-	-	-	✔	-
Hypersensitivity	-	-	-	✔	-	-	✔
Photosensitivity	-	-	<1	-	-	✔	-

✔ Percent not specified
- Event not reported

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[4-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acetic acid and oxyquinoline	One applicatorful, administered intravaginally, morning and evening; duration of treatment may be determined by the patient's response to therapy	Safety and efficacy in children have not been established	Vaginal Jelly: Acetic acid 0.9% and oxyquinoline 0.025%
Acetic acid, ricinoleic acid, and oxyquinoline	One applicatorful, administered intravaginally, morning and evening; duration of treatment may be determined by the patient's response to therapy	Safety and efficacy in children have not been established	Vaginal Jelly: Acetic acid 0.921%, ricinoleic acid 0.7%, and oxyquinoline 0.025%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Hexachlorophene	Apply 5 mL cleanser and water to area to be cleansed; lather and rinse under running water	Apply 5 mL cleanser and water to area to be cleansed; lather and rinse under running water	Liquid: 3%
Mafenide	Apply to the affected area 1-2 times daily	Apply to the affected area 1-2 times daily	Cream: 8.5% Powder: 50 g packet to prepare 5% topical solution
Silver nitrate	Apply a cotton applicator dipped in solution on the affected area 1-3 times a week for 2-3 weeks	Apply a cotton applicator dipped in solution on the affected area 1-3 times a week for 2-3 weeks	Solution: 0.5%
Silver sulfadiazine	Apply to the affected area 1-2 times daily	Apply to the affected area 1-2 times daily	Cream: 1%
Sulfanilamide	One applicatorful (about 6 g) intravaginally 1-2 times daily	Safety and efficacy have not been established in children	Cream: 15%

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
Smylie, et al.[26] (1973) Period 1: Hexachlorophene 3% Period 2: chlorhexidine 4% Period 3: hexachlorophene % Period 4: povidone-iodine	OL Operating team consisting of surgeons, nurses, and assistants.	Period 1: 154 operations Period 2: 228 operations Period 3: 262 operations Period 4: 222 operations	Primary: Reduction of post-operative colony-forming units (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). 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 5 significantly more often (P <0.001) than did the other periods. Of the three preparations, the members of the team found chlorhexidine to be more acceptable for use than either povidone-iodine or hexachlorophene.
Bodey et al.[23] (1976) Hexachlorophene 3% vs. P-300® (bar soap containing tribromosalan and triclosan)	RCT, AC Patients with acute leukemia hospitalized in isolation units	N=26 ≤14 weeks	Primary: Reduction of colony-forming units (CFUs)	Primary: Bathing with either P-300® or hexachlorophene resulted in a major reduction in the number of CFUs on each body site. After 1 week of bathing, the median number of CFUs was reduced to 0-100 per body site in the P-300® group and to 0-50 in the hexachlorophene treatment group.
Barret et al.[21] (2000)	RCT, AC	N=20	Primary: Pain relief, length	Primary: Patients treated with Biobrane® had a significantly shorter length of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Silver sulfadiazine (SSD) 1%, applied BID following superficial debridement vs. Biobrane® (bilaminar temporary skin substitute), applied BID following superficial debridement	Patients ≤17 years of age with second-degree noninfected burns admitted within 24 hours of the burn, with total body surface area burned 2%-29%	3 days	of stay, wound healing time, pain and anxiolytic medication use	stay, wound healing time, and decreased requirement of pain medications compared to patients in the SSD group (P<0.05). While patients in the Biobrane® treatment group experienced significant pain relief compared to baseline (P<0.001), patients treated with SSD 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.
Dire et al.[22] (1995) Bacitracin zinc, applied to the wound TID vs. bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound TID vs. silver sulfadiazine, applied to the wound TID vs.	RCT, DB, PC, PRO Patients with uncomplicated soft tissue wound admitted to the emergency department (ED) within 12 hours of injury	N=426 1 day	Primary: Infection rate	Primary: The wound infection rates for the treatment groups were 5.5% in the bacitracin group, 4.5% in the bacitracin, neomycin sulfate, and polymyxin B group, 12.1% in the silver sulfadiazine group, and 17.6% in the placebo group (*P*=0.0034).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
petrolatum, applied to the wound TID				
Heinle et al.[24] (2001) Mafenide 5% solution, administered until autograft vascularization was observed vs. historical control treated with similar protocol but without mafenide	RETRO, HC 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 debridements, mean wound closure procedures, mortality rate	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 debridements 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).
Kucan et al.[25] (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	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.
MacMillan et al.[28] (1967) Mafenide acetate 10% applied once daily with replenishment as needed vs.	OL Patients with second-and third-degree burn wounds requiring topical antibacterial therapy	N=52 Variable follow-up	Primary: Bacterial flora of the burn wounds and complications	Primary: Of 13 patients treated with mafenide, 2 died of pneumonia (15%). One patient in this group developed *Pseudomonas* septicemia, but recovered. Of 18 patients treated with silver nitrate, 2 (11%) died, both of whom developed *Pseudomonas* septicemia. Of 10 patients treated with gentamicin, none died, but 2 developed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
silver nitrate 0.5% dressings changed twice daily and saturated every 2 hours vs. gentamicin ointment applied as an occlusive dressing and changed every 2 to 3 days vs. control group treated with occlusive dressings and no topical drugs *Patients also received systemic antibiotic and gamma globulin therapy in addition to study medications.				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, 4 (36%) died, 3 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.
Pegg et al.[27] (1979) Mafenide vs. silver sulfadiazine vs.	OL All patients over 12 years of age with burn injuries requiring admission	N=645 9 years of follow-up	Primary: Wound infection and complications	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], *E. 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], *E. coli* [P<0.01], *Candia* albicans [P<0.01].

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
control				Silver sulfadiazine was more effective than mafenide in reducing the clinical infection rate of *Pseudomonas* and *Staphylococcus*. Both treatment groups were comparable in reducing *E. 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).
Livingston et al.[29] (1990) Silver nitrate 0.5% (Ag) vs. neomycin (1 g/L) and bacitracin (50,000 units/L) (NB) vs. ringers lactate (RL)	RCT Patients admitted to the adult burn unit with thermal injury who required skin grafting	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 (TBSA). Graft loss of 10% or more occurred in 67% of patients with large burns (>40% TBSA). There was no difference in the incidence of graft loss between the treatments. In patients with 20% to 40 % TBSA burns, the use of either antimicrobial (Ag or NB) resulted in a 7% graft loss rate compared to a 67% graft loss rate in the RL group (P<0.05). The rate of graft loss in the Ag group was significantly lower than in the RL group (P=0.02). There was no difference in the rate of graft loss between the NB and RL treatment groups (P=0.10) Infection in the area of graft loss was caused by antibiotic-resistant organisms or yeast in 50% of the RL group and the entire neomycin plus bacitracin group. No graft infections were caused by resistant organisms or yeast in the Ag group.

Drug regimen abbreviations: QD=once daily, BID=twice daily
Study design abbreviations: AC=active-control, HC=historical-control, MC=multicenter, OL=open-label , PRO=prospective, RCT=randomized trial, RETRO=retrospective

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
Acetic acid and oxyquinoline	vaginal jelly	Relagard®*	$$	$
Acetic acid, ricinoleic acid, and oxyquinoline	vaginal jelly	N/A	N/A	$$
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

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

X. Conclusions

The skin and mucous membrane miscellaneous local anti-infectives have a variety of uses, including treatment of vaginal infections, antiseptic cleansing, and prevention/treatment of burn wounds. Current guidelines on the management of vaginal infections do not specifically mention or recommend the use of acetic acid/oxyquinoline (with or without ricinoleic acid) or sulfanilamide. There were no published clinical trials 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.[13]

Hexachlorophene is a bacteriostatic cleansing agent which is FDA-approved for use as a surgical scrub and a bacteriostatic skin cleanser. The Centers for Disease Control 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.[20] Studies of hexachlorophene as a hygienic hand wash and surgical scrub demonstrated only modest efficacy after a single handwash.[20] 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.[20] As a result, it is seldom used as a surgical scrub.[20] Hexachlorophene should not be used to bathe patients with burns or extensive areas of susceptible, sensitive skin. Current guidelines recommend against the routine bathing of neonates with hexachlorophene because of its potential neurotoxic effects.[20]

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 treatment options for the prevention and treatment of burn wounds.[19] Silver sulfadiazine is the most frequently used agent because of its low toxicity and ease of use.[19] Mafenide rapidly penetrates burn eschar; however, the application must be limited because of systemic toxicity associated with prolonged or extensive use.[19] 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 clinical trials directly comparing the miscellaneous topical anti-infective agents.[21-22,24-25,27-28] MacMillan et al. reported similar efficacy with mafenide and silver nitrate in patients with second-and third-degree burn wounds requiring topical antibacterial therapy.[28] Pegg et al. demonstrated similar efficacy with mafenide and silver sulfadiazine in patients with burn injuries requiring admission.[27]

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Therefore, all brand skin and mucous membrane miscellaneous local anti-infective products within the class reviewed are comparable to each other and to the generics and OTC 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Anti-inflammatory Agents
AHFS Class 840600
May 13, 2009

I. Overview

The skin and mucous membrane anti-inflammatory agents are indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. This includes anogenital pruritus, atopic dermatitis, localized neurodermatitis, psoriasis, seborrheic dermatitis, and the inflammatory phase of xerosis. 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.[1] Therefore, these agents have the potential to elicit a wide variety of biologic responses.[1] Corticosteroids reduce inflammation, possess antimitotic activity, and induce cutaneous vasoconstriction.[2]

The topical corticosteroids are classified based on their relative potency; super potent (Class I), potent (Classes II–III), intermediate (Classes IV–V), and mild (Classes VI–VII).[2] The super potent agents are used to treat severe dermatoses over non-facial and non-intertriginous areas.[2] Intermediate and potent agents are often used for the treatment of mild to moderate non-facial and non-intertriginous dermatoses. Mild to intermediate potency agents are used when large areas need to be treated due to the potential for systemic absorption. Only mild potency agents should be used on the eyelids and genital areas.[2]

The efficacy and safety of the topical corticosteroids depend on a variety of factors, including potency, type and location of lesions being treated, vehicle used, application method, and specific patient factors, such as age. These topical corticosteroids are available in a variety of vehicles, including ointments, creams, lotions, solutions, gels, and foams.[2] 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.[2] 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 the other vehicles, foams require a special delivery system due to the pressurized nature of the product.

The skin and mucous membrane anti-inflammatory agents that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. The relative potency ratings of the topical corticosteroids are listed in Table 2. There is at least one topical corticosteroid from each potency category available in a generic formulation. Hydrocortisone is also available in various formulations over-the-counter. This class was last reviewed in February 2007.

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)
Alclometasone	cream, ointment	Aclovate®*	alclometasone
Amcinonide	cream, lotion, ointment	N/A	amcinonide
Betamethasone dipropionate	cream, gel, lotion, ointment	N/A	betamethasone dipropionate
Betamethasone dipropionate and propylene glycol	cream, lotion, ointment	Diprolene®*, Diprolene AF®*	betamethasone dipropionate and propylene glycol
Betamethasone valerate	cream, foam, lotion, ointment	Luxiq®	betamethasone valerate
Clobetasol	cream, foam, gel, lotion, ointment,	Clobex®, Cormax®*, Olux®*, Olux-Olux-E®,	clobetasol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	shampoo, solution, spray	Olux-E®, Temovate®*	
Clocortolone	cream	Cloderm®	none
Desonide	cream, foam, gel, lotion, ointment	Desonate®, Desowen®*, Verdeso®	desonide
Desoximetasone	cream, gel, ointment	Topicort®*, Topicort LP®*	desoximetasone
Diflorasone	cream, ointment	Apexicon®*, Apexicon E®, Psorcon E®	diflorasone
Fluocinolone	cream, oil, ointment, shampoo, solution	Capex Shampoo®, Derma-Smoothe/FS®	Capex Shampoo®, Derma-Smoothe/FS®, fluocinolone
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
Halobetasol and ammonium lactate	combination package	Ultravate PAC®	none
Hydrocortisone‡	cream, lotion, ointment, rectal cream, rectal enema, solution	Aquanil HC®*, Beta HC®*, Cortaid®*, Cortenema®*, Dermolate Anti-Itch®*, Hytone®*, Preparation H®*, Proctocort®*, Proctocream-HC®*, Sarnol-HC®*	hydrocortisone
Hydrocortisone and aloe vera‡	cream, ointment	N/A	hydrocortisone and aloe vera
Hydrocortisone, mineral oil, and white petrolatum	ointment	N/A	hydrocortisone, mineral oil, and white petrolatum
Hydrocortisone acetate‡	cream, ointment, rectal cream, rectal foam	Corticaine®*, Cortifoam®, Medi-Cortisone®*	hydrocortisone acetate
Hydrocortisone acetate and aloe vera‡	cream, gel, liquid	Nuzon®*, Nucort®	hydrocortisone acetate and aloe vera
Hydrocortisone acetate and pramoxine	rectal foam, rectal lotion	Analpram-HC®, Proctofoam-HC®	none
Hydrocortisone acetate and urea	cream	Carmol HC®*, U-Cort®*	hydrocortisone acetate and urea
Hydrocortisone butyrate	cream, liquid, ointment, solution	Locoid®*, Locoid Lipocream®	hydrocortisone butyrate
Hydrocortisone probutate	cream	Pandel®	none
Hydrocortisone valerate	cream, ointment	Westcort®*	hydrocortisone valerate
Mometasone	cream, ointment, solution	Elocon®*	mometasone
Prednicarbate	cream, ointment	Dermatop®*	prednicarbate
Triamcinolone	aerosol, cream, dental paste, lotion, ointment	Kenalog®, Oralone in Orabase®*	triamcinolone

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
PDL=Preferred Drug List
N/A=Not available

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

Group* (I=Highest Potency; VII = Lowest Potency)	Generic Name(s)	Strength	Formulation(s)
I	betamethasone dipropionate and propylene glycol	0.05%	cream, lotion, ointment
I	clobetasol	0.05%	cream, foam, gel, lotion, ointment, shampoo, solution, spray
I	fluocinonide	0.1%	cream
I	flurandrenolide	4 mcg/cm^2	tape
I	halobetasol	0.05%	cream, ointment
II	amcinonide	0.1%	lotion, ointment
II	betamethasone dipropionate	0.05%	ointment
II	betamethasone dipropionate	0.1%	aerosol
II	desoximetasone	0.05%	gel
II	desoximetasone	0.25%	ointment
II	diflorasone	0.05%	ointment
II	fluocinonide	0.05%	cream, gel, ointment, solution
II	halcinonide	0.1%	ointment
III	amcinonide	0.1%	cream
III	betamethasone dipropionate	0.05%	cream, gel
III	betamethasone valerate	0.1%	ointment
III	desoximetasone	0.25%	cream
III	diflorasone	0.05%	cream
III	fluticasone	0.005%	ointment
III	halcinonide	0.1%	cream, solution
III	mometasone	0.1%	ointment
III	triamcinolone	0.5%	cream, ointment
IV	betamethasone valerate	0.12%	foam
IV	desoximetasone	0.05%	cream
IV	fluocinolone	0.025%	ointment
IV	flurandrenolide	0.05%	ointment
IV	fluticasone	0.05%	cream, lotion
IV	hydrocortisone valerate	0.2%	ointment
IV	mometasone	0.1%	cream, lotion
IV	prednicarbate	0.1%	ointment
IV	triamcinolone	0.1%	ointment
V	betamethasone dipropionate	0.05%	lotion
V	betamethasone valerate	0.1%	cream, lotion
V	clocortolone	0.1%	cream
V	fluocinolone	0.025%	cream
V	flurandrenolide	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
V	triamcinolone	0.1%	cream, lotion, paste
VI	alclometasone	0.05%	cream, ointment
VI	desonide	0.05%	cream, lotion, ointment
VI	fluocinolone	0.01%	cream, oil, shampoo, solution

Group* (I=Highest Potency; VII = Lowest Potency)	Generic Name(s)	Strength	Formulation(s)
VI	triamcinolone	0.025%	aerosol, cream, lotion, ointment
VII	hydrocortisone, hydrocortisone acetate	all strengths	cream, enema, foam, gel, lotion, ointment, packet, rectal suppository, solution, spray

*Potency ratings are given following the Stoughton-Cornell classification of topical glucocorticoid 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)
Primary Care Dermatology Society & British Association of Dermatologists: **Guidelines for the Management of Atopic Eczema**[6] **(2006)**	• 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. • As a rough guide, steroid use should be limited to a few days to a week for acute eczema and up to 4–6 weeks to gain initial remission for chronic eczema. • The weakest steroid that controls the disease effectively should be chosen; this may involve either a step-up approach, less potent to more potent, or a step-down approach, more potent to less potent. • In each approach, regular review of steroid use in terms of potency and quantity (especially when using potent steroids) is essential. • Potent steroids should not be used without specialist advice in infants with atopic eczema in primary care. • Rarely, very potent corticosteroids may be indicated in resistant severe eczema on the hands and feet of adults, again with regular review of use. • 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, and ideally emollients should not be applied shortly after application of a topical steroid (30 minutes is recommended).
American Academy of Dermatology (AAD), Clinical Guidelines Task Force: **Guidelines of Care for Atopic Dermatitis**[7] **(2004)**	• Topical corticosteroids are the standard of care to which other treatments are compared. • 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. • Tachyphylaxis is a clinical concern, but there is no experimental documentation. • The use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies.

Clinical Guideline	Recommendation(s)
Joint Task Force on Practice Parameters (ACAAI, AAAAI, JCAAI): **Disease Management of Atopic Dermatitis: An Updated Practice Parameter[8] (2004)**	• Topical corticosteroids, applied to areas of eczema, are effective treatment for atopic dermatitis. • Low-potency agents are recommended for maintenance therapy, whereas intermediate- and high-potency agents should be used for clinical exacerbations and should be applied over short periods of time. • Potent fluorinated agents should be avoided on the face, eyelids, genitalia, intertriginous areas, and in infants. • Low-potency agents are generally recommended for areas with increased potential for transepidermal penetration, including mucous membranes, genitalia, and eyelids, face, and intertriginous areas. • Intermediate-potency agents can be used for longer periods of time than high-potency agents to treat chronic conditions involving the trunk and extremities. • High-potency agents should only be used for short periods of time (up to 3 weeks) for clinical exacerbations. • Ultrahigh-potency agents should only be used for very short periods of time (up to several days) and limited to lichenified areas.
American Academy of Dermatology. **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapies[3] (2009)**	• Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis, particularly those with limited disease. • They are available in many strengths and formulations, which allows for versatility of use. The choice of the appropriate potency corticosteroid and its vehicle should take into consideration the disease severity, the location being treated, patient preference, as well as the age of the patient. • Lower potency corticosteroids should generally be used for limited periods of time on the face, intertriginous areas, areas with thin skin, and in infants. In other areas and in adults, mid- or high-potency agents are generally recommended as initial therapy. Patients with thick, chronic plaques often require treatment with the highest potency corticosteroids. • For class I corticosteroids, the available data allow for 2 to 4 weeks of use with increased risk of both cutaneous side effects and systemic absorption if used continuously for longer periods of time. The optimal end point for the use of the less potent agents is not known. • When topical corticosteroids are used to treat psoriasis, it is recommended that a gradual reduction in the frequency of usage following clinical response be instituted, although the exact details of this tapering are not well established. • Many factors can alter the efficacy of topical corticosteroids, including the vehicle, the area of usage, the presence or absence of occlusion, patient preference, and the age of the patient. • Efficacies of the different classes of topical corticosteroids vary widely even among agents of the same class, ranging from 41% up to 92%. In addition, it is important to understand the specifics of the primary end point used in each study as this will have an important bearing on the percentage of improvement noted.
Finnish Medical Society Duodecim: **Psoriasis[5] (2007)**	<u>Plaque Psoriasis</u> • Topical corticosteroids (potent to very potent, i.e. group III to IV) have a rapid onset of action and will also alleviate itchiness, which is present in about 70% of patients. • They should initially be used continuously for 2 to 4 weeks followed by gradual dose reduction and cessation. • Abrupt cessation should be avoided as it will lead to early recurrence.

Clinical Guideline	Recommendation(s)
	• An attempt must be made to avoid the emergence of known adverse effects of long-term use and the patient must be appropriately monitored. Plaque Psoriasis in Specific Areas • Psoriasis on the face may be treated by moderately potent corticosteroid preparations. • Flexural psoriasis may be managed with the same preparations as those used on the face. • The treatment of psoriasis on the palms and the soles of the feet consist of the above mentioned medicines used in plaque psoriasis. Guttate Psoriasis • If guttate psoriasis is not very extensive, the topical treatment forms described for plaque psoriasis may be used, particularly topical corticosteroids. Pustular Psoriasis and Erythrodermic Psoriasis • The principal treatment regime consists of systemic drugs, which may be supplemented with emollients and topical corticosteroids.
British Association of Dermatologists: **Psoriasis Guidelines**[4] **(2006)**	• Topical corticosteroids are effective, cosmetically acceptable, and safe if used carefully under supervision. • Topical corticosteroids are best used on limited areas of psoriasis. More resistant areas such as the hands, feet and scalp can initially be treated by potent corticosteroids from the onset. • There is no evidence that twice daily application of topical steroids is more effective than once daily application. • The strength of the steroid should be adjusted commensurate with clinical improvement. • In especially resistant psoriasis of the limbs, hands or feet, occlusive treatment in which the treatment area is covered by a thin polythene film will greatly enhance effectiveness (and also local and systemic toxicity). This measure should only be continued for a few days at a time. • No more than 100 g of a moderately potent or higher potency preparation should be applied per month. • Attempts should be made to rotate topical corticosteroids with alternative non-corticosteroid preparations. • Use of very potent or potent preparations should be under dermatological supervision. The fingertip unit is a measure which helps patients to know how much ointment or cream to apply. • No topical corticosteroid should be used regularly for more than four weeks without critical review. • Potent corticosteroids should not be used regularly for more than 7 days. • A topical corticosteroid can be used as a monotherapy or in conjunction with other topical agents including tar or dithranol. Some patients who fail to respond to one topical agent may respond to another and it is worthwhile rotating different classes of topical agents before abandoning topical treatment altogether.
Finnish Medical Society Duodecim: **Seborrhoeic Dermatitis**[9] **(2007)**	Treatment: • The treatment does not cure the disease permanently. 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 sulphur (but not Vaseline) or by wetting and washing. • Seborrhoeic skin should be washed more often than usual. Decreasing fungal growth:

Clinical Guideline	Recommendation(s)
	• Washing the scalp with ketoconazole shampoo or selenium sulphide 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 (mild to potent) • Corticosteroid creams for other parts of the body (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[10] (2004)**	• Treatment of hemorrhoids depends on their severity. • The cornerstone of therapy is adequate intake of 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[11] (2004)**	• The almost-universal recommendations are to add dietary fiber and to 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 symptomatic relief of 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[12-34]

Generic Name(s)	Relief of Inflammatory and Pruritic Manifestations of Corticosteroid-Responsive Dermatoses*
Alclometasone	✔
Amcinonide	✔
Betamethasone dipropionate	✔
Betamethasone dipropionate and propylene glycol	✔
Betamethasone valerate	✔
Clobetasol	✔
Clocortolone	✔
Desonide	✔
Desoximetasone	✔
Diflorasone	✔
Fluocinolone	✔
Fluocinonide	✔
Flurandrenolide	✔

Generic Name(s)	Relief of Inflammatory and Pruritic Manifestations of Corticosteroid-Responsive Dermatoses*
Fluticasone	✔
Halcinonide	✔
Halobetasol	✔
Halobetasol and ammonium lactate	✔
Hydrocortisone	✔
Hydrocortisone and aloe vera	✔
Hydrocortisone, mineral oil and white petrolatum	✔
Hydrocortisone acetate	✔
Hydrocortisone acetate and aloe vera	✔
Hydrocortisone acetate and pramoxine	✔
Hydrocortisone acetate and urea	✔
Hydrocortisone butyrate	✔
Hydrocortisone probutate	✔
Hydrocortisone valerate	✔
Mometasone	✔
Prednicarbate	✔
Triamcinolone acetonide	✔

*Dermatoses include anogenital pruritus, atopic dermatitis, psoriasis, seborrheic dermatitis, and inflammatory phase of xerosis

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane anti-inflammatory agents are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Skin and Mucous Membrane Anti-inflammatory Agents[12-34]

Generic Name(s)	Absorption (%)	Excretion
Alclometasone	3	No data
Amcinonide	No data	No data
Betamethasone dipropionate	Variable	No data
Betamethasone valerate	Variable	No data
Clobetasol	No data	No data
Clocortolone	Variable	Urine and feces
Desonide	Variable	No data
Desoximetasone	Variable	Urine and feces
Diflorasone	≤ 1	No data
Fluocinolone	Variable	Urine and feces
Fluocinonide	1-36	Urine and feces
Flurandrenolide	Variable	Urine and feces
Fluticasone	No data	No data
Halcinonide	Variable	Urine
Halobetasol	<6	No data
Hydrocortisone	Rapid	Urine
Hydrocortisone acetate	Rapid	Urine
Hydrocortisone butyrate	Rapid	Urine
Hydrocortisone probutate	Rapid	Urine
Hydrocortisone valerate	Rapid	Urine
Mometasone	0.1	No data
Prednicarbate	No data	No data
Triamcinolone	Variable	Urine and feces

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane anti-inflammatory agents, no significant drug interactions have been reported.[34]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane anti-inflammatory agents are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Anti-inflammatory Agents[12-34]

Adverse Events	Alclo-met-asone	Amcin-onide	Beta-meth-asone	Clo-beta-sol	Clo-cort-alone	Des-onide	Desoxi-metasone	Diflor-asone	Fluo-cin-olone	Fluo-cin-onide	Fluran-dren-olide	Flutic-asone	Halcin-onide	Halo-bet-asol	Hydro-corti-sone	Momet-asone	Predni-carbate	Triam-cino-lone
Central Nervous System																		
Anxiety	-	-	-	-	-	-	-	0-2	-	-	-	-	-	-	-	-	-	-
Asthenia	-	-	-	-	-	-	-	0-2	-	-	-	-	-	-	-	-	-	-
Blurred vision	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Dizziness	-	-	-	-	-	-	-	0-4	-	-	-	-	-	-	-	-	-	-
Headache	-	-	-	-	-	-	-	0-7	-	-	-	2	-	-	-	-	-	-
Hypokinesia	-	-	-	-	-	-	-	0-2	-	-	-	-	-	-	-	-	-	-
Migraine	-	-	-	-	-	-	-	0-2	-	-	-	-	-	-	-	-	-	-
Reversible HPA suppression	-	-	✔	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Dermatological																		
Acne	-	-	-	-	-	-	-	0-4	-	✔	-	-	✔	✔	-	-	-	-
Acneform eruptions	✔	✔	✔	✔	<1	✔	✔	-	✔	-	✔	✔	-	✔	✔	✔	✔	✔
Allergic contact dermatitis	✔	✔	✔	✔	-	✔	✔	0-33	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Alopecia	-	-	-	-	-	-	-	0-2	-	-	-	-	-	-	-	-	-	-
Application site reaction	-	-	-	-	-	-	-	70-84	-	-	-	-	-	-	-	-	-	-
Atopic dermatitis	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-
Bruising	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Burning	1-2	20	✔	<1	1-10	✔	0.8	-	✔	✔	✔	1-2	✔	1-15	✔	✔	✔	✔
Cracking	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dry skin	-	-	-	-	-	-	-	0-27	-	✔	-	7	-	2	-	-	-	-
Dryness	2	✔	✔	✔	1-10	✔	✔	-	✔	-	✔	-	✔	✔	✔	✔	-	✔
Edema	-	-	-	-	-	✔	-	0-4	-	-	-	✔	-	-	-	-	✔	-
Eczema	-	-	-	-	-	-	-	-	-	-	-	✔	-	✔	-	-	-	-

Adverse Events	Alclo-met-asone	Amcin-onide	Beta-meth-asone	Clo-beta-sol	Clo-cort-alone	Des-onide	Desoxi-metasone	Diflor-asone	Fluo-cin-olone	Fluo-cin-onide	Fluran-dren-olide	Flutic-asone	Halcin-onide	Halo-bet-asol	Hydro-corti-sone	Momet-asone	Predni-carbate	Triam-cino-lone
Erythema	1-2	-	-	✔	1-10	✔	-	-	-	-	-	-	-	2-15	-	-	-	-
Exfoliation	-	-	-	-	-	-	-	4-24	-	-	-	-	-	✔	-	-	-	-
Fissuring	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Folliculitis	✔	✔	✔	✔	-	✔	0.8	-	✔	✔	✔	<1	✔	✔	✔	✔	✔	✔
Herpes simplex	-	-	-	-	-	-	-	0-4	-	-	-	-	-	-	-	-	-	-
Hyper-pigmentation	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-
Hyper-trichosis	-	✔	✔	-	<1	-	✔	-	✔	✔	✔	-	✔	✔	✔	✔	-	✔
Hypo-pigmentation	✔	✔	✔	✔	<1	✔	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Irritation	2	✔	✔	0.5	1-10	✔	✔	-	✔	✔	✔	✔	-	✔	✔	✔	-	✔
Itching	1-2	20	✔	0.5	1-10	-	✔	-	✔	-	✔	-	✔	4.4	✔	-	-	✔
Leukoderma	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-
Loss of elasticity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Loss of normal skin markings	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Maceration of the skin	-	✔	✔	-	<1	-	✔	-	✔	✔	✔	-	✔	-	✔	-	-	✔
Maculo-papular rash	-	-	-	-	-	-	-	0-2	-	-	-	-	-	-	-	-	-	-
Miliaria	✔	✔	✔	✔	<1	✔	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Papular rash	2	-	-	-	1-10	-	-	-	-	-	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	-	-	8-20	-	-	-	-	-	✔	-	✔	✔	-
Perioral dermatitis	✔	✔	✔	✔	<1	✔	✔	-	✔	✔	✔	✔	-	✔	✔	✔	✔	✔
Petechiae	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-
Photo-sensitivity	-	-	-	-	-	-	-	0-3	-	-	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	✔	-	1-59	-	✔	-	1-2	-	5	-	✔	✔	-
Pustular rash	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Pustules	-	-	-	-	-	-	-	-	-	-	-	<1	-	✔	-	-	-	-

Adverse Events	Alclo-met-asone	Amcin-onide	Beta-meth-asone	Clo-beta-sol	Clo-cort-alone	Des-onide	Desoxi-metasone	Diflor-asone	Fluo-cin-olone	Fluo-cin-onide	Fluran-dren-olide	Flutic-asone	Halcin-onide	Halo-bet-asol	Hydro-corti-sone	Momet-asone	Predni-carbate	Triam-cino-lone
Rash	-	-	-	-	-	✔	-	0-35	-	-	-	1	-	✔	-	-	✔	-
Rosacea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Secondary infection	✔	✔	✔	✔	-	✔	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Shininess	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	✔	✔	-
Skin atrophy	✔	✔	✔	✔	<1	✔	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Soreness	-	20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stinging	-	20	-	1	-	-	-	-	-	-	-	1-5	-	1-4	-	✔	-	-
Striae	✔	✔	✔	✔	<1	✔	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Telan-giectasia	-	-	-	✔	-	-	-	-	-	✔	-	-	✔	✔	-	✔	✔	-
Thinness	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	✔	-
Urticaria	-	-	-	-	-	-	-	-	-	-	-	✔	-	✔	-	-	✔	-
Endocrine and Metabolic																		
Hyper-glycemia	-	-	✔	-	-	2	-	-	-	✔	-	✔	-	-	-	-	-	-
Hematologic																		
Leucopenia	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Thrombo-cytopenia	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Musculoskeletal																		
Arthralgia	-	-	-	-	-	-	-	0-2	-	-	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	-	-	-	0-3	-	-	-	-	-	-	-	-	-	-
Other																		
Cushing's Syndrome	-	-	✔	✔	-	-	-	-	-	✔	-	✔	✔	-	-	-	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane anti-inflammatory agents are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Anti-inflammatory Agents[12-34]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alclometasone	Apply a thin film to the affected area of the skin two or three times daily	Children 1 year of age and older: Apply a thin film to the affected area of the skin two or three times daily	Cream: 0.05% Ointment: 0.05%
Amcinonide	Apply to the affected area two to three times daily, lotion may be applied topically two times a day	Safety and efficacy in children have not been established	Cream: 0.1% Lotion: 0.1% Ointment: 0.1%
Betamethasone dipropionate	Cream, gel, and ointment: Apply 1-2 times daily Lotion: Apply a few drops 2 times daily	Children >13 years of age: Cream, gel and ointment: Apply 1-2 times daily Lotion: Apply a few drops 2 times daily	Cream: 0.05% Gel: 0.05% Lotion: 0.05% Ointment: 0.05%
Betamethasone dipropionate and propylene glycol	Cream and ointment: Apply 1-2 times daily Lotion: Apply a few drops 1-2 times daily	Children >13 years of age: Cream and ointment: Apply 1-2 times daily Lotion: Apply a few drops 1-2 times daily	Cream: 0.05% Lotion: 0.05% Ointment: 0.05%
Betamethasone valerate	Cream and ointment: Apply 1-2 times daily Foam and lotion: Apply 2 times daily	Children >13 years of age: Cream and ointment: Apply 1-2 times daily Foam and lotion: Apply 2 times daily	Cream: 0.1% Foam: 0.12% Lotion: 0.1% Ointment: 0.1%
Clobetasol	Cream, gel, lotion, and ointment: Apply a thin layer to the affected skin area 2 times daily for up to 2 weeks Foam and solution: Apply to scalp 2 times daily for up to 2 weeks Shampoo: Apply thin film to dry scalp once daily, leave in place for 15 minutes, add water, lather, and rinse Spray: Spray directly onto affected area 2 times daily and gently rub into skin for	Children >12 years of age: Cream, gel, lotion, and ointment: Apply a thin layer to the affected skin area 2 times daily for up to 2 weeks Foam and solution: Apply to scalp 2 times daily for up to 2 weeks Shampoo: Apply thin film to dry scalp once daily, leave in place for 15 minutes, add water, lather, and rinse Spray: Spray directly onto affected area 2 times daily	Cream: 0.05% Foam: 0.05%, 0.05%-0.05% Gel: 0.05% Lotion: 0.05% Ointment: 0.05% Shampoo: 0.05% Solution: 0.05% Spray: 0.05%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	up to 4 weeks	and gently rub into skin for up to 4 weeks	
Clocortolone	Apply sparingly to affected areas 3 times daily	Safety and efficacy in children have not been established	Cream: 0.1%
Desonide	Apply sparingly 2-3 times daily	Apply sparingly 2-3 times per day	Cream: 0.05% Foam: 0.05% Gel: 0.05% Lotion: 0.05% Ointment: 0.05%
Desoximetasone	Apply a thin film to affected area 2 times daily	Apply a thin film to affected area 2 times daily	Cream: 0.05%, 0.25% Gel: 0.05% Ointment: 0.25%
Diflorasone	Cream: Apply sparingly to affected area 2 times per day Ointment: Apply sparingly to affected area 1-3 times daily	Safety and efficacy in children have not been established	Cream: 0.05% Ointment: 0.05%
Fluocinolone	Cream, ointment, and solution: Apply a thin layer to affected areas 2-4 times per day Oil: Apply thin film to affected area 3 times daily Shampoo : Apply no more than 1 ounce to scalp 1 time daily, lather, keep on scalp for 5 minutes, and rinse thoroughly	Cream, ointment, and solution: Apply a thin layer to affected areas 2-4 times per day Oil: Apply to moistened skin 2 times daily Shampoo : Apply no more than 1 ounce to scalp 1 time daily, lather, keep on scalp for 5 minutes, and rinse thoroughly	Cream: 0.01%, 0.025% Oil: 0.01% Ointment: 0.025% Shampoo: 0.01% Solution: 0.01%
Fluocinonide	0.05% strength: Apply a thin layer to affected area 2-4 times daily 0.1% strength: Apply a thin layer 1-2 times daily	0.05% strength: Apply a thin layer to affected area 2-4 times daily 0.1% strength: Apply a thin layer 1-2 times daily	Cream: 0.05%, 0.1% Gel: 0.05% Ointment: 0.05% Solution: 0.05%
Flurandrenolide	Apply once daily (may be changed every 12 hours to minimize adverse effects)	Apply once daily (may be changed every 12 hours to minimize adverse effects)	Tape: 4 mcg/cm^2
Fluticasone	Atopic dermatitis: Apply sparingly to affected	Atopic dermatitis in children >3 months of age:	Cream: 0.05%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	area 1-2 times daily Corticosteroid-responsive dermatoses: Apply sparingly to affected area 2 times daily	Cream: apply sparingly to affected area 1-2 times daily Atopic dermatitis in children >1 year of age: Lotion: apply sparingly to affected area 1 time daily Corticosteroid-responsive dermatoses in children >3 months of age: Cream: apply sparingly to affected area 2 times daily	Lotion: 0.05% Ointment: 0.005%
Halcinonide	Apply sparingly 1-3 times daily, occlusive dressing may be used	Apply sparingly 1-3 times daily, occlusive dressing may be used	Cream: 0.1% Ointment: 0.1%
Halobetasol	Apply sparingly to skin 2 times daily, rub in gently and completely	Children 12 years of age and older: Apply sparingly to skin 2 times daily, rub in gently and completely	Cream: 0.05% Ointment: 0.05%
Halobetasol and ammonium lactate	Halobetasol ointment: Apply sparingly to skin 2 times daily, rub in gently and completely. Ammonium lactate lotion: Apply to dry skin 2 times daily or as directed; rub in completely.	Halobetasol: Children >12 years of age : Apply sparingly to skin 2 times daily, rub in gently and completely Ammonium lactate: Children >2 years of age: Apply to dry skin 2 times daily or as directed; rub in completely.	Combination package: Halobetasol 0.05% ointment and ammonium lactate 12% lotion
Hydrocortisone	Apply to affected area 2-4 times daily Enema: Use 10-100 mg 1-2 times daily for 2-3 weeks	Apply to affected area 2-4 times daily Enema: Safety and efficacy in children have not been established	Cream: 0.5%, 1%, 2.5% Lotion: 1%, 2.5% Ointment: 0.5%, 1%, 2.5% Rectal cream: 1%, 2.5% Rectal enema: 100 mg/60 ml Solution: 2.5%
Hydrocortisone and aloe vera	Apply to the affected area as a thin film 2-4 times daily depending on the severity of the condition.	Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen.	Cream: 1% Ointment: 1%
Hydrocortisone, mineral oil and white petrolatum	Apply to the affected area as a thin film 2-4 times	Administration of topical corticosteroids to children	Ointment: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily depending on the severity of the condition.	should be limited to the least amount compatible with an effective therapeutic regimen.	
Hydrocortisone acetate	Apply to affected area 2-4 times daily	Apply to affected area 2-4 times daily	Cream: 0.5%, 1% Ointment: 1% Rectal foam: 10% Rectal cream: 2.5%
Hydrocortisone acetate and aloe vera	Apply to the affected area as a thin film 2-4 times daily depending on the severity of the condition.	Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen.	Cream: 0.5% Gel: 2% Liquid: 2%
Hydrocortisone acetate and pramoxine	Apply to affected area 3-4 times daily.	Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen.	Rectal foam: 1%-1% Rectal lotion: 2.5%-1%
Hydrocortisone acetate and urea	Apply to the affected area as a thin film 2-4 times daily depending on the severity of the condition.	Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen.	Cream: 1%-10%
Hydrocortisone butyrate	Apply to affected area 2-3 times daily	Apply to the affected area once daily	Cream: 0.1% Liquid: 0.1% Ointment: 0.1% Solution: 0.1%
Hydrocortisone probutate	Apply to affected area 1-2 times daily	Safety and efficacy in children have not been established	Cream: 0.1%
Hydrocortisone valerate	Apply to affected area 2-3 times daily	Safety and efficacy in children have not been established	Cream: 0.2% Ointment: 0.2%
Mometasone	Cream and ointment: Apply a thin film to affected area of the skin once daily Solution: Apply a few drops to affected area once daily	Children 2 years of age and older (cream and ointment): Apply a thin film to affected area of the skin once daily Children 12 years of age and older (solution): Apply a few drops to affected area once daily	Cream:0.1% Ointment: 0.1% Solution: 0.1%
Prednicarbate	Apply a thin film to affected area 2 times daily	Safety and efficacy in children have not been established	Cream: 0.1% Ointment: 0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Triamcinolone	Aerosol: Apply to affected area 3-4 times daily Cream, lotion, and ointment: Apply a thin film 2-4 times daily Paste: Press a small dab (1/4 inch) to the lesion until a thin film develops up to 4 times daily	Aerosol: Apply to affected area 3-4 times daily Cream, lotion, and ointment: Apply a thin film 2-4 times daily Paste: Press a small dab (1/4 inch) to the lesion until a thin film develops up to 4 times daily	Aerosol: 0.147 mg/g Cream: 0.025%, 0.1%, 0.5% Dental paste: 0.1% Lotion: 0.025%, 0.1% Ointment: 0.025%, 0.05%, 0.1%, 0.5%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane anti-inflammatory agents are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Skin and Mucous Membrane Anti-inflammatory Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atopic Dermatitis				
Kuokkanen et al.[58] (1998) Alclometasone dipropionate 0.05% ointment, applied twice daily vs. hydrocortisone 1% ointment, applied twice daily	RCT, DB Children with eczema Alclometasone was applied to one side, and hydrocortisone to the other	N=34 3 weeks	Primary: Potential for induction of cutaneous atrophy; severity of erythema, induration, pruritus; global evaluation	Primary: At endpoint, the percent improvement in sign and symptom severity seen in the alclometasone and hydrocortisone treatment sides were 88% and 86%, respectively.
Bickers.[59] (1984) Amcinonide 0.1% cream, applied twice daily vs. halcinonide 0.1% cream, applied twice daily	RCT, DB, PG Patients aged 17-84 years with acute or subacute eczematous dermatitis	N=33 2 weeks	Primary: Itching, burning, pain, erythema, edema, excoriation, vesiculation, crusting, scaling, lichenification, plaques, pigmentation changes, secondary skin infection, fissuring Secondary: Cosmetic acceptability questionnaire	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 (0.25≤P≤0.82). Secondary: No significant difference in cosmetic acceptability was seen between the two treatment groups (P=0.92).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lassus[57] (1984) Alclometasone dipropionate 0.05% cream, applied twice daily vs. clobetasol butyrate 0.05% cream, applied twice daily	RCT, DB, PG Children with stable or worsening atopic dermatitis	N=43 2 weeks	Primary: Erythema, induration, pruritus, physician global evaluation	Primary: Average percent reduction in disease signs was greater for the clobetasol group (86%) compared to the alclometasone group (85%), respectively (P>0.10). Physicians deemed 9/22 patients in the alclometasone group cleared compared to 10/21 patients in the clobetasol group (P>0.10).
Guenther et al.[60] (1981) Amcinonide 0.1% cream, applied twice daily vs. halcinonide 0.1% cream, applied twice daily	DB, PG Patients aged 16 to 71 years 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 1 and 2, with the exception of pigmentation changes at week 1 (P=0.10 to 0.001). Halcinonide-treated patients had significantly greater improvements in fissuring at week 1; however, there was no apparent difference at week 2. At week 2, 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 amcinonide patients reported complete relief vs. 4 of 7 halcinonide patients). There were no major differences among other signs and symptoms between the groups at week 2. Secondary: No significant difference was reported between the two treatment groups.
Breneman et al.[85] (2005) Clobetasol lotion	RCT, AC, PC, MC, SB Patients with moderate to severe atopic	N=229 4 weeks	Primary: Success rate (derived from Global Severity	Primary: At the end of the 2 week treatment period (LOCF) the proportion of subjects who achieved "success" was significantly higher in the lotion group compared to the vehicle group (72.9% vs.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied twice daily for 2 weeks vs. clobetasol cream applied twice daily for 2 weeks vs. placebo lotion applied twice daily for 2 weeks	dermatitis		scale - GSS) Secondary: Global Severity Scale (full-scale); individual disease scores of erythema, excoriation, induration/papulation, lichenification, oozing/crusting, and dryness/scaling; pruritus, global improvement	36.4%; P=0.001). There was no difference between the active treatments (72.9% vs. 74.0%). At all other time points, success rates for the lotion group were significantly higher than for the vehicle group (P<0.05), and were non-inferior to the emollient cream group (P>0.05). After the 2-week treatment-free period, success rates for both the lotion and cream groups remained significantly higher relative to those observed in the lotion vehicle 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 2, the full-scale GSS for the lotion group was significantly lower than that for the vehicle group (P=0.001); there was no difference between the 2 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 vehicle 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 2 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 vehicle group (P=0.002). Global improvement at the 2 week endpoint demonstrated that the lotion group was more effective that the vehicle 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 showed improvement, whereas the majority of subjects in the vehicle group showed no changes.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wolkerstorfer et al.[61] (1998) Clobetasone butyrate (CB) 0.05% cream, applied twice a day vs. fluticasone propionate (FP) 0.05% cream, applied once daily	RCT, DB Children aged 3 to 8 with moderately active atopic dermatitis	N=21 4 weeks	Primary: Modified Scoring of Atopic Dermatitis system (SCORAD)	Primary: There were no statistically significant differences between the FP and the CB treatment groups in SCORAD improvements (P=0.8).
Jorizzo et al.[62] (1995) Desonide 0.05% ointment, applied twice daily vs. hydrocortisone 1% ointment, applied twice daily	RCT, MC, SB, PG Children no older than 12 years of age with mild to moderate atopic dermatitis	N=111 5 weeks (with a 6 month extension for 36 of the patients)	Primary: Global improvement, erythema, lichenification, excoriations, oozing or crusting, pruritus, induration	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.
Lucky et al.[63] (1997) Desonide 0.05% ointment, applied twice a day vs. hydrocortisone 2.5%	RCT Pediatric patients with atopic dermatitis affecting at least 20% of their body surface area Early morning cortisol levels were determined before treatment	N=15 28 days	Primary: Hypothalamic-pituitary-adrenal (HPA) axis suppression assessed by laboratory evaluation of early morning cortisol levels and by the	Primary: No significant differences were seen in either early morning cortisol levels or ACTH-stimulated mean cortisol values from baseline to endpoint.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ointment, applied twice a day	initiation and on days 14 and 28. Adrenocortico-tropic hormone (ACTH)-stimulated mean cortisol values determined before treatment and on day 28		determination of ACTH-stimulated mean cortisol values	
Ashton et al.[67] (1987) Desoxymethasone 0.25% cream, applied twice daily vs. desoxymethasone 0.05% cream, applied twice daily vs. betamethasone valerate 0.1% cream, applied twice daily vs. hydrocortisone 1%, cream applied twice daily	DB, PG, MC Patients aged 2 years and older with eczema	N=96 3 weeks	Primary: Erythema/redness, scaling, itching, extent of area affected	Primary: Based on final clinician assessment scores, the difference in erythema was most significant between the desoxymethasone 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 desoxymethasone 0.25% and hydrocortisone (P=0.014). There was a greater decrease in the extent of area affected final mean score for desoxymethasone 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 desoxymethasone 0.25% (4.3) and betamethasone (2.5) was significant (P=0.047). The difference between desoxymethasone 0.25% when compared to hydrocortisone at week 3 was also significant (P=0.001). The mean scores for scaling were 0.8 for desoxymethasone 0.25%, 1.5 for desoxymethasone 0.05%, 0.8 for betamethasone, and 3.0 for hydrocortisone (P=0.01). The patient mean scores for extent of affected area were 1.5 for desoxymethasone 0.25%, 2.6 for desoxymethasone 0.05%, 2.0 for betamethasone, and 3.8 for hydrocortisone (P=0.08).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The patient mean scores for itching were 1.2 for desoxymethasone 0.25%, 2.5 for desoxymethasone 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).
Delescluse et al.[64] (1996) Fluticasone propionate 0.005% ointment, applied twice daily vs. betamethasone dipropionate 0.05% ointment, applied twice daily	RCT, DB, PG, MC Patients with moderate-to-severe eczema	N=92 4 weeks	Primary: Physician assessment of clinical response, sign and symptom severity, patient assessment of treatment	Primary: Improvement was seen in sign and symptom severity in both treatment groups at 2 and 4 weeks. There was no statistically significant difference in efficacy variables between fluticasone and betamethasone.
Friedlander et al.[54] (2002) Fluticasone propionate 0.05% cream, applied twice a day	OL, MC Pediatric patients aged 3 months to 6 years with moderate to severe atopic dermatitis (greater than or equal to 35% of their body surface area)	N=51 4 weeks	Primary: Serum cortisol response, fluticasone levels	Primary: Mean stimulated and unstimulated cortisol levels were similar before and after treatment (13.76 ± 6.94 mcg/dL pre-stimulation and 30.53 ± 7.23 mcg/dL post-stimulation vs. 12.32 ± 6.92 mcg/dL pre-stimulation and 28.84 ± 7.16 mcg/dL post-stimulation). Two patients had endpoint post-stimulation less than 18.0 mcg/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).
Eichenfield et al.[86] (2006) Fluticasone 0.05% lotion applied once daily	RCT, DB, PC, PG Patients aged 3 months and older with moderate to severe atopic dermatitis	N=438 4 weeks	Primary: Treatment success (defined as PGA of 50% or more lesional clearance and	Primary: In study A, 75% of fluticasone-treated patients were considered to have a treatment success compared to 31% of vehicle-treated patients (P<0.001). In study B, 66% of fluticasone-treated patients were considered

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. vehicle lotion applied once daily publication reviews the results of two trials with same patient population and treatment strategy			stable/improved scores in 75% or more of the 20 sign/symptom assessments) Secondary: Physician's Global Assessment (PGA), sign/symptom severity, and subject/parent assessment	to have a treatment success compared to 26% of vehicle-treated patients (P<0.001). For subjects aged 3 to 12 months, there were 13 (76%) treatment successes on fluticasone compared with 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 vehicle-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 vehicle-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 vehicle-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 once daily vs. placebo cream applied once daily	RCT, DB, MC, PC Patients with atopic dermatitis	N=168 14 days	Primary: Severity of dermatitis signs based on the mean lesion score for: infiltration, scaling, erythema, lichenification, vesicles, papules, excoriation, pruritus Secondary: overall improvement;	Primary: At day 3 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 7 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 3, the investigators gave a rating of cleared, excellent, or good, in terms of overall improvement, to a total of 36/98 patients in the hydrocortisone group, compared to 6/58 patients in the placebo group (P=0.0004). The same ratings were given to 65/103 hydrocortisone patients and 17/60 in the placebo group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			overall treatment efficacy; cosmetic acceptability	on day 7 (P=0.0001); and, at endpoint, there were 72/93 in the hydrocortisone group compared to 19/54 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.[68] (2005) Hydrocortisone butyrate (HB) 0.1% cream, applied vs. fluticasone propionate (FP) 0.05% cream or prednicarbate (PC) 0.1% cream or mometasone furoate (MF) 0.1% cream	RCT, DB, MC, PG Patients aged 18-65 with moderate hand dermatitis or atopic dermatitis HB was applied to one side and either FP, PC, or MF was applied to the other	N=89 2 weeks	Primary: Investigator and subject ratings of signs and symptoms: erythema, cracking/fissuring, scaling, papules/ vesicles	Primary: Based on the investigators' observations, the rate of improvement of cracking/fissuring was greater in the HB (43%) group compared to the PC (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 HB (50%) group compared to the FP (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).
Roth et al.[69] (1978) Hydrocortisone valerate	RCT, DB Patients aged 2-75 years with chronic atopic	N=68 4 weeks (HC	Primary: Overall response, pruritus, erythema, scaling,	Primary: Overall response was in favor of the HCV group compared to the HC group, with 11 patients showing a better response compared to 3 patients, respectively (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(HCV) 0.2% cream, applied 3 times a day vs. hydrocortisone (HC) 0.1% cream, applied 3 times a day vs. betamethasone valerate (BMV) 0.1% cream, applied 3 times a day vs. vehicle applied 3 times a day	dermatitis	vs. placebo was 2 weeks)	excoriation, lichenification, overall judgment of response HCV vs. BMV: Overall improvement score HCV vs. placebo: Overall improvement score	A consistently greater improvement in signs and symptoms was seen in the HCV group compared to the HC group at days 5-9, 12-16, and 26-35 (there was insufficient data for days 17-25). The only instances that were not proven to be significant were erythema at days 5-9 (P<0.10) and lichenification at days 5-9 and days 12-16 (P>0.10 and P<0.10, respectively). HCV vs. BMV: Both treatment groups had moderate improvement in clearing which was not significantly different between the two groups. HCV vs. placebo: More patients in the HCV treatment group demonstrated excellent improvement or better compared to placebo, a difference that was significant.
Williamson[82] (1987) Hydrocortisone 1% and urea 10% cream applied twice daily to lesions on the left side of the body vs. betamethasone valerate 0.1% applied twice daily to lesions on the right side of the body	SB, RCT Males and females over the age of 12 years with bilateral, approximately symmetrical, lesions of dry exogenous eczema of the limbs or trunk	N=32 3 weeks	Primary: Assessment of eczema severity based on a scale of 0-7; severity of erythema, dryness/scaling, papules, itching, and excoriation using a 0-4 scale Secondary: Patient self-assessment questionnaire	Primary: Overall severity scores showed a steady improvement in the patients' eczema over the 3 weeks of the study, this being the same for both preparations. The results of the six individual measures also showed 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.[65] (2001)	RCT, SB Patients with refractory	N=27 4 weeks	Primary: Disease extent and severity	Primary: The difference in efficacy between the mometasone and fluticasone treatments was not statistically significant in terms of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mometasone furoate 0.1% ointment, applied once daily vs. fluticasone 0.005% ointment, applied once daily One treatment group applied medication without wet wrap dressings (Group I [fluticasone] and II [mometasone]); the other had 2 weeks without wet wrap dressings followed by 2 weeks of medication application under a wet wrap (Group III [fluticasone] and IV [mometasone])	atopic dermatitis			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 2-4 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 3 with P values of 0.043, 0.008, and 0.011, respectively (P=0.116 for Group I). During week 4, 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).
Lebwohl[66] (1999) Mometasone furoate 0.1% cream, applied once daily vs. hydrocortisone valerate 0.2% cream, applied twice daily	RCT, MC Pediatric patients aged 2-12 years with atopic dermatitis who had failed a topical hydrocortisone preparation	N=219 3 weeks	Primary: Total sign and symptom score, physician assessment of global clinical response	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Moshang.[55] (2001) Prednicarbate 0.1% emollient cream, applied twice daily	MC, OL Pediatric patients aged 4 months–12 years with atopic dermatitis that involved a minimum of 20% of their body surface	N=55 3 weeks	Primary: Global evaluations, sign/symptom scores, cosmetic acceptability	Primary: The percentage of patients who had greater than or equal to 75% clearance of their atopic dermatitis was 33% of patients on day 8 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 8, 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.
Korting et al.[70] (1992) Prednicarbate 0.25% cream or prednicarbate corresponding vehicle cream vs. betamethasone-17-valerate 0.1% cream or clobetasol-17-propionate 0.05% cream	DB, RCT Patients with atopic eczema Prednicarbate or its vehicle cream were applied to one forearm and betamethasone or clobetasol was applied to the other	N=24 6 weeks	Primary: Skin thickness	Primary: Clobetasol and betamethasone were found to decrease skin thickness greater than either prednicarbate or its vehicle. The decrease in skin thickness was greater with betamethasone compared to clobetasol, but this was statistically insignificant. Also, the decrease in skin thickness was greater with prednicarbate compared to its vehicle, but this was statistically insignificant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Psoriasis				
Huntley et al.[35] (1985) Amcinonide 0.1% ointment, applied twice daily vs. betamethasone dipropionate 0.05% ointment, applied twice daily	RCT, DB, PG 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 1 evaluation point, an overall investigator rating of either "excellent" or "good" was made for 14/16 patients in the amcinonide group compared to 8/15 patients in the betamethasone group (P<0.05). At the week 1 evaluation point, an overall patient rating of either "excellent" or "good" was made for 15/16 patients in the amcinonide group compared to 12/15 patients in the betamethasone group (P<0.05). There were no significant differences in the overall improvement between 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 1 (P=0.05) and itching at week 2 (P=0.01). Secondary: There was no difference in the secondary end points between the two treatment groups.
Cornell[36] (1983) Amcinonide 0.1% ointment, applied twice daily vs. fluocinonide 0.05% ointment, applied three times daily	RCT, DB, PG Patients with psoriasis for a minimum of 5 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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference was reported between the two treatment groups.
Engel[37] (1982) Amcinonide 0.1% ointment applied twice daily vs. fluocinonide 0.05% ointment applied 3 times a day	RCT, DB, PG Patients with psoriasis	N=50 3 weeks	Primary: Total score based on (a) severity of signs: crusting, erythema, papules/plaques, scales, pustules (b) severity of symptoms: itching, burning, pain	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 22/26 (85%) amcinonide patients and 18/24 (75%) fluocinonide patients, respectively.
Millikan et al.[38] (1986) Amcinonide 0.1% ointment, applied topically twice a day vs. halcinonide 0.1% ointment, applied topically twice a day	DB, PG Patients aged 18-75 years with psoriasis	N=32 2 weeks	Primary: Patient- and investigator-measured: itching, burning, pain, erythema, papules or plaques and scales Secondary: Patients completed a cosmetic acceptability questionnaire	Primary: Evaluation at day 7 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 7 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 7 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: Results of questionnaire were not reported
Katz et al.[39] (1995) Betamethasone	RCT, MC, SB, PG Patients 18 years of age and older with at least	N=193 2 weeks	Primary: Scaling, induration, erythema, pruritus,	Primary: At day 4, the mean percent improvement for the betamethasone group was 39.1% compared to 31.8% in the clobetasol group, respectively (P=0.010).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dipropionate 0.05% lotion, applied twice a day vs. clobetasol propionate 0.05% solution, applied twice a day	20% scalp-surface involvement of moderate-to-severe scalp psoriasis that had been stable or worsening for more than 1 week prior to enrollment		complied into a total sign and symptom score	The percent improvement was greater in the betamethasone group at day 8, 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).
Jacobson et al.[40] (1986) Betamethasone dipropionate 0.05% ointment, applied twice daily vs. clobetasol propionate 0.05% ointment, applied twice daily Betamethasone was applied to one side and clobetasol to the other	MC, DB 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	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 (3 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).
Shupack et al.[41] (1993) Betamethasone	RCT, DB, PG Patients aged 18 years and older who have had	N=44 2 weeks	Primary: Erythema, scaling, induration, investigator's	Primary: No statistically significant differences were found between the treatment groups in erythema, scaling, and induration.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dipropionate 0.05% ointment vs. diflorasone diacetate 0.05% ointment	moderate-severe plaque-type psoriasis for at least 6 months		evaluation Secondary: Patient satisfaction	At the week 1 physician evaluation, 18/21 patients in both the betamethasone and diflorasone treatment groups were rated as either cleared or improved, with these results remaining virtually unchanged for week 2. Secondary: Patient satisfaction was considered high within both treatment groups.
Barsky[42] (1976) Betamethasone 0.025% gel, applied 3 times a day vs. fluocinonide 0.05% gel, applied 3 times a day Betamethasone was applied to one side and fluocinonide to the other	RCT, DB, MC Patients older than 2 years with psoriasis	N=263 3 weeks	Primary: Physician evaluation of therapeutic response Secondary: Physician and patient preference (2-definite preference for fluocinonide, 1-slight preference, 0- no preference, -2 definite preference for betamethasone, -1 slight preference	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: The mean physician preference score was 0.912, and the mean patient preference score was 0.908 (P<0.0001).
Pacifico et al.[43] (2006) Betamethasone valerate 0.12% cream, applied once daily vs.	RCT, PRO, SB Patients with mild to moderate psoriasis	N=42 30 days	Primary: Psoriasis Area and Severity Index (PASI) scores; hydration based on cutaneous trophism evaluation Secondary:	Primary Lesions treated with BMV tape had a greater reduction in the PASI score compared to the BMV cream with a mean percentage reduction of 59.3% and 38.4%, respectively (P<0.001). The self-administered PASI score (SAPASI) had a greater percentage reduction on the tape side (61.8%) compared to the cream side (34.0%), respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
betamethasone valerate (BMV) 0.1% tape, applied once daily BMV cream was applied to one side and BMV tape was applied to the other			Patient quality-of-life questionnaire	The mean percentage of skin hydration was increased with the BMV 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.
Bergstrom et al.[44] (2003) Clobetasol propionate 0.05% foam, applied to the skin and scalp vs. clobetasol cream 0.05%, applied to the skin and clobetasol 0.05% solution, applied to the scalp	RCT, SB, Patients with psoriasis	N=32 14 days	Primary: Patient quality of life (QOL); effectiveness, user satisfaction; severity based on the psoriasis area and severity index (PASI) and self-administered PASI (SAPASI)	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 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jegasothy[45] (1990) Clobetasol propionate 0.05% ointment, applied twice a day vs. diflorasone diacetate 0.05% ointment, applied twice a day Clobetasol was applied to one side and diflorasone the other	RCT, DB 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 8, day 15, and at follow-up when compared to diflorasone (P<0.05).
Decroix et al.[51] (2004) Clobetasol propionate lotion, applied twice daily vs. clobetasol propionate lotion vehicle, applied twice daily vs. clobetasol propionate cream, applied twice daily	RCT, MC, SB, PC, PG Patients aged 18 years and older with moderate to severe plaque type psoriasis	N=213 4 weeks	Primary: Dermatologic Sum Score (DSS), Global Severity Score (GSS) Secondary: Patient cosmetic acceptability survey	Primary: Both the DSS and the GSS had a greater improvement in the lotion and cream groups when compared to the vehicle 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 vehicle 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).
Lowe et al.[52] (2005)	RCT, MC, SB, PC, PG Patients with moderate	N=192 4 weeks	Primary: Erythema, plaque elevation, scaling,	Primary: The difference in DSS between clobetasol lotion and its vehicle was statistically significant, with values of 2.21 and 5.93,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clobetasol propionate lotion, applied twice daily vs. clobetasol propionate emollient cream, applied twice daily vs. clobetasol lotion vehicle, applied twice daily	to severe plaque-type psoriasis		Dermatological Sum Score (DSS), pruritus, global improvement global severity	respectively (P<0.001). When compared with the cream, the lotion resulted in no significant difference in DSS improvement. The number of patients that had mild or no signs and symptoms was greater in the lotion group compared to its vehicle (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).
Mraz et al.[84] (2008) Clobetasol 0.05% spray applied twice daily for up to 4 weeks vs. clobetasol 0.05% foam applied twice daily for 2 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 (BSA) 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). 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.[46] (1986) Desoximetasone 0.05%	RCT, DB, MC, PG Patients with scalp psoriasis	N=123 2 weeks	Primary: Mean sign and symptom score based on severity	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	Sample Size and Study Duration	End Points	Results
gel, applied twice daily vs. fluocinonide 0.05% gel, applied twice daily			of erythema, scaling, thickening, and pruritus Secondary: Patient cosmetic acceptability	Eighty-nine percent (54/61) of patients in the desoximetasone group and 82% (49/60) 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[47] (1976) Desoximetasone 0.25%, applied twice daily vs. hydrocortisone butyrate 0.1%, applied twice daily Desoximetasone was applied to one side and hydrocortisone to the other	RCT, DB Patients with psoriasis	N=27 2 weeks	Primary: Erythema, induration, scaling, pruritus, pustulation Secondary: Patient preference	Primary: After 2 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: 13 patients preferred desoximetasone, and 3 patients preferred hydrocortisone (P<0.05).
Anonymous[48] (1985) Desoximetasone 0.25% ointment, applied twice a day vs. fluocinonide 0.05% ointment, applied twice a day	RCT, MC, SB, PG Patients 3 years of age and older 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 4 (P=0.065); 2.0 and 2.28, respectively at day 7 (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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The percentage of patients with an excellent improvement was greater in the desoximetasone group compared to the fluocinonide group at day 4 and 14 (day 4: 32% vs. 18%, respectively, P=0.046; day 14: 42% vs. 25%, respectively, P=0.028).
Kruger et al.[49] (1987) Flurandrenolide tape, 4 mg/cm^2 applied to lesions on one side of the body once daily for up to 16 hours vs. diflorasone diacetate 0.05% ointment, applied contralaterally twice daily	RCT, SB Patients 18 years of age and older with stable, bilaterally symmetric plaque psoriasis with up to 10% of body surface area involved	N=30 4 weeks	Primary: Lesions were evaluated for erythema, scaling, and induration, all measured on a 0-3 scale (0=none, 3=severe); the sum of these scores (ESI), was evaluated by the investigator at baseline, week 2, and week 4	Primary: At baseline, the ESI values for both groups was 5.8 (P=0.68). At the week 2 evaluations, the ESI 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 4 evaluation, the ESI was also less for the flurandrenolide tape group versus the diflorasone group, with values of 1.6 and 2.7, respectively. Compared to baseline, the ESI score for the flurandrenolide tape group decreased by 72%, and the diflorasone ointment group decreased by 53% (P<0.01). Flurandrenolide-tape-treated psoriatic plaques showed more positive results in overall treatment success with a rate of 60% at week 2 and 64% at week 4. The overall treatment success rates for diflorasone ointment at week 2 and week 4 were 22% and 33%, respectively (P<0.01).
Swinehart et al.[50] (1989) Mometasone furoate 0.1% lotion, applied once daily vs. triamcinolone acetonide 0.1% lotion, applied twice daily	RCT, PG, MC 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	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			treatment	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.[53] (1988) Mometasone furoate 0.1% ointment or cream, applied once daily vs. fluocinolone acetonide 0.025% ointment or cream, applied 3 times daily and mometasone furoate 0.1% ointment or cream, applied once daily vs. triamcinolone acetonide 0.1% ointment or cream, applied twice daily	RCT, SB, PG, MC Patients with chronic moderate to severe psoriasis vulgaris that had been stable or worsening for more than a week were enrolled in 1 of the 4 studies	N=764 21days	Primary: Evaluation of individual disease signs in the target areas and change in disease sign score; change in overall disease status	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). 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).
Multiple Dermatoses				
Rocha et al.[71] (1976) Amcinonide 0.1% cream, applied twice a	DB Patients with atopic dermatitis, contact dermatitis, and eczema	N=60 3 weeks	Primary: Investigator assessment of clinical response, patient assessment	Primary: Amcinonide and betamethasone treatment groups demonstrated improvement in objective and subjective parameters over the course of 3 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
day vs. betamethasone valerate 0.1% cream, applied twice a day			of clinical response Secondary: Cosmetic acceptability	Investigator's overall ratings of efficacy was comparable for the 2 treatment groups (P=0.38). All 30 amcinonide patients rated its efficacy as excellent compared to 27/30 betamethasone patients (the remaining 3 gave a rating of good; P=0.24). Secondary: No significant difference was found between treatment groups (0.42≤P≤1.00).
Rosenberg[72] (1979) Amcinonide 0.1% cream, applied twice a day vs. betamethasone valerate 0.1% cream, applied twice a day	RCT, DB, PG 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	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).
Rhodes et al.[73] (1983) Betamethasone dipropionate (Diprosone®) 0.05% cream, applied twice daily vs. betamethasone valerate	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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
0.1% cream, applied twice daily				
Levy[74] (1977) Betamethasone dipropionate 0.05% cream, applied twice daily vs. halcinonide 0.1% in a water-miscible base, applied once daily	RCT Patients with acute and chronic dermatoses, including psoriasis, lichen chronicus simplex, eczema, contact dermatitis, neurodermatitis, and atopic 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 infiltration and remission of chronic inflammation Acute dermatoses at the exacerbation stage (eczema, contact dermatitis, neurodermatitis): relief of acute inflammation, pruritus	Primary: Psoriasis: There was a greater improvement in the 4 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. Eczema: 6/8 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.
Bluefarb[75] (1972) Betamethasone valerate 0.1% cream vs. desonide 0.05% cream	RCT, DB 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	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%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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%).
Vollum et al.[76] (1979) Betamethasone valerate 0.1% ointment applied to one side of the face vs. halcinonide 0.1% applied to the other side of the face	RCT, DB Patients with lesions of bilateral eczema or psoriasis	N=38	Primary: Improvement in lesions on one side of the patient's face compared to the other	Primary: There were 10 clinicians who chose betamethasone valerate, 0 that preferred halcinonide, and 5 that found no difference (P<0.05). Among patients with eczema, there was no statistical difference between the two medications.
Wishart et al.[77] (1993) Betamethasone valerate 0.1% cream, applied twice daily vs. mometasone furoate 0.1% cream, applied once daily	RCT, MC, PG 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	Primary: At 4 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.
Jegasothy et al.[78] (1985) Clobetasol propionate 0.05% cream, applied three times daily vs.	DB, PG, MC Patients aged 13-75 years with either psoriasis or chronic eczema	N=227 2 weeks	Primary: Physician global assessment, sign and symptom severity, patient evaluation of improvement	Primary: After 2 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluocinonide 0.05% cream, applied three times daily				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 2 weeks, 89% of eczema patients treated with clobetasol had 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.
Bleeker[79] (1975) Clobetasol propionate 0.05% cream, applied twice daily vs. halcinonide 0.1%, applied twice daily	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	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, 7 had either marked or slight improvement with halcinonide, compared to 6 with clobetasol. The remaining 14 patients had an equal response to both treatments. Eczema: Among the 20 patients with atopic dermatitis, 1 had either marked or slight improvement with halcinonide, compared to 5 with clobetasol. The remaining 14 patients had an equal response to both treatments.
Barsky[80] (1976) Desonide 0.05% cream, applied twice daily vs.	RCT, DB Patients with dermatologic disorders, including eczema, seborrheic dermatitis, contact dermatitis, and	N=78 2 weeks	Primary: Erythema, scaling, pruritus, palpable induration Secondary: Physician's scoring	Primary: The desonide group had a greater improvement in erythema and scaling compared to the fluocinonide group in week 1 (P<0.05); however, the difference was not statistically significant in week 2. There was no significant difference between the treatment groups in all other signs and symptoms (all P values >0.25 or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluocinonide 0.05% cream, applied twice daily	lichen simplex		of improvement	more). Secondary: There was no significant difference in the overall physician evaluation between treatment groups at week 1 or endpoint (P>0.20 and P>0.60, respectively).
Kelly et al.[81] (1991) Mometasone furoate (MF) 0.1% cream, applied once daily vs. betamethasone dipropionate (BD) 0.05% cream, applied twice daily	RCT, SB, MC, PG Patients 15 years of age and older 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 15/33 patients in the MF group who left the study prior to day 85 due to the fact that their lesions were cleared. This corresponds to 18/32 patients in the BD patients. The difference in mean sign and symptom scores at end point was not statistically significant between the 2 treatment groups (MF mean=3.0; BD mean=2.5; P=0.68). The mean percent improvement was not statistically significant; there was a 74.4% improvement for the MF group and an 80.1% improvement in the BD side (P=0.51). Secondary: The only instance in which the mean plasma cortisol levels between the 2 groups reached statistical significance was at day 8. The change in mean plasma cortisol level for the MF group at day 8 was 6.1, and for the BD group the change was -86.0 (P=0.02).
Other				
Greer et al.[83] (1984) Hydrocortisone 1% and pramoxine 1% in a water-miscible mucoadhesive foam base, applied four times daily	RCT, DB, PC 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	Primary: No significant difference was found between mean total daily scores on days 1 or 3, but a significant difference existed in favor of placebo on day 5. Secondary: Subjective response to treatment showed no difference between groups (P>0.1) although healing was better with placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. simple aqueous foam as placebo, applied four times daily			(the higher the score, the greater the severity of the symptoms) Secondary: Healing and overall subjective response to treatment at day 5	Mean individual criterion scores were also compared, but showed no difference except in edema on day 5, mobility on day 3, and analgesic requirements on days 3 and 5, when placebo was more effective.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, SB=single-blind, DB=double-blind, LOCF=last observation carried forward, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, 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 Anti-inflammatory Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alclometasone	cream, ointment	Aclovate®*	$$-$$$$	$
Amcinonide	cream, lotion, ointment	N/A	N/A	$$
Betamethasone dipropionate	cream, gel, lotion, ointment	N/A	N/A	$-$$$
Betamethasone dipropionate and propylene glycol	cream, lotion, ointment	Diprolene®*, Diprolene AF®*	$$$-$$$$	$-$$$
Betamethasone valerate	cream, foam, lotion, ointment	Luxiq®	$$$$-$$$$$	$
Clobetasol	cream, foam, gel, lotion, ointment, shampoo, solution, spray	Clobex®, Cormax®*, Olux®*, Olux-Olux-E®, Olux-E®, Temovate®*	$$-$$$$$	$-$$$$
Clocortolone	cream	Cloderm®	$$-$$$$	N/A
Desonide	cream, foam, gel, lotion, ointment	Desonate®, Desowen®*, Verdeso®	$$$$$	$-$$
Desoximetasone	cream, gel, ointment	Topicort®*, Topicort LP®*	$$$-$$$$	$$$-$$$$
Diflorasone	cream, ointment	Apexicon®*, Apexicon E®,	$$-$$$$	$$-$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
		Psorcon E®		
Fluocinolone	cream, oil, ointment, shampoo, solution	Capex Shampoo®, Derma-Smoothe/FS®	$$-$$$$	$
Fluocinonide	cream, gel, ointment, solution	Vanos®	$$$-$$$$$	$
Flurandrenolide	tape	Cordran®	$$-$$$	N/A
Fluticasone	cream, lotion, ointment	Cutivate®*	$$$$-$$$$$	$$
Halcinonide	cream, ointment	Halog®	$$$-$$$$	N/A
Halobetasol	cream, ointment	Ultravate®*	$$$-$$$$	$$-$$$
Halobetasol and ammonium lactate	combination package	Ultravate PAC®	$$$$	N/A
Hydrocortisone‡	cream, lotion, ointment, rectal cream, rectal enema, solution	Aquanil HC®*, Beta HC®*, Cortaid®*, Cortenema®*, Dermolate Anti-Itch®*, Hytone®*, Preparation H®*, Proctocort®*, Proctocream-HC®*, Sarnol-HC®*	$	$
Hydrocortisone and aloe vera‡	cream, ointment	N/A	N/A	$
Hydrocortisone, mineral oil, and white petrolatum	ointment	N/A	N/A	$-$$
Hydrocortisone acetate‡	cream, ointment, rectal cream, rectal foam	Corticaine®*, Cortifoam®, Medi-Cortisone®*	$-$$$$	$
Hydrocortisone acetate and aloe vera‡	cream, gel, liquid	Nuzon®*, Nucort®	$-$$	$-$$
Hydrocortisone acetate and pramoxine	rectal foam, rectal lotion	Analpram-HC®, Proctofoam-HC®	$$$	N/A
Hydrocortisone acetate and urea	cream	Carmol HC®*, U-Cort®*	$$$	$
Hydrocortisone butyrate	cream, liquid, ointment, solution	Locoid®*, Locoid Lipocream®	$$$$	$-$$
Hydrocortisone probutate	cream	Pandel®	$$$-$$$$$	N/A
Hydrocortisone valerate	cream, ointment	Westcort®*	$$-$$$$	$
Mometasone	cream, ointment, solution	Elocon®*	$$$	$$
Prednicarbate	cream, ointment	Dermatop®*	$$$-$$$$	$$-$$$
Triamcinolone	aerosol, cream, dental paste, lotion, ointment	Kenalog®, Oralone in Orabase®*	$$-$$$	$-$$

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
N/A=Not available

X. Conclusions

The skin and mucous membrane anti-inflammatory agents are indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. This includes anogenital pruritus, atopic dermatitis, localized neurodermatitis, psoriasis, seborrheic dermatitis, and the inflammatory phase of xerosis.

Guidelines for the management of atopic dermatitis state that topical corticosteroids are the standard of care to which other treatments are compared; however, they do not give preference to one agent over another.[6-8] Rather, selection of the topical corticosteroid should take into account the disease severity, location of the lesions, patient's age, and anticipated duration of therapy.[6-8] Low-potency agents are recommended for maintenance therapy, whereas intermediate- and high-potency agents should be used for clinical exacerbations and should be applied over short periods of time.[6,8] Numerous clinical trials have demonstrated similar efficacy among the various topical corticosteroids for the treatment of atopic dermatitis.[57-61,63-65,68-72,74,76-77,79-82,85] Some clinical trials have demonstrated greater efficacy with one agent over another; however, these studies were comparing corticosteroids with different potencies.[62,66-67,69-70,73,75,78]

Guidelines for the management of psoriasis state that topical corticosteroids are the cornerstone of treatment for the majority of patients, particularly those with limited disease; however, they do not give preference to one agent over another.[3-5] As with atopic dermatitis, the selection of the topical corticosteroid should take into account the disease severity, location of the lesions, patient's age, and anticipated duration of therapy.[3] Lower potency corticosteroids should generally be used for limited periods of time on the face, intertriginous areas, areas with thin skin, and in infants.[3] In other areas and in adults, mid- or high-potency agents are generally recommended as initial therapy.[3-5] Patients with thick, chronic plaques often require treatment with the highest potency corticosteroids. Topical corticosteroids should not be used regularly; it is recommended that a gradual reduction in the frequency of usage following clinical response be instituted.[3-5] Several clinical trials have demonstrated similar efficacy among the various topical corticosteroids for the treatment of psoriasis.[35-38,41,46,74,77,79,81] Some clinical trials have demonstrated greater efficacy with one agent over another; however, these studies were comparing corticosteroids with different potencies.[40,45,47,49-50,53,75,78]

Topical corticosteroids are just one of many treatment options for seborrheic dermatitis.[9] Guidelines recommend liquid preparations (mild to potent) for the scalp and creams for other parts of the body (mild to potent).[9] Clinical trials in patients with multiple dermatoses, including seborrheic dermatitis, have demonstrated similar efficacy among the various topical corticosteroids.[72,77,80]

Guidelines for the treatment of hemorrhoids state that the cornerstone of therapy is adequate fiber intake and water.[10-11] Corticosteroid creams may ameliorate local perianal inflammation, but no data suggest that they actually reduce hemorrhoidal swelling, bleeding, or protrusion.[11] Over-the-counter topical agents and suppositories are often used in the empirical treatment of hemorrhoids, however data supporting their use is lacking.[11] A literature search did not reveal any published studies evaluating the use of the various hydrocortisone rectal preparations for the treatment of hemorrhoids.

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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antipruritics and Local Anesthetics
AHFS Class 840800
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I. Overview

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

Local anesthetics inhibit the conduction of nerve impulses from sensory nerves.[1-3] In general, 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.

Doxepin is a tricyclic antidepressant which blocks histamine receptors; however, the exact mechanism by which it exerts its antipruritic effect is unknown.[2] Hydrocortisone, a topical corticosteroid, has been combined with several local anesthetic products to reduce inflammation and alleviate itching.

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 antipruritic and local anesthetic products are available in a generic formulation. Pramoxine is also available over-the-counter. This class was last reviewed in February 2007.

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)
Benzocaine	lubricant	Americaine®	none
Doxepin	cream	Prudoxin®, Zonalon®	none
Ethyl chloride	spray	N/A	ethyl chloride
Hydrocortisone and lidocaine	cream, lotion, medi-pad, rectal cream, rectal kit	Anamantle HC®*, Anamantle HC Forte®*, Lidamantle HC®*, Peranex HC®	hydrocortisone and lidocaine
Hydrocortisone, lidocaine, and aloe vera	rectal gel, rectal kit	Anamantle HC®*, Peranex HC®*, Rectagel HC®*	hydrocortisone, lidocaine, and aloe vera
Lidocaine	cream, lotion, ointment, solution, transdermal patch	Lidamantle®*, Lidoderm®	lidocaine
Lidocaine, hydrocortisone, and psyllium husk	rectal kit	Xyralid RC®	none
Lidocaine, hydrocortisone, and skin cleanser no. 6	topical kit, combination package	Xyralid®, Xyralid LP®	none
Lidocaine and prilocaine	cream	EMLA®*	lidocaine and prilocaine
Lidocaine and tetracaine	topical patch	Synera®	none
Pramoxine‡	foam, gel	Proctofoam®, Pramox®	none
Tetracaine	solution	Pontocaine®	none

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
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 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)
American Academy of Dermatology (AAD), Clinical Guidelines Task Force: **Guidelines of Care for Atopic Dermatitis**[23] **(2004)**	• Topical corticosteroids are the standard of care to which other treatments are compared. • Emollients are a standard of care, steroid sparing, and useful for both prevention and maintenance therapy. • Calcineurin inhibitors, pimecrolimus, and tacrolimus have been shown to reduce the extent, severity, and symptoms of atopic dermatitis in adults and children. • Short-term adjunctive use of topical doxepin may aid in the reduction of pruritus, but the development of side effects may limit usefulness. • Oral antibiotics can be highly beneficial when skin infection is present. • Topical antibiotics can be effective when infection is present; however, development of resistance is a concern. • There is little evidence that sedating or nonsedating antihistamines are effective in relieving itch or urticarial symptoms associated with atopic dermatitis.
American Gastroenterological Association Medical Position Statement: **Diagnosis and Treatment of Hemorrhoids (2004)**[24]	• Treatment of hemorrhoids depends on their severity. • The cornerstone of medical therapy is adequate intake of 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**[25] **(2004)**	• The almost-universal recommendations are to add dietary fiber and to 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 symptomatic 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.
American Academy of Neurology: **Treatment of Postherpetic Neuralgia: An Evidence-Based Report of the Quality Standards Subcommittee**[26] **(2004)**	• Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), 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[1-19]

Indications	Benzocaine	Doxepin	Ethyl Chloride	Hydrocortisone, Lidocaine	Lidocaine	Lidocaine, Prilocaine	Lidocaine, Tetracaine	Pramoxine	Tetracaine
Lubricant and topical anesthetic on catheters, nasogastric/endoscopic tubes, laryngoscopes, proctoscopes, sigmoidoscopes, and vaginal specula.	✔								
Relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation			✔	✔	✔				
Relief of pruritus and pruritic eczemas				✔	✔				
Relief of pain and itching, soreness or burning associated with anorectal disorders.				✔	✔			✔	
Short-term (up to 8 days) management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus		✔							
Local anesthetic in minor operative procedures			✔		✔				
Relief of pain caused by myofascial and visceral pain syndromes			✔						
Relief of pain associated with post-herpetic neuralgia					✔ [a]				
Use on normal intact skin for local analgesia						✔	✔		
Use on genital mucosal membranes for superficial minor surgery and as pretreatment for infiltration anesthesia						✔			
Topical use in the nose and throat as an anesthetic for diagnostic procedures									✔

[a] Lidoderm only.

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[1-19]

Generic Name(s)	Onset	Duration	Absorption
Benzocaine	15-30 seconds	12-15 minutes	Poor through intact skin; Well absorbed from mucous membranes and traumatized skin
Doxepin	1.3 hours	No data	Plasma levels range from undetectable to those achieved after oral administration
Ethyl chloride	0.5-2 minutes	up to 1 minute	No data
Hydrocortisone and lidocaine	No data	No data	Variable
Lidocaine	3-5 minutes	No data	3% (patch)
Lidocaine and prilocaine	15 – 60 minutes	1-2 hours post-removal; 5-45 minutes for genital application	Minimal
Lidocaine and tetracaine	No data	Dose/procedure dependent	Variable
Pramoxine	3-5 minutes	Up to 5 hours	No data
Tetracaine	30 seconds	30 minutes	No data

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[2]

Generic Name(s)	Significance Level	Interaction	Mechanism
Doxepin	1	Monoamine oxidase inhibitors (MAOIs)	Altered catecholamine uptake and metabolism may occur when doxepin and MAOIs are taken concurrently. This may result in hyperpyrexia, convulsions, and death.
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.

Generic Name(s)	Significance Level	Interaction	Mechanism
Prilocaine	2	Drugs associated with drug-induced methemoglobinemia*	Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition, and co-administration of medications also known to cause drug-induced methemoglobinemia increase the risk of developing this condition.

Significance Level 1 = major severity
Significance Level 2 = moderate severity
*Sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine

VI. Adverse Drug Events

FDA issued a public health advisory to remind patients, healthcare professionals, and caregivers about potentially serious hazards of using topical anesthetics for relieving pain from medical tests and conditions.[20] 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.[20] The most common adverse drug events reported with the skin and mucous membrane antipruritics and local anesthetics are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-19]

Adverse Events	Benzocaine	Doxepin	Ethyl Chloride	Hydrocortisone, Lidocaine	Lidocaine	Lidocaine, Prilocaine	Lidocaine, Tetracaine	Pramoxine	Tetracaine
Cardiovascular									
Arrest	-	-	-	-	✔	✔	-	-	-
Bradycardia	-	-	-	-	✔	✔	-	-	-
Hypotension	-	-	-	-	✔	✔	-	-	-
Shock	-	-	-	-	✔	✔	-	-	-
Central Nervous System									
Anxiety	-	<1	-	-	✔	✔	-	-	-
Apprehension	-	-	-	-	✔	✔	-	-	-
Confusion	-	-	-	-	✔	✔	-	-	-
Convulsions	-	-	-	-	✔	✔	-	-	-
Dizziness	-	2	-	-	✔	✔	<1	-	-
Drowsiness	-	22	-	-	✔	✔	-	-	-
Emotional changes	-	2	-	-	-	-	-	-	-
Euphoria	-	-	-	-	✔	✔	-	-	-
Headache	-	-	-	-	-	-	<1	-	-
Lightheadedness	-	-	-	-	✔	✔	-	-	-
Nervousness	-	-	-	-	✔	✔	-	-	-
Paresthesia	-	-	-	-	✔	-	<1	-	-
Seizure	-	-	-	-	✔	✔	-	-	-
Somnolence	-	-	-	-	-	-	<1	-	-
Tinnitus	-	-	-	-	✔	✔	-	-	-
Unconsciousness	-	-	-	-	✔	✔	-	-	-
Dermatological									
Blanching	-	-	-	✔	-	37	12	-	-
Blisters	-	-	-	-	✔	✔	<1	-	-
Bruising	-	-	-	-	✔	-	-	-	-
Burning sensation	✔	23	-	✔	✔	17	-	✔	-

Adverse Events	Benzocaine	Doxepin	Ethyl Chloride	Hydrocortisone, Lidocaine	Lidocaine	Lidocaine, Prilocaine	Lidocaine, Tetracaine	Pramoxine	Tetracaine
Contact dermatitis	✔	-	-	-	✔	-	<1	✔	-
Edema	-	1	-	-	✔	6-10	12	✔	✔
Erythema	✔	-	-	✔	✔	30	71	-	-
Hyperpigmentation	-	-	-	-	-	56	-	-	-
Paleness	-	-	-	-	-	37	-	-	-
Papules	-	-	-	-	✔	-	-	-	-
Pruritus	✔	-	-	-	✔	2	<1	-	-
Rash	✔	-	-	-	✔	✔	<1	-	-
Redness	-	-	-	-	-	21	-	-	-
Skin irritation	-	-	-	-	✔	-	<4	-	-
Skin pigment alteration	-	-	1-10	-	-	-	<4	-	-
Skin reaction	-	-	-	-	✔	-	-	-	-
Stinging	✔	23	-	✔	-	✔	-	✔	-
Tenderness	✔	-	-	-	-	-	-	✔	-
Urticaria	✔	-	-	-	✔	✔	<1	✔	✔
Gastrointestinal									
Nausea	-	-	-	-	-	-	<1	-	✔
Taste alteration	-	2	-	-	-	✔	-	-	-
Vomiting	-	-	-	-	-	✔	<1	-	✔
Xerostomia	-	10	-	-	-	-	-	-	-
Laboratory Test Abnormalities									
Methemoglobinemia	✔	-	-	-	✔	✔	-	✔	-
Musculoskeletal									
Tremor	-	-	-	-	✔	✔	-	-	-
Twitching	-	-	-	-	✔	✔	-	-	-
Respiratory									
Bronchospasm	-	-	-	-	-	✔	-	-	-
Respiratory depression	-	-	-	-	✔	✔	-	-	-
Other									
Allergic reaction	-	-	-	-	✔	✔	<1	-	✔
Anaphylactoid reaction	-	-	-	-	✔	✔	-	-	✔
Angioedema	1-10	-	-	-	✔	✔	-	✔	-
Diplopia	-	-	-	-	✔	✔	-	-	-
Hypersensitivity	✔	-	-	-	-	✔	-	-	✔
Infection	-	-	-	-	-	-	<1	-	-
Mucous membrane irritation	-	-	1-10	-	-	-	-	-	-
Pain	-	-	-	-	-	-	<1	-	-

Adverse Events	Benzocaine	Doxepin	Ethyl Chloride	Hydrocortisone, Lidocaine	Lidocaine	Lidocaine, Prilocaine	Lidocaine, Tetracaine	Pramoxine	Tetracaine
Sensitivity to temperature extremes	-	-	-	-	✔	7	-	-	-
Tongue numbness	-	<1	-	-	-	-	-	-	-
Visual changes	-	-	-	-	✔	✔	-	-	-

✔ Percent not specified
- Event not reported

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[1-19]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Benzocaine	Lubricant: Apply evenly to exterior of instrument prior to use.	Children ≥2 years Lubricant: Apply evenly to exterior of instrument prior to use.	Lubricant: 20%
Doxepin	Apply a thin film to affected area 4 times per day with at least 3-4 hours between applications. Do not use for more than 8 days	Safety and efficacy in children have not been established	Cream: 5%
Ethyl chloride	Dose varies with use	Safety and efficacy in children have not been established	Spray: 100%
Hydrocortisone and lidocaine	Topical: Apply to affected area 2-3 times per day Rectal: Use 1 applicatorful twice daily	Safety and efficacy in children have not been established	Topical cream: 0.5%-3% Topical lotion: 0.5%-3% Topical medicated pad: 1%-3% 2%-2% Rectal cream: 0.5%-3% Rectal kit: 0.5%-3%, 1%-3%
Hydrocortisone, lidocaine, and aloe vera	Topical: Apply to affected area 2-3 times per day Rectal: Use 1 applicatorful 2-3 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	Cream, lotion: Apply to the affected area 2-3 times per day Ointment, solution: Apply to affected area ≤3 times daily (maximum 300 mg daily) Patch: Apply up to 3 patches to the most painful area, for up to 12 hours within a 24-hour period	Cream, lotion: Apply to the affected area 2-3 times per day (Lidamantle®)	Cream: 3% Lotion: 3% Ointment: 5% Patch: 5% Solution: 4%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Lidocaine, hydrocortisone, and psyllium husk	Rectal cream: Apply to the affected area twice daily. Psyllium: Mix contents of 1 packet with any beverage in a 10-12 ounce cup with a lid and shake for 3-5 seconds.	Safety and efficacy in children have not been established	Kit: lidocaine / hydrocortisone cream 3%-1% and individual psyllium fiber packettes with reusable shaker cup
Lidocaine, hydrocortisone, and skin cleaner no. 6	Lotion: Apply to the affected area 2-3 times per day Cleanser: Apply soap-free cleanser daily (Clere®)	Safety and efficacy in children have not been established	Kit: lidocaine / hydrocortisone 3%-1% and Clere® cleanser Combination package: lidocaine / hydrocortisone 3%-0.5% and Clere® cleanser
Lidocaine and prilocaine	Minor dermal procedures*: Apply 2.5 g (1/2 of the 5 g tube) over 20-25 cm^2 of skin surface for at least 1 hour and cover with an occlusive dressing Major dermal procedures†: Apply 2 g per 10 cm^2 of skin and leave on for at least 2 hours and cover with an occlusive dressing 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. Adult female genital mucous membranes: Apply a thick layer (5-10 g) to mucous membranes for 5-10 minutes and perform procedure immediately following removal of the cream (occlusion is not necessary)	0-3 months of age or <5 kg: Apply 1 g to up to 10 cm^2 of skin for 1 hour and cover with an occlusive dressing 3-12 months of age and >5 kg: Apply 2 g up to 20 cm^2 of skin for 4 hours and cover with an occlusive dressing 1-6 years of age and >10 kg: Apply 10 g up to 100 cm^2 of skin for 4 hours and cover with an occlusive dressing 7-12 years of age and >20 kg: Apply 20 g up to 200 cm^2 of skin for 4 hours and cover with an occlusive dressing Do not use in neonates <37 weeks gestational age or in infants less than 12 months who are being treated with other agents associated with methemoglobinemia.	Cream: 2.5%-2.5%
Lidocaine and tetracaine	Venipuncture or intravenous cannulation: Apply to intact skin for 20-30 minutes Superficial dermatological	Children ≥ 3 years: Venipuncture or intravenous cannulation: Apply to intact skin for 20-30 minutes	Topical patch: 70 mg – 70 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	procedures: Apply to intact skin for 30 minutes	Superficial dermatological procedures: Apply to intact skin for 30 minutes	
Pramoxine	Apply every 3-4 hours to affected area (maximum 200 mg daily)	Safety and efficacy in children have not been established	Foam: 1% Gel: 1%
Tetracaine	Apply directly to mucous membranes or administer via nebulization (maximum dose 20 mg)	Safety and efficacy in children have not been established	Solution: 2%

*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.[27] (1995) Doxepin 5% cream BID at the baseline visit and then QID for a total of 7 days vs. placebo cream BID at the baseline visit and then QID for a total of 7 days	RCT, DB, PC Patients 12-65 years of age diagnosed with lichen simplex chronicus, nummular eczema, or contact dermatitis experiencing moderate to severe pruritus on a daily basis for at least 1 week	N=309 7 days	Primary: Pruritus severity rating scale, Physician's Global Evaluation for Pruritus Relief (PGE-PR), patient's assessment of Pruritus Relief on a Visual Analogue Scale (VAS-PR)	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 ($P \leq 0.04$). After 7 days, the response to doxepin ranged from 76%-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 experienced at least a 50% reduction in pruritus for all forms of eczema studied, though significant differences were only observed in the lichen simplex chronicus group compared to placebo (VAS-PR, $P=0.001$). At day 7, patients in the doxepin group experienced at least a 70% reduction in pruritus for all forms of eczema studied, though significant differences were only observed in the lichen simplex chronicus group compared to placebo (VAS-PR, $P=0.001$). In the first 24 hours, a greater percentage of patients in the doxepin group experienced pruritus relief compared to the placebo group, though significant differences were only observed in lichen simplex chronicus and nummular eczema (PGE-PR, $P \leq 0.02$). At day 7, a greater percentage of patients in the doxepin group experienced pruritus relief compared to the placebo group, though significant differences were only observed in lichen simplex chronicus and nummular eczema (PGE-PR, $P \leq 0.02$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ramsook et al.[28] (2001) Ethyl chloride spray vs. isopropyl alcohol spray	RCT, PC, DB Patients 3-18 years of age who presented to the emergency department (ED) requiring intravenous (IV) cannulation for fluids or medication administration, or venipuncture for diagnostic tests	N=222 1 day	Primary: Results of the Faces Pain Scale (used for patients 3-10 years of age) and the Numeric Pain Score (used for patients 10-18 years of age)	Primary: Pain scores reported by the patients did not differ between groups. There was no statistically significant difference in pain scores between groups when stratified for age (<6 years, 6-12 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).
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 (Ametop®, not available in the U.S.) applied to site of the venipuncture, covered with and occlusive dressing, and left in place for 30-45 minutes	XO Patients with a mean age of 8.6 years being admitted for measurement of glomerular filtration rate (GFR) which involved a series of 3 venipunctures in a 4 hour period (the first 2 venipunctures constituted the cross-over 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	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 2, with ethyl chloride being remarkably lower.
Robinson et al.[49] (2007) Ethyl chloride sprayed for 5–10 seconds 15–20 cm from intended site	RCT Patient 15 years of age or older requiring IV cannulation	N=300 1 day	Primary: Pain from IV cannulation using a visual analog scale (VAS)	Primary: Lidocaine IV, ethyl chloride and nitrous oxide reduced the pain of IV cannulation. Lidocaine IV 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
of cannulation vs. nitrous oxide inhaled for 1 minute prior to and during cannulation vs. lidocaine (IV) 0.1 mL 1% injected intradermally with a 26-gauge needle vs. immediate cannulation with no anesthesia				Lidocaine IV provided the greatest reduction in the pain of cannulation (median VAS 1 mm vs control VAS 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 VAS 11 mm, vs control VAS 20 mm, P≤0.003), but this did not reach clinical significance. Nitrous oxide reduced the pain of cannulation compared to control (median VAS 13 mm vs control VAS 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.
Kokinsky et al.[30] (1999) Lidocaine 10% aerosol vs. placebo aerosol vs. control group	RCT, PC, DB Pediatric patients 9 months to 11 years old 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, 1, 4, and 12 hours postoperatively, and reaction scores after gentle palpation of the wound by the nurse Secondary: Plasma	Primary: At 1 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 1, 4, or 12 hours postoperatively. At 1 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			concentrations of lidocaine	endpoint at 0, 4, or 12 hours. Secondary: The mean peak lidocaine plasma concentration was 0.40 mcg/mL.
Minassian et al.[31] (2002) Lidocaine ointment 5% applied up to every 4 hours vs. placebo ointment applied up to every 4 hours	RCT, DB, PC Female patients 21-23 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: Amount of pain relief obtained (measured by amount of ointment used and total number of pain pills taken by the patient) 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 1 or 2 (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).
Corkill et al.[32] (2001) Lidocaine 2% gel applied up to every 4 hours vs.	RCT, DB, PC 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 [measured on the 101-point Numerical Rating Scale (NRS-101)]	Primary: There were no significant differences between the lidocaine and placebo groups at 24 hours according to the NRS-101 (P=0.5). Secondary: At 48 hours, the lidocaine group reported significantly less pain compared to the placebo group according to the NRS-101 (P=0.023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo gel applied up to every 4 hours			Secondary: Perineal pain 48 hours post-delivery, the consumption of additional analgesia, maternal satisfaction	There was no significant difference observed in the amount of additional analgesia used between the 2 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.
Luhmann et al.[33] (2004) Lidocaine 5% cream (ELA-Max®) covered with an occlusive dressing 30 minutes before intravenous (IV) insertion vs. buffered lidocaine subcutaneously (SQ) 5 minutes before IV insertion	RCT, SB Patients 4-17 years of age requiring peripheral IV (PIV) insertion	N=69 1 day	Primary: Visual analogue scales (VAS) ranging from 1-10 (higher scores indicate greater pain, anxiety, satisfaction, or technical difficulty) completed pre- and post-IV insertion by patients, parents, and blinded observer	Primary: Nurses successfully inserted the IV on the first attempt in 77% of patients. 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.
Galer et al.[34] (1999) Lidocaine 5% patch for 12 hours daily (up to 4 patches could be applied at once) vs. placebo patch for 12 hours daily (up to 4 patches could be	RCT, PC, XO Patients 62-96 years of age with post-herpetic neuralgia (PHN) already enrolled in the open-label protocol and using lidocaine patches on a regular basis for at least 1 month	N=33 28 days	Primary: Time to exit the study [(patients exited the study when their verbal pain relief rating decreased by 2 or more categories for any 2 consecutive days when compared to pre-study open-label pain report (6-item	Primary: The median time to exit was >14 days in the lidocaine group compared with 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 subjects reporting moderate or greater pain relief was 29 in the lidocaine group compared to 13 in the placebo group. A total of 7 subjects used rescue pain relief medications

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
applied at once)			scale from 0=worse to 5=complete relief)	throughout the study (3 in the lidocaine group and 4 in the placebo group).
Meir et al.[35] (2003) Lidocaine 5% patch applied for 12 hours daily (up to 4 patches could be applied at once) vs. placebo applied for 12 hours daily (up to 4 patches could be applied at once)	RCT, PRO, DB, PC, XO Patients 21 years of age and older 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 (during the first 8 hours, every 2 hours after patch application on day 1, and 1 hour after daily removal of the patch) allodynia, quality of neuropathic symptoms, and quality of sleep	Primary: At all time points, ongoing pain intensity decreased compared with pretreatment values in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at 2 hours (P=0.003), 4 hours (P=0.004), day 4 (P=0.03), day 5 (P=0.02), and day 7 (P=0.002). Area-under-the-curve (AUC) values show that lidocaine was more effective during the first 8 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 with pretreatment values in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at 2 hours (P=0.005), 4 hours (P=0.009), 6 hours (P=0.017) after the first patch application and at day 5 (P=0.035). Adjusted AUC values show better allodynia relief compared with 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 at any time. No significant differences were observed between the lidocaine and placebo groups in quality of sleep.
Devers et al.[36] (2000) Lidocaine 5% patch	OL Patients 23-85 years of age diagnosed with	N=16 12 weeks	Primary: Degree of pain relief using a verbal scale of	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
applied for 12 hours daily (up to 3 patches could be applied at once)	peripheral neuropathic pain		0=worse to 5=complete relief	mechanical allodynia. All patients who responded to medication continued to experience relief throughout the duration of the study.
Galer et al.[37] (2002) Lidocaine 5% patch vs. placebo patch	RCT, DB, PC, PG Adult patients diagnosed with post-herpetic neuralgia (PHN) 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 3 in Neuropathic Pain Scale (NPS)	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).
Katz et al.[38] (2002) Lidocaine 5% patch applied for 12 hours daily (up to 3 patches could be applied at once)	OL Patients 20-99 years of age diagnosed with post-herpetic neuralgia (PHN)	N=332 28 days	Primary: Changes in pain intensity, pain interference in quality of life (QOL), pain relief, and patient and physician global assessments	Primary: Mean scores for all measures of pain intensity were significantly lower than baseline scores at all evaluations (P=0.0001). At the end of the study 40% of patients experienced a ≥50% reduction in average daily pain intensity. Mean pain interference with QOL 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				improvement was reported in approximately 15% of patients, and no change was reported in 20% of patients.
Lin et al.[46] (2008) Lidocaine patch 5% applied at 12-hour intervals twice a day for 2 consecutive days vs. vehicle patch applied at 12-hour intervals twice a day for 2 consecutive days	RCT, DB, PC, PG Patients suffering from moderate to severe pain caused by acute herpes zoster infection within 4 weeks of onset	N=46 48 hours	Primary: Analgesic efficacy (using a 100-mm visual analog scale) and adverse events	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.
McCluskey et al.[40] (2003) Lidocaine and prilocaine cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol mixed with saline vs. placebo cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol mixed	RCT, PC, DB Patients 18-70 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	Primary: There was a significant reduction in the incidence of pain associated with insertion of the cannula in the lidocaine and prilocaine group compared to the other 2 groups (P=0.015). There was no significant difference in the frequency of pain associated with injection of propofol between the lidocaine and prilocaine group compared to the placebo group. Significantly greater pain frequency was seen in the lidocaine and prilocaine group compared to the lidocaine and propofol mixed injection group (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with saline vs. placebo cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol mixed with lidocaine				
Koh et al.[41] (2004) Lidocaine and prilocaine cream (EMLA®) applied to the skin for 60 minutes vs. lidocaine 4% cream (ELA-Max®) applied to the skin for 30 minutes	RCT, DB Patients 8-17 years of age having an intravenous (IV) insertion prior to surgery	N=60 1 day	Primary: Pain scores according to the Visual Analogue Scale (VAS), difficulty of placing the IV according to the investigator	Primary: There was no significant difference in pain ratings according to the VAS between the 2 groups (P=0.87). There was no significant difference in the investigator ratings of difficulty of the procedure between the 2 groups (P=0.73). There was significantly more blanching in the lidocaine and prilocaine group compared to the lidocaine group (P=0.04).
Kuvaki et al.[42] (2003) Lidocaine and prilocaine cream applied to the outer half of the inferior orbital margin at least 45 minutes prior to retrobulbar injection vs. lidocaine 5% ointment applied to the outer half	RCT, DB Patients presenting for day case cataract surgery under local anesthesia	N=103 1 day	Primary: Subjective pain intensity on a 10-point scale	Primary: There were no significant differences in pain scores reported between the lidocaine/prilocaine treatment group or the lidocaine treatment group (P=0.67).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of the inferior orbital margin at least 45 minutes prior to retrobulbar injection				
Gursoy et al.[21] (2007) Lidocaine/prilocaine cream 60 minutes before ultrasound-guided fine-needle aspiration biopsy vs. placebo cream 60 minutes before ultrasound-guided fine-needle aspiration biopsy	DB, PC Patients with nodular thyroid disease undergoing fine-needle aspiration biopsy	N=99	Primary: Patient-rated pain using a 100-mm visual analog scale (VAS), an 11-point numeric rating scale (NRS), and a 4-category verbal rating scale (VRS) Secondary: Adverse events	Primary: For patients receiving lidocaine/prilocaine, the mean VAS score was 25.0±22.3 mm versus 40.0±30.5 mm in the placebo group (P=.006). For patients receiving lidocaine/prilocaine, the mean NRS score was 2.9±2.3 points versus 4.0±2.6 points in the placebo group (P=.02). The absolute numbers according to VRS score in each group was also significantly different (P=.01). No adverse events from the use of EMLA were reported.
Berman et al.[43] (2005) Lidocaine and tetracaine patch applied 30 minutes prior to procedure vs. placebo patch applied 30 minutes prior to procedure	PRO, RCT, PC, DB Patients 20-80 years of age presenting for minor dermatological procedures not requiring sutures	N=49 1 day	Primary: Pain intensity according to the Visual Analogue Scale (VAS), patients' overall assessment of the effectiveness of the patch, the need for rescue medication, investigator ratings of patients' pain intensity and anesthetic efficacy	Primary: Median VAS scores were significantly lower in the lidocaine and tetracaine group compared to the placebo group (P<0.001). Median VAS 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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).
Schecter et al.[44] (2005) Lidocaine and tetracaine patch applied 30 minutes prior to minor dermatological procedures vs. placebo patch applied 30 minutes prior to minor dermatological procedures	RCT, DB, PC Patients over the age of 65 presenting for minor dermatological procedures	N=79 1 day	Primary: Pain rating according to the Visual Analogue Scale (VAS) Secondary: Patient's assessment of anesthesia, investigator's assessment of the degree of anesthesia	Primary: The VAS scores were significantly lower in the lidocaine and tetracaine group compared to the placebo group in patients undergoing excisions (P=0.020) and procedures on the head and neck (P=0.043). 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.[45] (2005) Lidocaine and tetracaine patch applied for 20 minutes prior to the procedure vs. placebo patch applied	RCT, PRO, DB, PC Patients 3-17 years old requiring intravenous (IV) 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 4-point scale	Primary: Significantly lower pain scores were reported in patients in the lidocaine and tetracaine group compared to the placebo group (P<0.001). No pain was reported in 59% of patients in the lidocaine and tetracaine group compared to 20% in the placebo group (P<0.001). Investigator and independent observer evaluations show significant pain relief in the lidocaine and tetracaine group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 20 minutes prior to the procedure				compared to the placebo group (P<0.001).
George et al.[47] (2008) Lidocaine and tetracaine patch applied for 20 minutes followed by saline infiltration (3 mL) vs. placebo patch applied for 20 minutes followed by infiltration with 2% lidocaine (3 mL)	RCT Women who were considering labor epidural analgesia, who were older than 18 yr with a body mass index <45 kg/m^2	N=33 1 day	Primary: Provider/patient assessment of discomfort with epidural needle insertion (using a verbal rating scale extending from 0–10, where 0 is no pain and 10 is the worst pain imaginable; ease of epidural insertion	Primary: The subjects' 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 subjects required additional deep infiltration (P = 0.02). The four-point scale, used to subjectively estimate the quality of subject cooperation during epidural placement, was not significantly different between groups. The subjects' recorded verbal rating scale and the anesthesiologists' verbal rating scale rating scores were similar in the two groups.
Singer et al.[48] (2008) Lidocaine/tetracaine patch applied for 20 minutes prior to IV cannulation vs. placebo patch applied for 20 minutes prior to IV cannulation	RCT, DB, PC Patients aged 3 to 17 years who required nonemergency IV cannulation	N=40 1 day	Primary: Pain of cannulation measured using a validated 100-mm visual analogue scale (VAS) or Wong Baker scale	Primary: The median pain of IV 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 treatment group (75% [95% confidence interval (CI) 53% to 89%] versus 35% in the placebo group [95% CI 18% to 57%]. The number of successful IV cannulations after the first attempt was similar in both the lidocaine/tetracaine and the placebo groups (90% [95% CI 70% to 97%] versus 85% [95% CI 64% to 95%].
Curry et al.[22] (2007) Lidocaine/tetracaine patch applied for 20 minutes prior to	RCT, DB, PC Adults undergoing a vascular access procedure	N=40 1 day	Primary: Pain intensity using a 100 mm visual analog scale (VAS), patient perception of pain	Primary: The median subject VAS score was lower for lidocaine/tetracaine compared with placebo (5 mm vs 28 mm). Forty-nine percent of subjects had lower VAS scores with lidocaine/tetracaine than placebo, and 17% had lower VAS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vascular access procedure vs. placebo patch applied for 20 minutes prior to vascular access procedure			relief, investigator and independent observer rating of patients' pain, investigator's perception of pain relief	scores with the placebo (P<0.001). More subjects reported adequate anesthesia following lidocaine/tetracaine compared with placebo (73% vs 31%). Fifty-nine percent of subjects 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 subjects indicated they would use lidocaine/tetracaine again compared with placebo (70% vs 33%). Fifty-one percent of subjects 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 subjects as having no pain with lidocaine/tetracaine treatment compared with 33% of subjects with the placebo treatment. Investigators considered 46% of subjects to have less pain with lidocaine/tetracaine than placebo, and 15% of subjects to have less pain with the placebo than lidocaine/tetracaine (P=0.021). Independent observers rated 68% of subjects having no pain with lidocaine/tetracaine compared with 38% with the placebo. The independent observers considered 46% of subjects to have less pain with lidocaine/tetracaine than placebo, and 15% of subjects to have less pain with the placebo than lidocaine/tetracaine (P=0.015). For the overall rating, the investigators considered more subjects to have adequate anesthesia with lidocaine/tetracaine compared with placebo (60% vs 23%). They considered 54% of subjects to have adequate anesthesia with lidocaine/tetracaine and not the placebo, and considered 15% of subject to have

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adequate anesthesia with the placebo and not lidocaine/tetracaine (P=0.004).
Yosipovitch et al.[39] (1997) Pramoxine 1% lotion vs. vehicle lotion	RCT, DB, PC, XO Healthy patients 34-52 years of age who were injected with histamine into the forearms	N=15 2 procedure days (at least 3 days apart)	Primary: Itch magnitude and duration	Primary: Pramoxine significantly shortened the duration of itch from baseline (P=0.03). Pramoxine significantly decreased the itch magnitude (P<0.01). There was a significant difference seen between the pramoxine and vehicle groups between 2 and 6 minutes after histamine injection (P<0.05). The vehicle lotion did not significantly shorten the itch duration (P=0.4).

Drug regimen abbreviations: BID=twice daily, QID=four times daily
Study abbreviations: DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, 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
Benzocaine	lubricant	Americaine®	$	N/A
Doxepin	cream	Prudoxin®, Zonalon®	$$$$	N/A
Ethyl chloride	spray	N/A	N/A	$
Hydrocortisone and lidocaine	cream, lotion, medi-pad, rectal cream, rectal kit	Anamantle HC®*, Anamantle HC Forte®*, Lidamantle HC®*, Peranex HC®	$$$-$$$$$	$$-$$$$
Hydrocortisone, lidocaine, and aloe vera	rectal gel, rectal kit	Anamantle HC®*, Peranex HC®*, Rectagel HC®*	$$$$-$$$$$	$$$-$$$$
Lidocaine	cream, lotion, ointment, solution, transdermal patch	Lidamantle®*, Lidoderm®	$$$$-$$$$$	$-$$
Lidocaine, hydrocortisone, and psyllium husk	rectal kit	Xyralid RC®	$$$$	N/A
Lidocaine, hydrocortisone, and skin cleanser no. 6	topical kit, combination package	Xyralid®, Xyralid LP®	$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Lidocaine and prilocaine	cream	EMLA®*	$$$	$$
Lidocaine and tetracaine	topical patch	Synera®	$$$$	N/A
Pramoxine‡	foam, gel	Proctofoam®, Pramox®	$	N/A
Tetracaine	solution	Pontocaine®	$-$$$	N/A

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
N/A=Not available

X. Conclusions

The skin and mucous membrane antipruritics and local anesthetics have a variety of indications, including relief of itching and pain caused by insect bites, minor burns, sunburns, atopic dermatitis, eczema, lichen simplex chronicus, and hemorrhoids. They are also used to prevent and treat pain due to postherpetic neuralgia, minor operative/dermatological procedures, endoscopic/diagnostic procedures, venipuncture, intravenous cannulation, as well as other procedures. Due to the variety of products, dosage forms and FDA-approved indications, direct comparisons of agents within this class is difficult. There are also few clinical guidelines that discuss the use of these agents.

Doxepin cream is indicated for the short-term (<8 days) management of moderate pruritus in adult patients with atopic dermatitis and lichen simplex chronicus. The American Academy of Dermatology guidelines on atopic dermatitis state that topical corticosteroids and emollients are the standard of care.[23] The short-term use of topical doxepin may relieve pruritus; however, adverse events limit its usefulness.[23] A study conducted by Drake et al. demonstrated that topical doxepin was more effective than placebo at controlling pruritus over the course of 7 days.[27]

There are no treatment guidelines that address the use of topical ethyl chloride. Two clinical trials evaluated the use of ethyl chloride spray as an anesthetic prior to intravenous (IV) cannulation.[28,49] Ramsook et al. reported no significant difference in pain scores compared to isopropyl alcohol.[28] Robinson et al. demonstrated that intradermal lidocaine was significantly more effective than ethyl chloride at reducing the pain of IV cannulation.[49]

Guidelines for the treatment of hemorrhoids state that the cornerstone of therapy is adequate fiber intake and water.[24-25] 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 are several topical anesthetics that are available by prescription and over-the-counter. When used appropriately, these products may provide safe and effective pain relief. There are no treatment guidelines that specifically discuss the use of topical anesthetics for pain relief. Numerous clinical trials have found lidocaine, lidocaine/prilocaine, lidocaine/tetracaine, and pramoxine to be more effective at relieving pain than placebo.[21-22,30,34-35,37,39-40,43-46,48] There are few clinical trials directly comparing the topical anesthetics. Comparative studies found no differences in pain relief with lidocaine (cream, ointment, transdermal injection) and lidocaine/prilocaine (cream).[33,41-42] A literature search did not reveal any published studies evaluating the use of benzocaine 20% lubricant or tetracaine 2% solution.

FDA remains concerned about the potential for topical anesthetics to cause life-threatening adverse events such as arrhythmias, seizures, respiratory difficulties, coma and death.[20] If a topical anesthetic is prescribed, patients should use the least amount that will relieve the pain, apply the product sparingly and only to the area where pain exists or is expected to occur, and do not apply the product to broken or irritated skin.[20] 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.[20]

Therefore, all brand skin and mucous membrane antipruritic and local anesthetic products within the class reviewed are comparable to each other and to the generics and OTC 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Astringents
AHFS Class 841200
May 13, 2009

I. Overview

The skin and mucous membrane astringents are used to treat hyperhidrosis, which is defined as excessive sweating in amounts greater than physiologically needed for thermoregulation.[1] Hyperhidrosis is usually a chronic idiopathic condition, which may have social, emotional and professional consequences.[2]

Idiopathic (primary) hyperhidrosis usually affects the axillae, palms and soles.[2] The onset of symptoms generally presents in childhood or adolescence, and the condition persists throughout adult life.[2] Episodes of excessive sweating usually occur at least once per week and do not occur during periods of sleep. Generalized (secondary) hyperhidrosis is likely to be due to medications or a systemic illness. Unlike primary hyperhidrosis, episodes of excessive sweating occur during sleep with secondary hyperhidrosis.[2]

The diagnosis of primary hyperhidrosis is based on the patient's medical history and visible signs of sweating. Treatment includes topical therapy, systemic medications, iontophoresis, botulinum toxin, and surgery.[2] Topical therapy includes the use of an antiperspirant which contains a metal salt (such as aluminum chloride). It is thought that treatment with antiperspirants leads to physical obstruction of the sweat gland ducts or atrophy of the secretory cells.[2]

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. Aluminum chloride is available in a generic formulation. This class was last reviewed in February 2007.

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®*, Xerac AC®	aluminum chloride

*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 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[3] (2006)**	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, botulinum toxin A (BTX-A) injections are the next line of treatment. • Should a patient not respond BTX-A, or require such frequent re-injections as to be impractical, surgical measures may be considered. Palmar: • Topical aluminum chloride antiperspirants are often considered the

Clinical Guideline	Recommendation(s)
	first line of treatment for palmar hyperhidrosis, keeping in mind that a higher concentration of active ingredients (up to 30%) than is used to treat axillary hyperhidrosis is often required. • Many experts, however, 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: botulinum toxin type A (BTX-A) injections, on-going use of systemic medications, or endoscopic thoracic sympathectomy (ETS). <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 higher concentration of active ingredients – up to 30% – than is used to treat axillary hyperhidrosis is often required). • Many experts, however, 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. 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[4]

Generic Name(s)	Hyperhidrosis
Aluminum chloride	✔

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[4-5]

Generic Name(s)	Systemic Absorption	Distribution	Excretion (Renal)
Aluminum chloride	Minimal	No data	No data

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane astringents, no significant drug interactions have been reported.[4]

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[4-5]

Adverse Events	Aluminum chloride
Dermatological	
Burning	✔
Itching	✔
Prickling sensation	✔
Skin irritation	✔
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[4-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aluminum chloride	Apply to affected area once daily at bedtime. Once excessive sweating is controlled, apply once or twice weekly as needed. To reduce the risk of irritation, these products should be applied to dry skin between episodes of sweating and washed off in the morning. The use of a hair dryer to quickly dry the application, or to use baking soda powder in the morning to neutralize any remaining aluminum chloride may also be helpful. Low potency corticosteroid creams (such as 2.5 percent hydrocortisone cream) can help alleviate the axillary irritation that frequently occurs.	Safety and efficacy have not been established in pediatric patients.	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	Sample Size and Study Duration	End Points	Results
Scholes et al.[7] (1978) 20% aluminum chloride hexahydrate in absolute alcohol , applied nightly	MC Patients 14-51 years of age with axillary hyperhidrosis for 2-25 years	N=65 15 months	Primary: Symptomatic relief Secondary: Adverse effects	Primary: Sixty four patients or 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.
Rayner et al.[8] (1980) 20% aluminum chloride, applied on alternate nights vs. placebo	DB, PC, XO Patients 18-41 years of age with axillary hyperhidrosis	N=36 6 months	Primary: Symptomatic relief, avoidance of surgery Secondary: Adverse effects	Primary: After 2 weeks, 24 patients had achieved considerable relief, 6 patients showed no improvement, 2 patients obtained relief with placebo, and 4 patients obtained relief with both solutions. After 6 months of treatment, 68% opted for surgery. Secondary: Significant local reaction was seen in 55% of the patients.
Goh[9] (1990) Aluminium chloride hexahydrate 20% at night	SB Patients with symptomatic idiopathic palmar hyperhidrosis	N=12 4 weeks of treatment 2 weeks of follow-up	Primary: Rate of skin water vapor loss (SVL) Secondary: Adverse events	Primary: The mean SVL of treated palms was significantly lower than untreated palms at 1, 2, and 4 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 3. The mean SVL of treated palms returned to baseline at week 5. Secondary: Four patients developed skin irritation from treatment; in three this disappeared after 1 week and therapy was continued.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Flanagan et al.[10] (2008) Botulinum toxin type A (BTX-A) 50 unites injected in each axillae bilaterally once at baseline vs. aluminum chloride 20% applied nightly	SC, RCT, PG, OL Patients >18 years of age with moderate to severe primary idiopathic axillary hyperhidrosis	N=25 12 weeks	Primary: Treatment response by an improvement of ≥2 grades on the Hyperhidrosis Disease Severity Scale (HDSS) from baseline to week 4 Secondary: Treatment response at week 8 and week 12 using HDSS scores, patient satisfaction, irritation	Primary: At week 4, 91.7% of the subjects in the BTX-A group achieved treatment response compared with 33.3% of the subjects in the aluminum chloride group (P<0.0001). At weak 4, 71% of subjects in the aluminum chloride group did not tolerate treatment and/or did not achieve an improvement of ≥2 points in their HDSS score, and crossed over to BTX-A. Secondary: At week 8, 88% of subjects remained in the BTX-A group and 90.9% were treatment responders. At week 8, 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 7 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 4, 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

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®*, 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 in this class and it is indicated for the treatment of hyperhidrosis. Nightly application is effective and once excessive sweating is controlled, treatment frequency can be reduced to once or twice weekly as needed. The use of aluminum chloride is often associated with skin irritation, but this may be managed by applying the product on dry skin at bedtime and washing it off in the morning.[2] Other strategies include the use of a hair dryer to quickly dry the application site, the use of baking soda powder in the morning to neutralize the aluminum chloride or the use of a low potency corticosteroid cream to relieve irritation.[2]

There are limited guidelines on the treatment of hyperhidrosis. The International Hyperhidrosis Society guidelines state that topical aluminum chloride antiperspirants are the first-line treatment for axillary, palmar and plantar hyperhidrosis.[3] Higher concentrations of aluminum chloride are often necessary to treat palmar and plantar hyperhidrosis.[3] If a patient does not adequately respond to topical antiperspirant therapy or if the side effects are intolerable, botulinum toxin A, systemic medications, and surgery are also treatment options.[3]

Although aluminum chloride has been available for many years, there are very few clinical trials assessing the efficacy and safety of this agent. Aluminum chloride has been shown to be effective in reducing axillary and palmar hyperhidrosis; however, clinical trials have enrolled small numbers of patients.[7-9] Flanagan et al. compared treatment with aluminum chloride and botulinum toxin type A (BTX-A) in patients with moderate to severe axillary hyperhidrosis.[10] BTX-A was more effective than aluminum chloride at week 4 and provided greater patient satisfaction. Rayner et al. reported that, after 6 months of treatment with aluminum chloride, 68% of study patients opted for surgery.[8]

Therefore, all brand skin and mucous membrane astringents within the class reviewed are comparable to each other and to the generics and OTC 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Keratolytic Agents
AHFS Class 842800
May 13, 2009

I. Overview

The skin and mucous membrane keratolytic agents are used to treat a variety of hyperkeratotic skin conditions, including psoriasis, xerosis, ichthyosis, eczema, corns, calluses, cutaneous verrucae, as well as others. They are also used for the treatment of damaged, ingrown, and devitalized nails. 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.[1] Normal skin contains more than 10% hydration.[1] When the water content is less than 10%, disruption in the stratum corneum can occur, leading to scaling, cracking, and irritation.

Psoriasis is a chronic, immune-mediated disorder which results in hyperproliferation and abnormal differentiation of the epidermis.[2] It is characterized by erythematous plaques which appear as silvery scales. Xerosis, or excessive dryness of the skin, is characterized by redness, dry scaling, and fissures.[1] Ichthyosis is a genetic hyperkeratotic skin disorder, characterized by dry and scaly skin that resembles the scales of a fish.[1,7] Eczema is a chronic inflammatory skin condition which is characterized by one or more symptoms, including redness, edema, pruritus, dryness, crusting, flaking, blistering, cracking, oozing, and bleeding.[3] Cutaneous verrucae (warts) are caused by the human papilloma virus (HPV) and have a variable clinical presentation based on the skin surface location and morphology.[4]

Keratolytics increase the ability of the skin to retain water, which dissolves the intracellular matrix. This causes the cornified tissue to swell, soften, macerate, and desquamate.[12]

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. This class was last reviewed in February 2007.

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)
Salicylic acid	cream, foam, gel, lotion, shampoo	Akurza®*, Salex®*, Salitop®*, Salkera®	salicylic acid
Urea	cream, emulsion, foam, gel, lotion, ointment, solution, suspension, towelette	Carmol 40®*, Kerafoam®, Keralac®*, Kerol®*, Remeven®*, Umecta®*, Umecta PD®, Vanamide®*	urea
Urea, lactic acid, and salicylic acid	suspension	Kerol®*	urea, lactic acid, and salicylic acid
Urea, lactic acid, and zinc undecylenate	emulsion, solution	Kerol®, Kerol ZX®	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 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**[8] **(2009)**	• While there are no placebo-controlled studies verifying the efficacy and safety of salicylic acid used alone, salicylic acid is often combined with other topical therapies, including corticosteroids and topical immunomodulators. • The improvements in efficacy of combination therapy compared with salicylic acid alone are likely due to the increased skin penetration that occurs because of the keratolytic effects of salicylic acid.
British Association of Dermatologists: **Psoriasis Guidelines**[32] **(2006)**	• It is important to use a keratolytic agent (e.g. 5% salicylic acid in emulsifying ointment) first when there is significant scaling, or other treatments will fail. • Keratolytic creams should be applied for a few hours or overnight. A different treatment for day- and night-time is a useful approach. • For scalp psoriasis, a tar-based shampoo should be tried first; this can be combined with the use of either a 2-5% salicylic acid 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.

Finnish Medical Society Duodecim: **Psoriasis**[9] **(2007)**	Plaque Psoriasis
	• If the lesions are covered by a thick layer of scales it may be appropriate to start the treatment with scale removal. Salicylic acid preparations (5%) are available over the counter, and should be applied for a couple of days. Scales must not be removed by scratching or rubbing.
	Plaque Psoriasis in Specific Areas
	• Scalp psoriasis is treated with frequent shampooing. If necessary, salicylic acid exfoliation may be used initially followed by a corticosteroid solution.
	  o A layer of scales will prevent the penetration of medicated preparations.
	  o Salicylic acid is often used as a 5% to 10% mixture in a cream, castor oil or macrogol ointment base.
	• The treatment of psoriasis on the palms and the soles of the feet consists of the above mentioned medicines used in plaque psoriasis. To treat hyperkeratosis, salicylic acid may be mixed up to 20% potency.
	Guttate Psoriasis
	• If guttate psoriasis is not very extensive, the topical treatment forms described for plaque psoriasis may be used.

Finnish Medical Society Duodecim: **Seborrhoeic Dermatitis**[10] **(2007)**	Treatment: • The treatment does not cure the disease permanently. 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 sulphur (but not Vaseline) or by wetting and washing. • Seborrhoeic skin should be washed more often than usual. Decreasing fungal growth: • Washing the scalp with ketoconazole shampoo or selenium sulphide shampoo. • Topical treatment with creams containing imidazole derivatives • Antimycotic on skin creases (rarely necessary)

Clinical Guideline	Recommendation(s)
	• 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**[11] **(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[12-25]

Indication	Salicylic Acid	Urea	Urea, Lactic Acid, Salicylic acid	Urea, Lactic Acid, Zinc Undecylenate
Topical aid in the removal of excessive keratin in hyperkeratotic skin disorders, including verrucae, and the various ichthyoses (vulgaris, sex-linked and lamellar), keratosis palmaris and plantaris, keratosis pilaris, pityriasis rubra pilaris, and psoriasis (including body, scalp, palms and soles).	✔			
Topical aid in the removal of excessive keratin on dorsal and plantar hyperkeratotic lesions. Topical preparations of 6% salicylic acid have been reported to be useful adjunctive therapy for verrucae plantares.	✔			
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.		✔	✔	✔
Treatment of hyperkeratotic conditions such as dry, rough skin, dermatitis, psoriasis, xerosis, ichthyosis, eczema, keratosis, keratoderma, corns, and calluses.		✔	✔	✔
Treatment of damaged, ingrown and devitalized nails.		✔	✔	✔

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[12-25]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolites (%)	Excretion (%)
Salicylic acid	9.3-25.1	50-80	Salicyluric acid (52), salicylate glucuronides (42), free salicylic acid (6)	Renal (95)
Urea	No data	No data	No data	No data
Urea, lactic acid, and salicylic acid	No data	No data	No data	No data
Urea, lactic acid, and zinc undecylenate	No data	No data	No data	No data

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane keratolytics, no significant drug interactions have been reported.[13]

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[12-25]

Adverse Events	Salicylic acid	Urea	Urea, Lactic Acid, Salicylic acid	Urea, Lactic Acid, Zinc Undecylenate
Dermatological				
Burning	-	✔	✔	✔
Erythema	✔	-	✔	✔
Irritation	-	✔	✔	✔
Itching	-	✔	✔	✔
Scaling	✔	-	✔	✔
Stinging	-	✔	✔	✔

✔ Percent not specified
\- Event not reported

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[12-25]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Salicylic acid	Apply to the affected area at night after washing; cover the area and wash medication off in the morning.	Children > 2 years of age: Apply to the affected area at night after washing; cover the area and wash medication off	Cream: 6% Foam: 6%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		in the morning.	Gel: 6% Lotion: 6% Shampoo: 6%
Urea	Apply to the affected area twice per day.	Apply to the affected area twice per day.	Cream: 40%, 50% Emulsion: 40% Foam: 30%, 40% Gel: 40%, 50% Lotion: 35%, 40% Ointment: 50% Solution: 50% Suspension: 40% Towelette: 42%
Urea, lactic acid, and salicylic acid	Apply to the affected area twice per day.	Apply to the affected area twice per day.	Suspension: 50%
Urea, lactic acid, and zinc undecylenate	Apply to the affected area twice per day.	Apply to the affected area twice per day.	Emulsion: 50% Solution: 50%

VIII. Effectiveness

Although the keratolytic agents have been available for many years, there are limited clinical trials evaluating the use of salicylic acid (6%) and urea (30% - 50%). Clinical studies evaluating the safety and efficacy of the skin and mucous membrane keratolytic agents are summarized in Table 7.

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
Ademola et al.[28] (2002) Urea cream 40% (Carmol 40®) applied twice daily for 14 days vs. ammonium lactate topical lotion 12% (Lac-Hydrin 12%®) applied twice daily for 14 days	RCT, DB, PG Patients aged 18 to 65 years with a clinical diagnosis of dry skin of at least grade 2 (moderate to severe) on the plantar surface of both feet	N=25 28 days	Primary: Investigators' clinical observations, instrumental measurements, and subjects' self assessment	Primary: At the end of the second week of treatment, 12% 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 40% urea cream during the same treatment period. After the second week of treatment, 40% urea cream was associated with statistically significant improvement ($P < 0.05$) in skin roughness, fissures, thickness and dryness compared with 12% 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 with the 12% ammonium lactate lotion plantar surfaces. There was no significant difference between 12% ammonium lactate lotion or 40% urea cream treated plantar surface by patient self assessment. A preference questionnaire completed by the study participants at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				end of the 14th day, indicated that subjects significantly (P < 0.05) preferred 12% ammonium lactate over 40% urea cream lotion, primarily for its effect on skin texture. 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). Subject self assessments also indicated that by day 28, therapeutic differences disappeared.
Carroll et al.[29] (2005) Salicylic acid gel 6% plus vehicle twice daily on half of the body for 8 weeks vs. salicylic acid gel 6% plus tacrolimus ointment 0.1% on the other half of the body for 8 weeks (This was an inter-subject left-right comparison study)	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 2 treatment groups at weeks 1, 2, and 8, 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 8, 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).
Goldstein et al.[30] (2008) Urea emollient foam 30% (Kerafoam®)	SC, OS, PRO, OL Patients ≥18 years of age with hyperkeratosis with	N=10 28 days	Primary: Clinical assessment of specified symptom skin score (SRRC)	Primary: Significant improvements in clinicians' SRRC scores were noted at the day 14 and day 28 visits compared to baseline (P=0.007 and <0.001, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	a specified symptom skin score (SRRC) ≥5 and not receiving any other treatments		from baseline to day 14 and day 28 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)	There was a 64.3% improvement in aggregate quality of life scores with comparable improvements noted for symptoms (63.4%), emotions (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.

Study abbreviations: DB=double-blind, 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
Salicylic acid	cream, foam, gel, lotion, shampoo	Akurza®*, Salex®*, Salitop®*, Salkera®	$$$-$$$$	$$-$$$
Urea	cream, emulsion, foam, gel, lotion, ointment, solution, suspension, towelette	Carmol 40®*, Kerafoam®, Keralac®*, Kerol®*, Remeven®*, Umecta®*, Umecta PD®, Vanamide®*	$$$-$$$$$	$-$$$
Urea, lactic acid, and salicylic acid	suspension	Kerol®*	$$$$	$$$-$$$$
Urea, lactic acid, and zinc undecylenate	emulsion, solution	Kerol®, Kerol ZX®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
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. Salicylic acid is also indicated for the treatment of cutaneous verrucae. Urea is also indicated for the treatment of damaged, ingrown, and devitalized nails. Both agents are generally well tolerated, with side effects limited to local skin reactions.

There are very few guidelines available which discuss the use of salicylic acid or urea for the treatment of hyperkeratotic skin conditions. Guidelines for the management of psoriasis recommend salicylic acid as one of many treatment options.[8-9,32] Salicylic acid is also recommended for treating seborrheic dermatitis to help soften scales.[10] The guidelines for the management of cutaneous warts state that there is no single treatment that is 100% effective.[11] Salicylic acid is one of many treatment options; however, there is not enough evidence to conclude that other therapies are more effective than salicylic acid.[11,31] There is no mention of urea in the available clinical guidelines.[8-11]

Although the keratolytic agents have been available for many years, there are limited clinical trials evaluating the efficacy and safety of salicylic acid (6%) and urea (30% - 50%).[28-30] The available studies have been of short duration and included small numbers of patients.[29-30] There are no head-to-head studies directly comparing salicylic acid and urea. Both agents are available in a generic formulation.

Therefore, all brand skin and mucous membrane keratolytic agents within the class reviewed are comparable to each other and to the generics and OTC 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Keratoplastic Agents
AHFS Class 843200
May 13, 2009

I. Overview

The skin and mucous membrane keratoplastic agents are used to treat psoriasis, seborrheic dermatitis and dandruff. Psoriasis is a chronic, immune-mediated disorder which results in hyperproliferation and abnormal differentiation of the epidermis.[1] It is characterized by erythematous plaques which appear as silvery scales. Seborrheic dermatitis is an inflammatory skin condition characterized by erythema and the formation of white or yellow flaky scales, which appear on oily areas, such as the scalp, face and upper trunk.[2] Dandruff (seborrheic dermatitis of the scalp) is characterized by scaling on the scalp, but not erythema.

The keratoplastic agents include anthralin and coal tar. Anthralin is a synthetic substitute for chrysarobin, a skin irritant derived from the bark of the araroba tree. It may cause transient discoloration of skin, hair, and fingernails, as well as staining of clothing and bed sheets.[3] Coal tar is a complex hydrocarbon mixture derived from the distillation of coal, which is a mixture of thousands of compounds.[4, 8] It is a greasy compound associated with an unpleasant odor, which may stain clothing and bed sheets. Both products have been used to treat psoriasis for more than 100 years. Although their mechanism of action is not completely understood, it is thought that these agents decrease mitotic activity and proliferation of epidermal cells by inhibiting DNA synthesis.[3-4,8]

The skin and mucous membrane keratoplastic agents that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Coal tar is available in a generic formulation and is also available over-the-counter. This class was last reviewed in February 2007.

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Anthralin	cream	Psoriatec®	none
Coal tar‡	cream, liquid, lotion, oil, shampoo	Betatar®, DHS Tar®*, Doak Tar®*, Doak Tar Distillate®, Doak Tar Oil®, Fototar®, Ionil T®, Ionil T Plus®, Oxipor VHC®, Pentrax®, Polytar®*, X-Seb T Plus®, Zetar®	coal tar
Coal tar and lanolin‡	liquid	Balnetar®	none

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
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 keratoplastic agents are summarized in Table 2.

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

Clinical Guideline	Recommendation(s)
American Academy of Dermatology: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapies[5] (2009)**	• Treatment should be tailored to meet individual patients' needs. These needs vary depending on body location, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Vehicle types are numerous and may include ointments, creams, solutions, gels, foams, tape, sprays, shampoos, oils, and lotions.

Clinical Guideline	Recommendation(s)
	Different vehicles are indicated for different body sites. The optimal choice is generally the vehicle the individual patient will most likely use. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis, particularly those with limited disease. • 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. • In a double-blind, randomized, controlled trial of 324 patients with mild to moderate psoriasis that compared 1% coal tar lotion with 5% coal tar extract, there was better improvement in both PASI (Psoriasis Area and Severity Index) score and total sign score in patients treated with 1% lotion than with 5% extract. • Anthralin is most commonly used as short contact (20-30 minutes) therapy in the outpatient setting, starting at 1% concentration with increasing concentration over time as tolerated. • The most common side effects of anthralin are skin irritation and staining of lesional and adjoining skin, nails, clothing, and other objects with which patients come into contact. • There is no evidence of any long-term toxicities related either to skin exposure or to systemic issues. • There is limited placebo-controlled trial data, but as monotherapy, anthralin appears to have lower efficacy than more potent topical corticosteroids or vitamin D derivatives.
British Association of Dermatologists: **Psoriasis Guidelines**[6] **(2006)**	• Coal tar is an effective treatment for inducing remission in psoriasis. • Coal tar preparations of between 1 and 5% in white or yellow soft paraffin are as effective as higher concentrations. The use of higher concentrations, which has been traditionally advocated, has no evidence-based foundation and is best avoided, especially as it restricts outpatient use. • There are reports suggesting that tar and topical steroids have a synergistic effect, and some dermatologists adopt a regimen of a moderately potent topical steroid by day, with tar by night, for ease of patient use. • No firm epidemiological evidence that topical tar products cause cutaneous or internal cancer. • Anthralin has been used in the treatment of stable plaque psoriasis and remains an effective topical remedy, without long term local, systemic or teratogenic effects. • Treatment is started at a lower concentration with each course of treatment and gradually increased within the patient's tolerance, reducing the strength if there is burning and increasing it where possible. Response can be gauged by palpating the plaque. Once lesions are palpably flat dithranol should be discontinued. • The unwanted effects of skin staining and irritancy limit its use.
Finnish Medical Society Duodecim: **Psoriasis**[7] **(2007)**	• Tars and anthralin are old and effective treatment forms but due to the smell and mess are not well tolerated and, therefore, they are no longer used in some countries.
Finnish Medical Society Duodecim: **Seborrhoeic Dermatitis**[16]	Treatment: • The treatment does not cure the disease permanently. Therefore it must be repeated when the symptoms recur, or even prophylactically.

Clinical Guideline	Recommendation(s)
(2007)	Removing the Thick Scales and Decreasing the Amount of Sebum: • The scales can be softened with a cream containing salicylic acid and sulphur (but not Vaseline) or by wetting and washing. • Seborrhoeic skin should be washed more often than usual. Decreasing fungal growth: • Washing the scalp with ketoconazole shampoo or selenium sulphide 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.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane keratoplastic 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 Keratoplastic Agents[3-4,8-9]

Generic Name(s)	Treatment of Psoriasis	Topical Treatment for Controlling Dandruff, Seborrheic Dermatitis, or Psoriasis
Anthralin	✔	
Coal tar		✔
Coal tar and lanolin		✔

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Keratoplastic Agents[3-4,8-9]

Generic Name(s)	Systemic Absorption	Distribution	Excretion (Renal)
Anthralin	Minimal	No data	Skin, substantial (non-systemic)
Coal tar	Minimal	No data	No data
Coal tar and lanolin	Minimal	No data	No data

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane keratoplastic agents, no significant drug interactions have been reported.[9]

VI. Adverse Drug Events

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

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Keratoplastic Agents[8-9]

Adverse Events	Anthralin	Coal tar	Coal tar and Lanolin
Dermatological			
Contact allergic reactions	✔	-	-
Contact dermatitis	-	✔	✔
Erythema	✔	-	-
Folliculitis	-	✔	✔
Heat sensations	✔	✔	✔
Herpes lesions	-	✔	✔
Inflammation	✔	-	-
Irritation	✔	✔	✔
Keratocystomatosis	-	✔	✔
Necrosis	✔	-	-
Pain	✔	-	-
Photosensitivity	-	✔	✔
Psoriasis	-	✔	✔
Pustular rash	✔	-	-
Redness	✔	-	-
Skin ulcerations	-	✔	✔
Status varicoses	-	✔	✔
Swelling	✔	-	-
Temporary discoloration of skin, hair, and fingernails	✔	-	-
Verruca vulgaris	-	✔	✔
Worsening of disease	-	✔	✔
Other			
Bacterial infection	-	✔	✔
Carcinogen effect	-	✔	✔
Hypersensitivity reaction	✔	✔	✔
Neutrophilia	✔	-	-
Renal irritation	✔	-	-

✔ Percent not specified
\- Event not reported

VII. Dosing and Administration

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

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Keratoplastic Agents[3-4,8-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Anthralin	Psoriasis: Skin: apply once a day to psoriatic lesions for 5-10 minutes using the lowest strength possible for at least 1 week; contact time may increase up to 20-30 minutes as tolerated Scalp: comb hair to remove scalar	Safety and efficacy in children have not been established.	Cream: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	debris; wet and part hair; rub cream into lesions; avoid spreading cream onto the forehead; remove by washing or showering		
Coal tar	Dandruff: Apply 2 times a week for the first 2 weeks then once weekly or as needed Seborrheic dermatitis: Apply to the affected area 1-4 times daily; decrease frequency to 2-3 times a week once the condition has been controlled Atopic dermatitis: 2%-5% coal tar cream may be applied once daily or every other day to reduce inflammation Psoriasis: Apply at bedtime; if thick scales are present, use product with salicylic acid and apply several times during the day	Dandruff: Apply 2 times a week for the first 2 weeks then once weekly or as needed Seborrheic dermatitis: Apply to the affected area 1-4 times daily; decrease frequency to 2-3 times a week once the condition has been controlled Atopic dermatitis: 2%-5% coal tar cream may be applied once daily or every other day to reduce inflammation Psoriasis: Apply at bedtime; if thick scales are present, use product with salicylic acid and apply several times during the day	Cream: 2% Liquid: 40% Lotion: 5% Oil: 2% Ointment: 1%, 2% Shampoo: 0.5%, 1%, 2%, 2.5%
Coal tar and lanolin	Seborrheic dermatitis: Apply to the affected area 1-4 times daily; decrease frequency to 2-3 times a week once the condition has been controlled Psoriasis: Apply at bedtime; if thick scales are present, use product with salicylic acid and apply several times during the day	Seborrheic dermatitis: Apply to the affected area 1-4 times daily; decrease frequency to 2-3 times a week once the condition has been controlled Psoriasis: Apply at bedtime; if thick scales are present, use product with salicylic acid and apply several times during the day	Liquid: 2.5%

VIII. Effectiveness

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

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Psoriasis				
Langner et al.[10] (1983) Coal tar gel, applied daily for 6 days and coal tar shampoo, applied twice a week during remission vs. non-tar shampoo, applied twice a week during remission	RCT Patients aged 7-70 years with scalp psoriasis	N=112 7 days	Primary: Extent of lesions, severity of lesions Secondary: Response of patients who failed other treatments; duration of remission phase	Primary: Complete clearing or marked improvement was seen in 83% of patients in the treatment group. Secondary: Among the 35 patients that were unresponsive to other treatments 29 (82.8%) showed significant improvement. The duration of the remission phase was longer in patients who used coal tar shampoo compared to non-tar shampoo. The median time to relapse among patients using non-tar shampoo was 3.22 months compared to 8.37 months for those using coal tar shampoo (P=0.003).
Smith et al.[11] (2000) Coal tar 1% lotion with esterified essential fatty acids (Exorex®), applied twice daily vs. coal tar 1% lotion, applied twice daily One side received coal tar with fatty acid component and the other side received coal	RCT, DB Patients aged 18 years and older with mild to moderate chronic plaque psoriasis	N=20 8 weeks	Primary: Efficacy evaluation based on score of erythema, induration, and desquamination Secondary: Psoriasis Area and Severity Index (PASI); cosmetic acceptability	Primary: No significant difference was found between the two treatment groups in the primary endpoints (P=0.52). Secondary: No significant difference was found between the two treatment groups in the secondary endpoints.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tar without fatty acid component				
Goodfield et al.[12] (2004) Coal tar 1% lotion, applied 3 times a day vs. coal tar 5% lotion, applied 3 times a day	RCT, DB, MC, PG Patients aged 16 years and older with chronic mild to moderate plaque psoriasis	N=324 12 weeks	Primary: Total Sign Score (TSS), or the sum of erythema, induration and scaling (range of 0-12); Psoriasis Area and Severity Index (PASI) Secondary: Investigator and patient assessed effect of medication; patient cosmetic acceptability evaluation	Primary: There was a greater percentage change in the TSS at week 12 compared to baseline in the coal tar 1% group (5.6 to 3.2) when compared to the coal tar 5% group (5.5 to 3.2; P=0.02). The percentage decrease in mean PASI at week 12 compared to baseline was not significantly different in the coal tar 1% group (6.8 to 4.4) compared to the coal tar 5% group (6.7 to 5.2; P=0.06). Secondary: A greater number of patients in the coal tar 1% group (38%) showed an improvement in clearance of their psoriasis compared to the to the coal tar 5% group (27%) based on investigator global assessments of improvement. Patient assessments showed that a slightly higher proportion of patients treated with 1% coal tar lotion compared to those treated with 5% coal tar lotion considered that their psoriasis had shown some improvement over the 12-week period (68% versus 60%, respectively). Cosmetic acceptability was high for both products and there was little perceived difference between the two treatments.
Jones et al.[13] (1985) Dithranol 1%, 2%, and 3% ointment, short contact therapy vs. dithranol 1%, 2%, and 3% ointment, overnight	RCT, SB Outpatients with plaque psoriasis	N=30 12 weeks	Primary: Lesions evaluated based on the Psoriasis Area and Severity Index (PASI) Secondary: Degree of staining, irritation	Primary: No statistically significant difference was found between the short contact therapy and the overnight therapy at any point during the study. Improvement in PASI scores was found to be comparable in both the short contact and overnight therapy. Secondary: Over the course of the study, overnight therapy caused more staining than short contact therapy (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy Short contact therapy began with a 10 minute application and was tapered up to 30 minutes by day 18				Irritation of perilesional skin was greater with short contact therapy compared to the overnight therapy at week 4 (P<0.05) and week 6 (P<0.001). Irritation of psoriatic plaques was greater in the overnight therapy at week 6 (P<0.05).
Downey et al.[14] (1986) Crude coal tar (CCT) 30%, applied every morning for 1 hour then removed; dithranol was then applied and reapplied 6 hours later vs. placebo, applied every morning for 1 hour then removed; dithranol was then applied and reapplied 6 hours later Increasing strengths of dithranol were used	RCT, SB Patients with chronic plaque psoriasis	N=24 14 days	Primary: Severity score determination, erythema, scaling and thickness	Primary: No significant differences between the two treatment groups on day 7 or day 14. There was an improvement between day 0 and 14 in both treatment groups (P<0.01). Six patients stated that the CCT and dithranol combined regimen gave quicker resolution than dithranol alone, and 4 patients stated that dithranol alone gave quicker resolution than the CCT and dithranol combined regimen. Four patients withdrew from the study: 2 due to dithranol irritation, 1 due to inadequate response, and 1 due to social reasons.
Seborrheic dermatitis				
Pierard-Franchimont et al.[15] (2000) Coal tar 0.5% shampoo, applied 3 times a week vs.	RCT, DB Patients with moderate to marked dandruff	N=60 4 weeks	Primary: Scaliness of the scalp, *Malassezia* spp. count, severity of dandruff Secondary: Patient ratings	Primary: Both treatment groups were found to be effective at reducing the dandruff severity based on clinical scoring (*P*<0.001). By the end of treatment, both the coal tar and non-tar shampoo reduced the severity score to almost zero. According to squamometry assessment, the coal tar shampoo was as effective during the treatment phase at reducing the squamometry index; however, during the regression period the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salicylic acid 2% / piroctone 0.75% / elubiol 0.5% shampoo, applied 3 times a week Patients participated in a 3 week pre-treatment washout and a 4 week post-treatment regression				non-tar shampoo was more efficacious than the coal tar ($P<0.01$). The non-tar shampoo was better at reducing the *Malassezia* spp. count compared to the coal tar ($P<0.02$). Secondary: Both coal tar and non-tar shampoos received high approval ratings (≥70% of patients) in providing itching and flaking relief ($P<0.05$).

Study abbreviations: DB=double-blind, MC=multicenter, PG=parallel-group, 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 8. Relative Cost of the Skin and Mucous Membrane Keratoplastic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Anthralin	cream	Psoriatec®	$$$$	N/A
Coal tar‡	cream, liquid, lotion, oil, shampoo	Betatar®, DHS Tar®*, Doak Tar®*, Doak Tar Distillate®, Doak Tar Oil®, Fototar®, Ionil T®, Ionil T Plus®, Oxipor VHC®, Pentrax®, Polytar®*, X-Seb T Plus®, Zetar®	$	$
Coal tar and lanolin‡	liquid	Balnetar®	$	N/A

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
N/A=Not available

X. Conclusions

Topical coal tar and anthralin preparations are classified as keratoplastic agents. Coal tar is indicated for the treatment of psoriasis, seborrheic dermatitis and dandruff.[4,8-9] Whereas, anthralin is only indicated for the treatment of psoriasis.[3,8-9] Treatment options for psoriasis should be tailored to meet individual patients' needs and preferences.[5] This includes taking into consideration the location and characteristics of the lesions being treated (e.g., thickness, degree of erythema, and amount of scaling).[5] There are a variety of formulations to choose from and the optimal choice is generally the formulation the patient will most likely use.[5]

Guidelines for the treatment of psoriasis state that both coal tar and anthralin are effective treatment options.[5-7] Although coal tar and anthralin have been available for many years, there are limited clinical trials evaluating the efficacy and safety of these agents directly or compared to placebo.[10-15] Topical corticosteroids are often considered the cornerstone of treatment for the majority of patients with psoriasis.[1,5]

Guidelines for the treatment of seborrheic dermatitis do not specifically discuss the use of coal tar. In general, topical corticosteroids, antifungal agents and moisturizing emollients are the standard of care for seborrheic dermatitis.[2,16]

Coal tar products are often poorly tolerated because of staining and the tar odor, which may limit its use.[5-7] Coal tar is carcinogenic in animals; however, in humans, there is no firm evidence to indicate that it causes cancer.[5-6] Anthralin causes skin irritation and staining of skin, nails and clothing, which may limit its use.[5-7] There is no evidence of any long-term local or systemic toxicity with the use of anthralin.[5-6]

Therefore, all brand skin and mucous membrane keratoplastic agents within the class reviewed are comparable to each other and to the generics and OTC 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 keratoplastic 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Agents, Miscellaneous
AHFS Class 849200
May 13, 2009

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, genital/perianal warts, hemorrhoids, Kaposi's sarcoma, psoriasis, and wounds. The wide variety of products, as well as the range of 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.[1-2,6,23-24] Becaplermin promotes the chemotactic recruitment and proliferation of cells involved in wound repair.[3] Calcipotriene is a synthetic vitamin D_3 analogue, which regulates skin cell production and proliferation.[7] Collagenase can digest collagen in necrotic tissue, which contributes to the formation of granulation tissue and epithelialization.[8] Diclofenac reversibly inhibits cyclooxygenase-1 and 2 enzymes, which result in decreased formation of prostaglandin precursors.[9] Fluorouracil is an antineoplastic antimetabolite that interferes with synthesis of DNA and to a lesser extent inhibits the formation of RNA.[11-12] Imiquimod is an immune response modifier, which induces cytokines including interferon-alpha and others.[14] Pimecrolimus and tacrolimus bind to the intracellular protein FKBP-12, inhibiting calcineurin, which blocks cytokine transcription and inhibits T-cell activation.[16,19] Podophyllin resin is a cytotoxic agent that arrests mitosis in metaphase.[18] Podofilox is an active component of podophyllin resin.[17] The thrombin/fibrinogen/aprotinin/calcium chloride product is a two-component fibrin sealant made from pooled human plasma, which mimic the final stage of the blood coagulation cascade.[22]

The miscellaneous skin and mucous membrane agents included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Calcipotriene, fluorouracil, and podofilox are available in a generic formulation. Phenylephrine/shark liver oil/glycerin/white petrolatum and phenylephrine/shark liver oil/mineral oil/white petrolatum products are also available in a generic formulation and over-the-counter. This class was last reviewed in February 2007.

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)
Acitretin	kit	Soriatane® CK	none
Alitretinoin	gel	Panretin®	none
Becaplermin	gel	Regranex®	none
Betamethasone and calcipotriene	ointment, suspension	Taclonex®, Taclonex Scalp®	none
Bexarotene	gel	Targretin®	none
Calcipotriene	cream, solution	Dovonex®*	calcipotriene
Collagenase	ointment	Santyl®	none
Diclofenac	gel	Solaraze®	none
Fluorouracil	cream, kit, solution	Carac®, Efudex®*, Efudex® Occlusion Pack, Fluoroplex®	fluorouracil
Formaldehyde	solution	Formalaz®*, Lazerformalyde®*	formaldehyde
Imiquimod	cream	Aldara®	none
Phenylephrine, shark liver oil, glycerin, and white petrolatum‡	rectal cream	N/A	phenylephrine, shark liver oil, glycerin, and white petrolatum
Phenylephrine, shark liver oil, mineral oil, and white	rectal ointment	Preparation H®*	phenylephrine, shark liver oil, mineral oil, and white

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
petrolatum‡			petrolatum
Pimecrolimus	cream	Elidel®	none
Podofilox	gel, solution	Condylox®*	podofilox
Podophyllum resin	liquid	Podocon-25®	none
Sodium phosphate (monobasic/dibasic), potassium phosphate (monobasic/dibasic), zinc, and urea	spray	Constant- Clens®	none
Tacrolimus	ointment	Protopic®	none
Tazarotene	cream, gel	Tazorac®	none
Thrombin, fibrinogen, aprotinin, and calcium chloride	kit, syringe	Artiss®, Artiss® Duploject	none

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
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 Therapy Guidelines and Audit: **Guidelines for the Management of Actinic Keratoses[33] (2007)**	• No therapy, or emollient, is a reasonable option for mild actinic keratoses (AKs). • Sun block applied twice daily for 7 months may protect against development of AKs. • 5-Fluorouracil (5-FU) cream used twice daily for 6 weeks is effective for up to 12 months in clearance of the majority of AKs. 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 AKs. 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 8 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 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 AKs in trials comparing it with cryotherapy, with consistently good cosmetic result. It may be particularly good for superficial and confluent AKs, but is likely to be more expensive than most other therapies. It is of particular value where AKs 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 AKs unresponsive to other therapies, where invasive squamous cell carcinoma is possible.
Primary Care Dermatology	• Immunomodulatory agents (e.g. tacrolimus or pimecrolimus for short-

Clinical Guideline	Recommendation(s)
Society & British Association of Dermatologists: **Guidelines for the Management of Atopic Eczema**[30] **(2006)**	term use) are an alternative to topical steroids. They should only be considered if the patient is intolerant to or has failed with conventional corticosteroid therapy. • These drugs do not cause skin atrophy; however, they can cause a transient sensation of warmth or burning. • They should not be used in the context of recurrent herpes simplex infection, and patients should be advised on photoprotection. • The long-term adverse effects of tacrolimus and pimecrolimus are unknown. • Pimecrolimus by topical application is licensed for mild to moderate atopic eczema for short-term use to treat signs and symptoms and for intermittent use to prevent flares. • Tacrolimus is licensed for topical use in moderate to severe atopic eczema. • These agents should not usually be considered first-line treatments unless there is a specific reason to avoid or reduce the use of topical corticosteroids. • It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians with a special interest and experience in dermatology, after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options. General practitioners with specific recognition in the field of eczema care may initiate treatment with tacrolimus or pimecrolimus.
European Academy of Dermatology and Venereology: **Position Paper on Diagnosis and Treatment of Atopic Dermatitis**[31] **(2005)**	• Topical corticosteroids are a first-line anti-inflammatory therapy. Application 2-3 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. • Safety has been demonstrated in clinical trials and the most common adverse effect is transient burning or warmth at the application site. • 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 photocarcinogenicity, though ultraviolet (UV) protection is advised.
American Academy of Dermatology (AAD), Clinical Guidelines Task Force: **Guidelines of Care for Atopic Dermatitis**[32] **(2004)**	• Topical corticosteroids are the standard of care to which other treatments are compared. • Calcineurin inhibitors (tacrolimus and pimecrolimus) have demonstrated efficacy in reducing the severity and extent of symptoms in adults and children. The long-term safety of these agents (therapy for longer than 1 year) is unknown, including the potential for immunosuppression and malignancy.
National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: **Basal Cell and Squamous Cell Skin Cancers**[35] **(2009)**	• In patients with low-risk squamous cell carcinoma in situ, 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 (ALA), or vigorous cryotherapy) may be considered even though cure rate may be lower. • Actinic keratoses should be treated aggressively at first development. • Accepted treatment modalities for actinic keratoses include cryosurgery, topical 5-fluorouracil, topical imiquimod, photodynamic therapy (porfimer sodium, topical ALA), and curettage % electrodessication.

Clinical Guideline	Recommendation(s)
Joint British Association of Dermatologists and United Kingdom Cutaneous Lymphoma Group: **Guidelines for the Management of Primary Cutaneous T-Cell Lymphomas**[34] **(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 PUVA 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.
Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines**[37] **(2006)**	• No evidence exists to identify one treatment as more efficacious than another and no treatment is ideal for all patients with genital warts. • Treatment selection may be based on wart size and number, anatomic site of wart, wart morphology, and adverse effects of treatment. • Treatment modalities should be changed if a patient has not experienced substantial improvement within 3 months of therapy. • Patient-applied treatments include podofilox 0.5% gel and imiquimod 5% cream. If possible, the health-care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. • Provider-administered treatments include cryotherapy, podophyllin resin 10% - 25%, trichloroacetic acid, bichloracetic acid, and surgery. • Alternative treatments include intralesional interferon therapy and laser surgery.
American Gastroenterological Association: **Technical Review on the Diagnosis and Treatment of Hemorrhoids**[38] **(2004)**	• The almost-universal recommendations are to add dietary fiber and to 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 symptomatic relief of local pain/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.
American Academy of Dermatology: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapies**[26] **(2009)**	• Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis, particularly those with limited disease. • The combination of topical corticosteroids and vitamin D analogues appears to be more efficacious than either therapy alone, with fewer side effects noted in most, but not all, studies. • When using combination calcipotriene/betamethasone, the side effects of high-potency topical corticosteroids including HPA axis suppression, skin atrophy, among others may occasionally occur. • Owing to the potential irritancy of topical tazarotene, adding topical corticosteroids to a regimen of tazarotene is an appropriate option. Combination therapy may increase the duration of treatment benefit as well as length of remission. Another potential advantage of using combination tazarotene and topical corticosteroid is a potential decrease in steroid-induced atrophy.
American Academy of Dermatology: **Overview of Psoriasis and Guidelines of Care for the Treatment of Psoriasis with Biologics**[27] **(2008)**	• Acitretin is an effective systemic agent for the treatment of psoriasis that is not immunosuppressive. • Because it is teratogenic and should not be used in women who are pregnant, breast-feeding, or may become pregnant within 3 years of discontinuing acitretin, its use is substantially limited in female patients of childbearing potential.

Clinical Guideline	Recommendation(s)
	• Mucocutaneous side effects are frequent. Dyslipidemia may also ensue and require dose reduction or treatment with lipid-lowering agents. Hepatotoxicity rarely arises during therapy. • Acitretin is frequently used in combination therapy with UVB/PUVA.

Finnish Medical Society Duodecim: **Psoriasis**[28] **(2007)**	Plaque Psoriasis
	• Topical preparations of vitamin D and its derivatives (calcitriol and calcipotriol) are efficient and safe in long-term management of plaque psoriasis. Local skin reactions may occur. The use of topical vitamin D may be hampered by the need to apply the preparation regularly twice daily in order to achieve full efficacy and, moreover, treatment response will not be evident until after 4 to 6 weeks. This is the safest and most recommended treatment form, but only a few patients are able to continue long-term with the regular applications.
	• The combination ointment of calcipotriol and betamethasone dipropionate is the fasted and most effective topical treatment for plaque psoriasis. Once daily application is sufficient. The initial treatment period lasts for 4 weeks and should be followed by one of the following studied maintenance regimes:
	  o Calcipotriol once or twice daily long-term (OR)
	  o Calcipotriol on weekdays and the combination ointment on weekends (OR)
	  o The combination ointment when required.
	Plaque Psoriasis in Specific Areas
	• Psoriasis on the face may be treated by pimecrolimus and tacrolimus.
	• Flexural psoriasis may be managed with the same preparations as those used on the face. Some patients may also tolerate vitamin D preparations in flexural areas.
	• The treatment of psoriasis on the palms and the soles of the feet consists of the above mentioned medicines used in plaque psoriasis. In more severe cases, systemic acitretin may be prescribed.
	Guttate Psoriasis
	• If guttate psoriasis is not very extensive, the topical treatment forms described for plaque psoriasis may be used, particularly topical corticosteroids.

British Association of Dermatologists: **Psoriasis Guidelines**[29] **(2006)**	• Calcipotriene is an effective treatment for mild to moderate chronic plaque psoriasis, more so than coal tar and short contact anthralin. Only potent topical corticosteroids seem to have comparable efficacy at eight weeks. Although calcipotriene causes more skin irritation than topical corticosteroids this has to be balanced against the potential long term effects of corticosteroids. Skin irritation rarely led to withdrawal of calcipotriol treatment. • The combination of betamethasone and calcipotriene has greater efficacy than either constituent used alone. • Tazarotene is a topical retinoid which is effective in psoriasis. It is suitable for the treatment of moderate plaque psoriasis affecting up to 10% of skin area. As a retinoid this preparation is potentially teratogenic and should strictly be avoided in pregnancy.
American Diabetes Association: **Consensus Development Conference on Diabetic Foot Wound Care**[36] **(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.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous skin and mucous membrane agents are noted in Tables 3-4. 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 3. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous[1-14,23-24]

Indication	Acitretin	Alitretinoin	Becaplermin	Betamethasone, Calcipotriene	Bexarotene	Calcipotriene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Psoriasis	✔			✔		✔					
Actinic keratosis								✔	✔		✔
Kaposi's sarcoma		✔									
Superficial basal cell carcinoma									✔ *		✔
External genital and perianal warts											✔
Debriding chronic dermal ulcers and severely burned areas							✔				
Treatment of lower extremity diabetic ulcers which extend into subcutaneous tissue or beyond and have adequate blood supply			✔								
Drying agent for pre and post surgical removal of plantar and mosaic warts.										✔	
Treatment for excessive offensive foot odor and excessive moisture of feet										✔	
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					✔						

* Efudex® 5% only

Table 4. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous[15-24]

Indication	Phenylephrine, Shark Liver Oil, Glycerin, White Petrolatum	Phenylephrine, Shark Liver Oil, Mineral Oil, White Petrolatum	Pimecro-limus	Podo-filox	Podo-phyllum	Sodium Phosphate, Potassium Phosphate, Zinc, Urea	Tacro-limus	Tazaro-tene	Thrombin, Fibrinogen, Aprotinin, Calcium Chloride
Psoriasis								✔ *	
External genital and perianal warts				✔	✔				
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable			✔						
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable							✔		
Provide relief of burning, itching, and discomfort from hemorrhoids; shrink hemorrhoidal tissue, provide coating for relief from anorectal discomforts and protect anorectal surface to make bowel movements less painful		✔							
Shrink swelling of irritated hemorrhoidal tissue and provide relief of burning, itching, and discomfort from hemorrhoids	✔								
Treatment of exudative, contaminated, infected or problem wounds						✔			
Adherence of autologous skin grafts to surgically prepared wound beds resulting from burns in adults and children									✔

*Tazorac® is also indicated for the treatment of acne vulgaris

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous skin and mucous membrane agents are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Skin and Mucous Membrane Agents, Miscellaneous[1-24]

Generic Name(s)	Systemic Absorption (%)	Renal Excretion (%)	Active Metabolites (%)
Acitretin	60	93	13-cis-acitretin
Alitretinoin	Minimal	No data	No data
Becaplermin	Minimal	No data	No data
Betamethasone and calcipotriene	No data	No data	No data
Bexarotene	Minimal	Minimal	Yes
Calcipotriene	5-6 (ointment) 1 (scalp solution)	No	No
Collagenase	No data	No data	No data
Diclofenac	10%	No data	No data
Fluorouracil	No data (Carac®) 5.98 (Efudex®)	Minimal	0.055 (Carac®) 0.24 (Efudex®)
Formaldehyde	No data	No data	No data
Imiquimod	Minimal	0.11 (males) 2.41 (females)	No data
Phenylephrine, shark liver oil, glycerin, and white petrolatum	No data	No data	No data
Phenylephrine, shark liver oil, mineral oil, and white petrolatum	No data	No data	No data
Pimecrolimus	Minimal	No	No
Podofilox	Minimal	No data	No data
Podophyllum	No data	No data	No data
Sodium phosphate, potassium phosphate, zinc, and urea	No data	No data	No data
Tacrolimus	Minimal	No data	No data
Tazarotene	1-5	No	Yes
Thrombin, fibrinogen, aprotinin, and calcium	No data	No data	No data

V. Drug Interactions

Significant drug interactions with the miscellaneous skin and mucous membrane agents are listed in Table 6.

Table 6. Significant Drug Interactions with the Skin and Mucous Membrane Agents, Miscellaneous[24]

Generic Name(s)	Significance Level	Interaction	Mechanism
Acitretin	1	Ethanol	Enhanced formation of etretinate, with much longer half-life and greater potential for toxicity.
Acitretin	1	Methotrexate	↑ risk of drug-induced hepatotoxicity, possibly due to ↑methotrexate plasma levels
Acitretin	1	Low-dose progestin contraceptives	Interference with contraceptive effect; mechanism unknown
Acitretin	1	Tetracyclines	Concurrent administration may ↑ risk for development of pseudotumor cerebri; mechanism unknown
Acitretin	2	Vitamin A / oral retinoids	↑ risk of hypervitaminosis A; mechanism unknown

Generic Name(s)	Significance Level	Interaction	Mechanism
Alitretinoin	2	N,N-diethyl-m-toluamide (DEET)	Animal toxicology studies show an increased absorption of DEET and an increase in DEET toxicity when both agents are administered together.
Tazarotene	2	Dermatologic medications and cosmetics that have a drying effect on the skin	Administration of these products with tazarotene is likely to increase the drying effect on the skin.

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 7-8. The boxed warning for acitretin is listed in Table 9. The boxed warning for becaplermin is listed in Table 10. The boxed warning for pimecrolimus is listed in Table 11. The boxed warning for tacrolimus is listed in Table 12.

Table 7. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous[1-14,23-24]

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Cardiovascular											
Arrhythmias	-	-	-	-	-	-	-	-	-	-	✔
Atrial fibrillation	-	-	-	-	-	-	-	-	-	-	1
Capillary leak syndrome	-	-	-	-	-	-	-	-	-	-	✔
Cardiac failure	-	-	-	-	-	-	-	-	-	-	✔
Cardiomyopathy	-	-	-	-	-	-	-	-	-	-	✔
Chest pain	<1	-	-	-	-	-	-	1-2	-	-	1
Cyanosis	<1	-	-	-	-	-	-	-	-	-	-
Flushing	1-10	-	-	-	-	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-	-	1-2	-	-	-
Increased bleeding time	<1	-	-	-	-	-	-	-	-	-	-
Intermittent claudication	<1	-	-	-	-	-	-	-	-	-	-
Ischemia	-	-	-	-	-	-	-	-	-	-	✔
Myocardial infarction	-	-	-	-	-	-	-	-	-	-	✔
Peripheral ischemia	<1	-	-	-	-	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	-	-	-	-	-	✔
Syncope	-	-	-	-	-	-	-	-	-	-	✔
Central Nervous System											
Abnormal gait	<1	-	-	-	-	-	-	-	-	-	-
Agitation	-	-	-	-	-	-	-	-	-	-	✔
Anorexia	1-10	-	-	-	-	-	-	-	-	-	-
Anxiety	<1	-	-	-	-	-	-	-	-	-	1
Asthenia	-	-	-	-	6	-	-	2	-	-	-
Cerebrovascular	-	-	-	-	-	-	-	-	-	-	✔

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
accident											
Convulsions	-	-	-	-	-	-	-	-	-	-	✔
Depression	1-10	-	-	-	-	-	-	-	-	-	✔
Dizziness	<1	-	-	-	-	-	-	-	-	-	1
Dysphonia	<1	-	-	-	-	-	-	-	-	-	-
Emotional upset	-	-	-	-	-	-	-	-	✔	-	-
Fatigue	-	-	-	-	-	-	-	-	-	-	2
Headache	10	-	-	2.8	14	-	-	7	-	-	4-8
Hyperesthesia	-	-	-	-	-	-	-	3	-	-	-
Hypokinesia	-	-	-	-	-	-	-	2	-	-	-
Insomnia	1-10	-	-	-	-	-	-	-	✔	-	✔
Irritability	-	-	-	-	-	-	-	-	✔	-	-
Libido alterations	<1	-	-	-	-	-	-	-	-	-	-
Migraine	<1	-	-	-	-	-	-	1	-	-	-
Multiple sclerosis aggravation	-	-	-	-	-	-	-	-	-	-	✔
Nervousness	<1	-	-	-	-	-	-	-	-	-	-
Neuritis	<1	-	-	-	-	-	-	-	-	-	-
Paresis	-	-	-	-	-	-	-	-	-	-	✔
Paresthesia	10-25	3-22	-	-	6	-	-	8-20	-	-	-
Pseudotumor cerebri	<1	-	-	-	-	-	-	-	-	-	-
Rigors	10-25	-	-	-	-	-	-	-	-	-	-
Somnolence	<1	-	-	-	-	-	-	-	-	-	-
Suicide	-	-	-	-	-	-	-	-	-	-	✔
Dermatological											
Abnormal hair texture	1-10	-	-	-	-	-	-	-	-	-	-
Abnormal skin odor	1-10	-	-	-	-	-	-	-	-	-	-
Acne	<1	-	-	-	-	-	-	1	-	-	-
Alopecia	50-75	-	-	-	-	-	-	1-2	✔	-	1
Bleeding at site	-	-	-	-	-	-	-	-	-	-	2-3
Blistering	-	-	-	-	-	-	-	-	✔	-	-
Bullous eruption	1-10	-	-	-	-	-	-	-	-	-	-
Bullous pemphigoid	-	-	-	-	-	-	-	-	✔	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Burning sensation	-	-	-	0.2-1.4	-	-	-	-	-	-	-
Cellulitis	-	-	✔	-	-	-	-	-	-	-	-
Cold/clammy skin	1-10	-	-	-	-	-	-	-	-	-	-
Contact dermatitis	-	-	-	-	8-14	-	-	2-33	✔	-	-
Cracking	-	8	-	-	-	-	-	-	-	-	-
Crusting	-	8	-	-	-	-	-	-	✔	-	>10
Dermatitis	1-10	25-77	-	1	-	-	-	-	-	✔	-
Desquamation	-	3-9	-	-	-	-	-	-	-	-	-
Drainage	-	8	-	-	-	-	-	-	-	-	-
Dry skin	25-50	-	-	1-10	-	1-10	-	-	-	-	-
Ecchymosis	-	-	-	1	-	-	-	-	-	-	-
Eczema	<1	-	-	-	-	-	-	-	-	-	2
Erosion	-	-	-	-	-	-	-	-	24-63	-	>10
Erythema	-	25-77	-	1-10	-	1-10	-	-	89-96	-	>10
Eschar	-	8	-	-	-	-	-	-	-	-	-
Excoriation	-	8	-	-	-	-	-	-	-	-	>10
Exfoliation	-	-	-	-	-	-	-	6-24	-	-	-
Exfoliative dermatitis	-	3-9	-	-	6	-	-	-	-	-	✔
Flaking	-	3-9	-	-	-	-	-	-	-	-	>10
Fissure	-	8	-	-	-	-	-	-	-	-	-
Folliculitis	-	-	-	<4	-	<1	-	-	-	-	-
Fungal dermatitis	<1	-	-	-	-	-	-	-	-	-	-
Hair discoloration	<1	-	-	-	-	-	-	-	-	-	-
Herpes simplex	<1	-	-	-	-	-	-	2	✔	-	2
Hypoesthesia	<1	-	-	-	-	-	-	-	-	-	-
Hyperesthesia	10-25	-	-	-	-	-	-	-	-	-	-
Hyperkeratosis	<1	-	-	-	-	-	-	-	-	-	1-8
Hyper-pigmentation	-	-	-	0.1	-	<1	-	-	✔	-	-
Hypertrichosis	<1	-	-	-	-	-	-	-	-	-	-
Hypo-pigmentation	-	-	-	<1	-	-	-	-	-	-	>1
Ichthyosis	-	-	-	-	-	-	-	-	✔	-	-
Impaired healing	<1	-	-	-	-	-	-	-	-	-	-
Induration	-	-	-	-	-	-	-	-	-	-	>10
Irritation	-	25-77	-	10-15	-	10-15	-	-	1-2	-	1

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Itching	-	8-11	-	10-15	-	10-15	-	-	-	-	>10
Nail disorder	25-50	-	-	-	-	-	-	-	-	-	-
Oozing	-	8	-	-	-	-	-	-	-	-	-
Papules	-	-	-	-	-	-	-	-	-	-	1
Paronychia	10-25	-	-	-	-	-	-	-	-	-	-
Peeling	50-75	3-9	-	1-10	-	1-10	-	-	-	-	-
Photosensitivity	<1	-	-	-	-	-	-	3	✔	-	1
Pruritus	25-50	8-11	-	3-7	18-36	-	-	4-52	✔	-	1
Psoriasis form rash	1-10	-	-	-	-	-	-	-	-	-	-
Purpura	1-10	-	-	-	-	-	-	-	-	-	-
Pyogenic granuloma	1-10	-	-	-	-	-	-	-	-	-	-
Rash	1-10	25-77	-	1-10	56-72	1-10	-	2-46	✔	-	1-2
Redness	-	25-77	-	-	-	-	-	-	-	-	-
Scabbing	-	8	1-2	-	-	-	-	-	-	-	>10
Scaling	-	25-77	-	-	-	-	-	-	✔	-	>10
Scarring	-	-	-	-	-	-	-	-	✔	-	-
Scleroderma	<1	-	-	-	-	-	-	-	-	-	-
Seborrhea	1-10	-	-	-	-	-	-	-	-	-	-
Skin atrophy	1-10	-	-	0.1-1.9	-	<1	-	-	-	-	-
Skin carcinoma	-	-	-	-	-	-	-	2	-	-	-
Skin disorder	1-10	-	-	-	-	-	-	-	-	-	-
Skin inflammation	<1	-	-	-	-	-	-	-	-	-	-
Skin nodule	<1	-	-	-	-	-	-	-	-	-	-
Skin stickiness	10-25	-	-	-	-	-	-	-	-	--	-
Skin ulcer	-	-	-	-	-	-	-	1-2	✔	-	>10
Squamous carcinoma	-	-	-	-	-	-	-	-	-	-	4
Stinging	-	3-9	-	-	-	-	-	-	-	-	3
Sunburn	1-10	-	-	-	-	-	-	-	-	-	-
Suppuration	-	-	-	-	-	-	-	-	✔		-
Sweat gland disorder	<1	-	-	-	-	-	-	-	-	-	-
Sweating	<1	-	-	-	6	-	-	-	-	-	-
Telangiectasia	-	-	-	<1	-	-	-	-	✔	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Tinea cruris	-	-	-	-	-	-	-	-	-	-	>1
Verrucae	<1	-	-	-	-	-	-	-	-	-	<1
Vesicles	-	-	-	-	-	-	-	-	-	-	>10
Vesiculobullous rash	-	-	-	-	-	-	-	4	-	-	-
Weeping/exudate	-	-	-	-	-	-	-	-	-	-	>10
Worsening of psoriasis	<1	-	-	1-10	-	1-10	-	-	-	-	-
Endocrine and Metabolic											
Edema	-	3-8	-	-	10	-	-	3-4	14-60	-	-
Hyperglycemia	-	-	-	-	-	-	-	1	-	-	-
Hyperlipidemia	-	-	-	-	10	-	-	1	-	-	2
Increased triglycerides	66	-	-	-	-	-	-	-	-	-	-
Increased cholesterol	33	-	-	-	-	-	-	-	-	-	-
Decreased HDL	40	-	-	-	-	-	-	-	-	-	-
Jaundice	<1	-	-	-	-	-	-	-	-	-	-
Peripheral edema	-	-	-	-	6	-	-	-	-	-	-
Thyroiditis	-	-	-	-	-	-	-	-	-	-	✔
Gastrointestinal											
Abdominal pain	1-10	-	-	-	-	-	-	1-2	-	-	<1
Constipation	<1	-	-	-	-	-	-	-	-	-	-
Diarrhea	1-10	-	-	-	-	-	-	2	-	-	3
Dyspepsia	<1	-	-	-	-	-	-	2-3	-	-	2-3
Esophagitis	<1	-	-	-	-	-	-	-	-	-	-
Gastritis	<1	-	-	-	-	-	-	-	-	-	-
Gastroenteritis	<1	-	-	-	-	-	-	-	-	-	-
GERD	-	-	-	-	-	-	-	-	-	-	1
Glossitis	<1	-	-	-	-	-	-	-	-	-	-
Hemorrhoids	<1	-	-	-	-	-	-	-	-	-	-
Medicinal taste	-	-	-	-	-	-	-	-	✔	-	-
Melena	<1	-	-	-	-	-	-	-	-	-	-
Nausea	<1	-	-	-	-	-	-	-	-	-	1
Stomatitis	-	-		-	-	-	-	-	✔	-	-
Tenesmus	<1	-	-	-	-	-	-	-	-	-	-
Tongue disorder	<1	-	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Tongue ulceration	<1	-	-	-	-	-	-	-	-	-	-
Vomiting	-	-	-	-	-	-	-	-	-	-	1
Genitourinary											
Abnormal urine	<1	-	-	-	-	-	-	-	-	-	-
Dysuria	<1	-	-	-	-	-	-	-	-	-	-
Atrophic vaginitis	<1	-	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	-	-	-	2	-	-	-
Leukorrhea	<1	-	-	-	-	-	-	-	-	-	-
Proteinuria	-	-	-	-	-	-	-	-	-	-	✔
Urinary tract infection	-	-	-	-	-	-	-	-	-	-	1
Vaginal moniliasis	<1	-	-	-	-	-	-	-	-	-	-
Hematologic											
Abnormal WBC	-	-	-	-	6	-	-	-	✔	-	-
Eosinophilia	-	-	-	-	-	-	-	-	✔	-	-
Hypercalcemia	-	-	-	<1	-	<1	-	-	-	-	-
Leucopenia	-	-	-	-	6	-	-	-	-	-	-
Lymph-adenopathy	-	-	-	-	6	-	-	-	-	-	3
Platelet count decreases	-	-	-	-	-	-	-	-	-	-	✔
RBC decreases	-	-	-	-	-	-	-	-	-	-	✔
Thrombo-cytopenia	-	-	-	-	-	-	-	-	✔	-	-
Thrombocytosis	✔	-	-	-	-	-	-	-	-	-	-
Toxic granulation	-	-	-	-	-	-	-	-	✔	-	-
Hepatic											
Increased ALT	✔	-	-	-	-	-	-	-	-	-	-
Increased AST	✔	-	-	-	-	-	-	-	-	-	-
Increased GGT	✔	-	-	-	-	-	-	-	-	-	-
Increased LDH	✔	-	-	-	-	-	-	-	-	-	-
Musculoskeletal											
Arthralgia	10-25	-	-	-	-	-	-	2	-	-	1
Arthritis	1-10	-	-	-	-	-	-	-	-	-	1
Arthrosis	1-10	-	-	-	-	-	-	2	-	-	-
Bone disorder	<1	-	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Hypertonia	1-10	-	-	-	-	-	-	-	-	-	-
Myalgia	1-10	-	-	-	-	-	-	2-3	-	-	1
Osteodynia	1-10	-	-	-	-	-	-	-	-	-	-
Osteomyelitis	-	-	✔	-	-	-	-	-	-	-	-
Skeletal pain	-	-	-	-	-	-	-	-	-	-	1-2
Spinal/ peripheral joint hyperostosis	1-25	-	-	-	-	-	-	-	-	-	-
Tendonitis	<1	-	-	-	-	-	-	-	-	-	-
Respiratory											
Asthma	-	-	-	-	-	-	-	2	-	-	-
Bronchitis	-	-	-	-	-	-	-	-	-	-	1
Cough	<1	-	-	-	6	-	-	-	-	-	1-3
Dyspnea	-	-	-	-	-	-	-	2	-	-	✔
Laryngitis	<1	-	-	-	-	-	-	-	-	-	-
Nasal irritation	-	-	-	-	-	-	-	-	✔	✔	-
Nasopharyngitis	-	-	-	2.3	-	-	-	-	-	-	-
Pharyngitis	<1	-	-	-	6	-	-	2	-	-	1
Pneumonia	-	-	-	-	-	-	-	2	-	-	
Pulmonary congestion	-	-	-	-	-	-	-	-	-	-	<1
Respiratory tract irritation	-	-	-	-	-	-	-	-	-	✔	-
Rhinitis	25-50	-	-	-	-	-	-	2	-	-	2-3
Sinusitis	<1	-	-	-	-	-	-	2	1.6-4.7	-	2-7
Upper respiratory infection	-	-	-	<1	-	-	-	-	-	-	3-15
Other											
Abnormal/ blurred vision	1-10	-	-	-	-	-	-	-	-	-	-
Abrasion	-	-	-	-	-	-	-	-	-	-	3
Accidental injury	-	-	-	-	-	-	-	4	-	-	-
Alcohol intolerance	<1	-	-	-	-	-	-	-	-	-	-
Allergic reaction	-	-	-	-	-	-	-	1	1-3	-	-
Allergy aggravated	-	-	-	-	-	-	-	-	-	-	3
Altered saliva	<1	-	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Anal disorder	<1	-	-	-	-	-	-	-	-	-	-
Angioedema	-	-	-	-	-	-	-	-	-	-	✔
Back pain	1-10	-	-	-	-	-	-	2-4	-	-	4
Birth defect	✔	-	-	-	-	-	-	-	-	-	-
Blepharitis	1-10	-	-	-	-	-	-	-	-	-	-
Breast pain	<1	-	-	-	-		-	-	-	-	-
Burning	-	34	-	10-15	-	10-15	-	-	60-83	-	1-10
Ceruminosis	<1	-	-	-	-	-	-	-	-	-	-
Chalazion	<1	-	-	-	-	-	-	-	-	-	-
Cheilitis	>75	-	-	-	-	-	-	-	-	-	-
Common cold	-	-	-	-	-	-	-	-	2.4-4.7	-	-
Conjunctival hemorrhage	<1	-	-	-	-	-	-	-	-	-	-
Conjunctival reaction	-	-	-	-	-	-	-	-	✔	-	-
Conjunctivitis	1-10	-	-	-	-	-	-	2-4	-	-	<1
Corneal epithelial abnormality	1-10	-	-	-	-	-	-	-	-	-	-
Corneal reaction	-	-	-	-	-	-	-	-	✔	-	-
Corneal ulceration	<1	-	-	-	-	-	-	-	-	-	-
Cyst	<1	-	-	-	-	-	-	-	-	-	-
Deafness	<1	-	-	-	-	-	-	-	-	-	-
Decreased night vision/ blindness	1-10	-	-	-	-	-	-	-	-	-	-
Diplopia	<1	-	-	-	-	-	-	-	-	-	-
Ear pain	1-10	-	-	-	-	-	-	-	-	-	-
Ectropion	<1	-	-	-	-	-	-	-	-	-	-
Edema	1-10	-	-	-	-	-	-	-	-	-	-
Epistaxis	25-50	-	-	-	-	-	-	-	-	-	-
Eye irritation	-	-	-	-	-	-	-	-	3-7	-	-
Eye pain	1-10	-	-	-	-	-	-	2	-	-	-
Fatigue	1-10	-	-	-	-	-	-	-	-	-	1-2
Fever	<1	-	-	-	-	-	-	-	-	-	1
Flu symptoms	<1	-	-	-	-	-	-	-	-	-	1-3
Flu syndrome	-	-	-	0.9	-	-	-	1-10	-	-	-
Fungal infection	-	-	-	-	-	-	-	-	-	-	1
Furunculosis	<1	-	-	-	-	-	-	-	-	-	-

Adverse Events	Acitretin	Alitretinoin	Becaplermin	Betamethasone / Calcipotriene	Bexarotene	Calcipo-triene	Collagenase	Diclofenac	Fluorouracil	Formaldehyde	Imiquimod
Gingival bleeding	1-10	-	-	-	-	-	-	-	-	-	-
Gingivitis	1-10	-	-	-	-	-	-	-	-	-	-
Gum hyperplasia	<1	-	-	-	-	-	-	-	-	-	-
Hemorrhage	<1	-	-	-	-	-	-	-	-	-	-
Hernia	-	-	-	-	-	-	-	-	-	-	2
Hot flashes	1-10	-	-	-	-	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	-	✔	-	-	-	-
Infection	1-10	-	✔	-	18	-	-	4	-	-	<1
Increased appetite	1-10	-	-	-	-	-	-	-	-	-	-
Increased saliva	<1	-	-	-	-	-	-	-	-	-	-
Inflammation	-	3-8	-	-	-	-	-	-	-	-	-
Inflicted injury	-	-	-	-	-	-	-	-	-	-	1-9
Lacrimation	<1	-	-	-	-	-	-	-	✔	-	-
Malaise	<1	-	-	-	-	-	-	-	-	-	-
Neck pain	-	-	-	-	-	-	-	2	-	-	-
Otitis media	<1	-	-	-	-	-	-	-	-	-	-
Pain	1-10	34	-	0.3	30	-	-	2-26	30-60	-	1-8
Papilledema	<1	-	-	-	-	-	-	-	-	-	-
Photophobia	1-10	-	-	-	-	-	-	-	-	-	-
Sensitivity reaction	-	-	-	-	-	-	-	-	-	✔	-
Stomatitis	1-10	-	-	-	-	-	-	-	-	-	-
Swelling	-	3-8	-	-	-	-	-	-	✔	-	-
Taste loss/ perversion	1-10	-	-	-	-	-	-	-	-	-	-
Thirst	1-10	-	-	-	-	-	-	-	-	-	-
Tinnitus	<1	-	-	-	-	-	-	-	-	-	-
Ulcerative stomatitis	1-10	-	-	-	-	-	-	-	-	-	-
Urticaria	<1	-	-	-	-	-	-	-	✔	-	-
Xerophthalmia	10-25	-	-	-	-	-	-	-	-	-	-
Xerostomia	10-25	-	-	-	-	-	-	-	-	-	-

✔ Percent not specified
\- Event not reported

Table 8. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous[15-24]

Adverse Events	Phenylephrine, Shark Liver Oil, Glycerin, White Petrolatum	Phenylephrine, Shark Liver Oil, Mineral Oil, White Petrolatum	Pimecrolimus	Podofilox	Podophyllum Resin	Sodium Phosphate, Potassium Phosphate, Zinc, Urea	Tacrolimus	Tazarotene	Thrombin, Fibrinogen, Aprotinin, Calcium Chloride
Cardiovascular									
Chest pain	-	-	-	-	-	-	<1	-	-
Hypertension	-	-	-	-	-	-	1-2	-	-
Syncope	-	-	-	-	-	-	<1	-	-
Tachycardia	-	-	-	-	-	-	<1	-	-
Valvular heart disease	-	-	-	-	-	-	<1	-	-
Vasodilation	-	-	-	-	-	-	<1	-	-
Central Nervous System									
Abnormal thinking	-	-	-	-	-	-	<1	-	-
Anxiety	-	-	-	-	-	-	<1	-	-
Asthenia	-	-	-	-	-	-	1-3	-	-
Chills	-	-	-	-	-	-	<1	-	-
Depression	-	-	-	-	-	-	1	-	-
Dizziness	-	-	-	<5	-	-	<1	-	-
Headache	-	-	14-25	-	-	-	5-20	-	-
Hyperesthesia	-	-	-	-	-	-	3-7	-	-
Hypertonia	-	-	-	-	-	-	<1	-	-
Insomnia	-	-	-	<5	-	-	1-4	-	-
Malaise	-	-	-	-	-	-	<1	-	-
Migraine	-	-	-	-	-	-	<1	-	-
Paresthesia	-	-	-	-	✔	-	≥1	-	-
Polyneuritis	-	-	-	-	✔	-	-	-	-
Vertigo	-	-	-	-	-	-	<1	-	-
Dermatological									
Acne	-	-	-	-	-	-	1-7	-	-
Alopecia	-	-	-	-	-	-	≥1	-	-
Bleeding at site	-	-	-	<5	-	-	-	1-10	-
Burning sensation	-	-	-	-	-	✔	20-58	-	-
Cellulitis	-	-	-	-	-	-	≥1	-	-
Contact dermatitis	-	-	-	-	-	-	1-4	1-10	-
Cutaneous moniliasis	-	-	-	-	-	-	<1	-	-

Adverse Events	Phenylephrine, Shark Liver Oil, Glycerin, White Petrolatum	Phenylephrine, Shark Liver Oil, Mineral Oil, White Petrolatum	Pimecrolimus	Podofilox	Podophyllum Resin	Sodium Phosphate, Potassium Phosphate, Zinc, Urea	Tacrolimus	Tazarotene	Thrombin, Fibrinogen, Aprotinin, Calcium Chloride
Dermal cyst	-	-	-	-	-	-	-	-	✔
Desquamation	-	-	-	-	-	-	-	1-30	-
Dry skin			-	-	-		1-7	1-10	
Eczema herpeticum	-	-	0.8	-	-	-	1-3	-	-
Erosion	-	-	-	67	-	-	-	-	-
Erythema	-	-	-	-	-	-	9-28	10-30	-
Exfoliative dermatitis	-	-	-	-	-	-	1-3	-	-
Fissure	-	-	-	-	-	-	-	1-10	-
Folliculitis	-	-	-	-	-	-	2-11	-	-
Fungal dermatitis	-	-	-	-	-	-	1-6	-	-
Furunculosis	-	-	-	-	-	-	<1	-	-
Irritation	-	-	-	-	-	-	-	10-30	-
Itching	-	-	-	50-65	-	-	-	-	-
Leukoderma	-	-	-	-	-	-	<1	-	-
Maculopapular rash	-	-	-	-	-	-	2-4	-	-
Peeling	-	-	-	<5	-	-	-	-	-
Photosensitivity	-	-	-	-	-	-	<1	-	-
Pruritus	-	-	-	-	-	✔	25-46	10-30	>1
Pustular rash	-	-	-	-	-	-	2-8	-	-
Rash	-	-	-	-	-	-	2-5	1-10	-
Scarring	-	-	-	<5	-	-	-	-	-
Seborrhea	-	-	-	-	-	-	<1	-	-
Skin carcinoma	-	-	-	-	-	-	<1	-	-
Skin discoloration	-	-	-	-	-	-	<1	-	-
Skin disorder	-	-	-	-	-	-	1-4	-	-
Skin hypertrophy	-	-	-	-	-	-	<1	-	-
Skin infection	-	-	-	-	-	-	5-14	-	-
Skin inflammation	-	-	-	-	-	-	-	1-10	-
Skin irritation	-	-	-	-	-	✔	-	1-10	-
Skin neoplasm benign	-	-	-	-	-	-	1-2	-	-

Adverse Events	Phenylephrine, Shark Liver Oil, Glycerin, White Petrolatum	Phenylephrine, Shark Liver Oil, Mineral Oil, White Petrolatum	Pimecrolimus	Podofilox	Podophyllum Resin	Sodium Phosphate, Potassium Phosphate, Zinc, Urea	Tacrolimus	Tazarotene	Thrombin, Fibrinogen, Aprotinin, Calcium Chloride
Skin tingling	-	-	-	-	-	-	1-8	-	-
Skin ulcer	-	-	-	<5	-	-	<1	-	-
Stinging	-	-	-	-	-	-	-	10-30	-
Sunburn	-	-	-	-	-	-	1-2	-	-
Sweating	-	-	-	-	-	-	<1	-	-
Urticaria	-	-	-	-	-	-	1-6	-	-
Varicella zoster	-	-	-	-	-	-	1-5	-	-
Vesicles	-	-	-	<5	-	-	-	-	-
Vesiculobullous rash	-	-	-	-	-	-	2-4	-	-
Viral rash	-	-	4	-	-	-	-	-	-
Worsening of psoriasis	-	-	-	-	-	-	-	10-30	-
Endocrine and Metabolic									
Dehydration	-	-	-	-	-	-	<1	-	-
Edema	-	-	-	-	-	-	<1	-	-
Face edema	-	-	-	-	-	-	1-2	-	-
Hypothyroidism	-	-	-	-	-	-	1-2	-	-
Peripheral edema	-	-	-	-	-	-	1-4	-	-
Gastrointestinal									
Anorexia	-	-	-	-	-	-	<1	-	-
Abdominal pain	-	-	-	-	-	-	1-3	-	-
Colitis	-	-	-	-	-	-	<1	-	-
Constipation	-	-	-	-	-	-	<1	-	-
Cramps	-	-	-	-	-	-	<1	-	-
Diarrhea	-	-	8	-	-	-	2-5	-	-
Dyspepsia	-	-	-	-	-	-	1-4	-	-
Gastritis	-	-	-	-	-	-	<1	-	-
Gastroenteritis	-	-	7	-	-	-	2-4	-	-
Hernia	-	-	-	-	-	-	<1	-	-
Mouth ulceration	-	-	-	-	-	-	<1	-	-
Oral moniliasis	-	-	-	-	-	-	<1	-	-
Nausea	-	-	-	-	-	-	1-3	-	-
Paralytic ileus	-	-	-	-	✔	-	-	-	-
Periodontal	-	-	-	-	-	-	1	-	-

Adverse Events	Phenylephrine, Shark Liver Oil, Glycerin, White Petrolatum	Phenylephrine, Shark Liver Oil, Mineral Oil, White Petrolatum	Pimecrolimus	Podofilox	Podophyllum Resin	Sodium Phosphate, Potassium Phosphate, Zinc, Urea	Tacrolimus	Tazarotene	Thrombin, Fibrinogen, Aprotinin, Calcium Chloride
abscess									
Stomatitis	-	-	-	-	-	-	<1	-	-
Taste perversion	-	-	-	-	-	-	<1	-	-
Tooth disorder	-	-	-	-	-	-	1-2	-	-
Vomiting	-	-	9	<5	-	-	1-7	-	-
Genitourinary									
Cystitis	-	-	-	-	-	-	<1	-	-
Dysmenorrhea	-	-	-	-	-	-	1-4	-	-
Foreskin retraction	-	-	-	<5	-	-	-	-	-
Hematuria	-	-	-	<5	-	-	-	-	-
Moniliasis	-	-	-	-	-	-	<1	-	-
Pain with intercourse	-	-	-	<5	-	-	-	-	-
Urinary tract infection	-	-	-	-	-	-	1-2	-	-
Vaginitis	-	-	-	-	-	-	<1	-	-
Hematologic									
Anemia	-	-	-	-	-	-	<1	-	-
Bilirubinemia	-	-	-	-	-	-	<1	-	-
Ecchymosis	-	-	-	-	-	-	<1	-	-
Hyper-cholesterolemia	-	-	-	-	-	-	<1	-	-
Leucopenia	-	-	-	-	✔	-	≥1	-	-
Thrombo-cytopenia	-	-	-	-	✔	-	-	-	-
Musculoskeletal									
Arthralgia	-	-	-	-	-	-	≥1	-	-
Arthritis	-	-	-	-	-	-	<1	-	-
Back pain	-	-	-	-	-	-	1-3	-	-
Bone disorder	-	-	-	-	-	-	<1	-	-
Bursitis	-	-	-	-	-	-	<1	-	-
Joint disorder	-	-	-	-	-	-	<1	-	-
Neck disorder	-	-	-	-	-	-	<1	-	-
Tendon disorder	-	-	-	-	-	-	<1	-	-

Adverse Events	Phenylephrine, Shark Liver Oil, Glycerin, White Petrolatum	Phenylephrine, Shark Liver Oil, Mineral Oil, White Petrolatum	Pimecrolimus	Podofilox	Podophyllum Resin	Sodium Phosphate, Potassium Phosphate, Zinc, Urea	Tacrolimus	Tazarotene	Thrombin, Fibrinogen, Aprotinin, Calcium Chloride
Myalgia	-	-	-	-	-	-	1-3	-	-
Respiratory									
Asthma	-	-	-	-	-	-	4-16	-	-
Bronchitis	-	-	-	-	-	-	2-6	-	-
Cough	-	-	15-16	-	-	-	1-18	-	-
Dry mouth/nose	-	-	-	-	-	-	<1	-	-
Dyspnea	-	-	-	-	-	-	<1	-	-
Epistaxis	-	-	-	-	-	-	<1	-	-
Laryngitis	-	-	-	-	-	-	<1	-	-
Lung disorder	-	-	-	-	-	-	<1	-	-
Nasopharyngitis	-	-	15-26	-	-	-	-	-	-
Pharyngitis	-	-	8	-	-	-	3-10	-	-
Pneumonia	-	-	-	-	-	-	1-2	-	-
Rhinitis	-	-	13	-	-	-	2-6	-	-
Rhinorrhea	-	-	4	-	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	2-7	-	-
Upper respiratory infection	-	-	21-24	-	-	-	-	-	-
Wheezing	-	-	4	-	-	-	-	-	-
Special Senses									
Abnormal vision	-	-	-	-	-	-	<1	-	-
Blepharitis	-	-	-	-	-	-	<1	-	-
Cataract	-	-	-	-	-	-	<1	-	-
Conjunctival edema	-	-	-	-	-	-	<1	-	-
Conjunctivitis	-	-	-	-	-	-	1-3	-	-
Dry eyes	-	-	-	-	-	-	<1	-	-
Ear disorder	-	-	-	-	-	-	<1	-	-
Ear pain	-	-	-	-	-	-	1	-	-
Eye pain	-	-	-	-	-	-	<1	-	-
Otitis externa	-	-	-	-	-	-	<1	-	-
Otitis media	-	-	-	-	-	-	1-12	-	-
Other									
Abscess	-	-	-	-	-	-	<1	-	-
Accidental injury	-	-	-	-	-	-	3-12	-	-

Adverse Events	Phenylephrine, Shark Liver Oil, Glycerin, White Petrolatum	Phenylephrine, Shark Liver Oil, Mineral Oil, White Petrolatum	Pimecrolimus	Podofilox	Podophyllum Resin	Sodium Phosphate, Potassium Phosphate, Zinc, Urea	Tacrolimus	Tazarotene	Thrombin, Fibrinogen, Aprotinin, Calcium Chloride
Alcohol intolerance	-	-	-	-	-	-	3-7	-	-
Allergic reaction	-	-	-	-	-	-	4-15	-	-
Anaphylactoid reaction	-	-	-	-	-	-	<1	-	-
Angioedema	-	-	-	-	-	-	≥1	-	-
Breast neoplasm benign	-	-	-	-	-	-	<1	-	-
Chafing	-	-	-	<5	-	-	-	-	-
Coma	-	-	-	-	✔	-	-	-	-
Cyst	-	-	-	-	-	-	1-3	-	-
Death	-	-	-	-	✔	-	-	-	-
Exacerbation of untreated area	-	-	-	-	-	-	1	-	-
Fever	-	-	13-32	-	✔	-	1-21	-	-
Flu symptoms	-	-	-	-	-	-	22-35	-	-
Herpes simplex infection	-	-	-	-	-	-	2-4	-	-
Hypersensitivity	-	-	8	-	-	-	-	-	-
Inflammation	-	-	-	63-71	-	-	-	-	-
Influenza	-	-	13	-	-	-	-	-	-
Lack of effect	-	-	-	-	-	-	1-10	-	-
Lymph-adenopathy	-	-	-	-	-	-	1-3	-	-
Neoplasm benign	-	-	-	-	-	-	<1	-	-
Pain	-	-	-	50-72	-	-	1-4	-	-
Procedural complication	-	-	-	-	-	-	1	-	-
Skin graft failure	-	-	-	-	-	-	-	-	>1

✔ Percent not specified
\- Event not reported

Table 9. Boxed Warning for Acitretin[1,24]

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 3 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 3 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 2 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, and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3, and 3 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. **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 2 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 5 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 2 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 2 effective forms of contraception (birth control) simultaneously, at least 1 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 2 effective forms of contraception (birth control) simultaneously for at least 1 month prior to initiation of acitretin therapy, during acitretin therapy, and for at least 3 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 2 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 2 months after acitretin treatment has been discontinued.

If pregnancy does occur during acitretin therapy or at any time for at least 3 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 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 3 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 2 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 2 years, assuming a mean elimination half-life of 120 days, and greater than 98% of the etretinate formed would be eliminated in 3 years, based on the longest demonstrated elimination half-life of 168 days. However, etretinate was found in plasma and subcutaneous fat in 1 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 (9). 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, GI malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and 5 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 1 year but less than 2 years after the last dose. There were 3 reports of abnormal outcomes out of these 43 cases (involving limb malformation, GI tract malformations and premature birth). There were only 4 cases where conception occurred at least 2 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 1 year after the last dose of etretinate, acitretin or both. From these cases there are 3 reports of birth defects when the conception occurred at least 1 year but less than 2 years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and 4 reports of birth defects when conception occurred 2 or more years after the last dose of acitretin (including foot malformation, cardiac malformations [2 cases] and unspecified neonatal and infancy disorder). There were 3 additional abnormal outcomes in cases where conception occurred 2 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 US; for information, call the manufacturer at 1-800-526-6367.
- Patients should not donate blood during and for at least 3 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 3 years following acitretin therapy because women of childbearing potential must not receive blood from patients being treated with acitretin.

Samples of seminal fluid from 3 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, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome).

- When acitretin treatment was given at time of conception, there were 5 deliveries of healthy neonates (4 of 5 cases were prospective), 5 spontaneous abortions, and 1 induced abortion.
- When acitretin was discontinued approximately 4 weeks prior to conception, there was 1 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 6 to 8 months prior to conception, there was 1 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 US clinical trials, 2 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 1289 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 3-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 2 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 6 patients, the classification changed from class 0 (no pathology) to class I (normal fatty infiltration; nuclear variability and portal inflammation; both mild); for 7 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 1 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 AST, ALT, GGT (GGTP) or LDH have occurred in approximately 1 in 3 patients treated with acitretin. Of the 525 patients treated in clinical trials in the US, 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 US clinical trials of etretinate, of which acitretin is the active metabolite, had clinical or histologic hepatitis considered to 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 1 month or less before presenting with hepatic symptoms or signs.

Table 10. Boxed Warning for Becaplermin[3,24]

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 11. Boxed Warning for Pimecrolimus[16,24]

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 2 years of age.

Table 12. Boxed Warning for Tacrolimus[19,24]

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 2 years of age. Only tacrolimus 0.03% ointment is indicated for use in children 2 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 13.

Table 13. Usual Dosing Regimens for the Skin and Mucous Membrane Agents, Miscellaneous[1-24]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acitretin	25 mg to 50 mg per day, given as a single dose with the main meal	Safety and efficacy in children have not been established	Kit: Capsules: Acitretin 10mg, 25mg Foam: VersaFoam-EF
Alitretinoin	Apply generous coating to lesions 2 times daily; may increase to 3-4 times daily as tolerated	Safety and efficacy in children have not been established	Gel: 0.1%
Becaplermin	Apply appropriate amount of gel once daily with a cotton swab or similar tool, as a coating over the ulcer. The amount of gel used depends on the size of the ulcer: Estimation of gel requirement: <u>15 g tube:</u> length of gel (inches) = [length (in) x width (in)] x 0.6 <u>2 g tube:</u> length of gel (inches) = [length (in) x width (in)] x 1.3	Safety and efficacy in children have not been established	Gel: 0.01%
Betamethasone and calcipotriene	Ointment: Apply an adequate layer to affected area once daily for up to 4 weeks. The maximum weekly dose should not exceed 100 g. Treatment of more than 30% of body surface area is not recommended. Suspension: Apply suspension to affected areas on the scalp once daily for 2 weeks or until cleared. Treatment may be continued for up to 8 weeks. The maximum weekly dose should not exceed 100 g.	Safety and efficacy in children have not been established	Ointment: 0.05%-0.005% Suspension: 0.05%-0.005%
Bexarotene	Apply to lesions every other day for 1 week, then increase as tolerated to once daily for 1 week, then 2 times daily for 1 week, then 3 times daily for 1 week, then 4 times daily	Safety and efficacy in children have not been established	Gel: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Calcipotriene	Apply a thin layer to affected area 1-2 times per day and rub in completely	Safety and efficacy in children have not been established	Cream: 0.005% Solution: 0.005%
Collagenase	Apply directly to wound or to gauze pad affixed to the wound once daily or more frequently if dressing becomes soiled	Safety and efficacy in children have not been established	Ointment: 250 units/g
Diclofenac	Apply to lesions 2 times daily for 60-90 days	Safety and efficacy in children have not been established	Gel: 3%
Fluorouracil	Actinic keratosis: Carac®: apply a thin layer to lesions once daily for up to 4 weeks Efudex®: apply to lesions 2 times daily for 2-4 weeks Fluoroplex®: apply to lesions 2 times daily for 2-6 weeks Superficial basal cell carcinoma: Efudex® 5%: apply to lesions 2 times daily for 3-6 weeks	Safety and efficacy in children have not been established	Cream: 0.5%, 1%, 5% Solution: 2%, 5% Kit: fluorouracil cream 5% and adhesive bandages
Formaldehyde	Apply once daily to the affected area	Apply once daily to the affected area	Solution: 10%
Imiquimod	Actinic keratosis: apply to lesions 2 times per week for 16 weeks, apply to a contiguous area of 25 cm^2, continue therapy for 16 weeks External genital warts: apply to warts 3 times per week at bedtime and leave on for 6-10 hours, continue therapy for a maximum of 16 weeks Superficial basal cell carcinoma: apply to biopsy confirmed area 5 times per week at bedtime and leave on for 8 hours, continue therapy for 6 weeks	Safety and efficacy in children under the age of 12 have not been established	Cream: 5%
Phenylephrine, shark liver oil, glycerin, and white petrolatum	Apply to affected area 4 times per day, especially at night, in the morning, or after each bowel movement	Safety and efficacy in children have not been established	Cream: 0.25%-3%-12%
Phenylephrine, shark liver oil, mineral oil, and white petrolatum	Apply to affected area 4 times per day, especially at night, in the morning, or after each bowel movement	Safety and efficacy in children have not been established	Ointment
Pimecrolimus	Apply a thin layer to the affected skin and rub in completely 2 times daily	Children > 2 years of age: Apply a thin layer to the affected skin and rub in completely 2 times daily	Cream: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Podofilox	Apply to wart tissue 2 times daily (morning and evening) for 3 consecutive days then do not use for 4 consecutive days, may repeat up to 4 times until no visible wart tissue remains	Safety and efficacy in children have not been established	Gel: 0.5% Solution: 0.5%
Podophyllum resin	Apply sparingly to lesion with applicator and allow it to dry, limit contact time to 1-4 hours, rinse off with soap and water	Safety and efficacy in children have not been established	Liquid: 25%
Sodium phosphate (monobasic/dibasic), potassium phosphate (monobasic/dibasic), zinc, and urea	Spray onto wound prior to treatment and dressing changes	Spray onto wound prior to treatment and dressing changes	Spray
Tacrolimus	Apply a thin layer of 0.03% or 0.1% ointment to the affected skin and rub in completely 2 times daily until clearing occurs, and continue for 1 additional week	Children > 2 years of age: Apply a thin layer of the 0.03% ointment to the affected skin and rub in completely 2 times daily until clearing occurs, and continue for 1 additional week	Ointment: 0.03%, 0.1%
Tazarotene	Apply a thin layer to cover lesions only once daily in the evening. Apply to no more than 20% of body surface area.	Safety and efficacy in children under the age of 12 have not been established	Gel: 0.05%, 0.1% Cream: 0.05%, 0.1%
Thrombin, fibrinogen, aprotinin, and calcium chloride	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.	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.	Kit: Sealer protein concentrate, fibrinolysis inhibitor solution, thrombin, calcium chloride solution Pre-filled syringe

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous skin and mucous membrane agents are summarized in Table 14.

Table 14. 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				
Kose et al.[120] (2008) Diclofenac 3% gel applied once daily vs. imiquimod 5% cream applied three times/week	RCT, OL Patients with actinic keratosis	N=49 12 weeks	Primary: Complete response according to Investigator Global Improvement Indices (IGII) and Patient Global Improvement Indices (PGII)	Primary: According to the IGII results, a complete response was observed in 12% of the diclofenac group and 22% of the imiquimod group. There were no significant differences between the two groups (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. There were no significant differences between the two groups (P>0.05). Both treatments were well tolerated, with most adverse events related to skin.
Nelson et al.[111] (2007) Diclofenac sodium 3% gel twice daily for 90 days	OL, MC Patients diagnosed with actinic keratosis (AK) lesions of the upper and lower lip (both cutaneous and mucosal surfaces)	N=22 120 days	Primary: Target lesion clearance, cumulative lesion clearance, Investigator's Global Improvement Index Score (IGIIS), Patient satisfaction, Tolerability and degree of oozing, crusting, and erythema	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 target lesion number score (TLNS), improving to 42% at day 120. At day 90 of treatment, 32% of patients had 100% AK lesion clearance based on the cumulative lesion number score (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				79% at day 120. At day 30 of treatment, 66% of the patients evaluated were rated a 4 (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%) ($P \leq 0.0005$). Patients were highly satisfied with diclofenac sodium 3% gel. There were 2 reported adverse events for the 22 enrolled subjects. 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.
Nelson et al.[39] (2004) Diclofenac 3% gel BID	MC, OL Patients 48-100 years of age with a diagnosis of 5 or more actinic keratosis (AK) lesions contained in 1-3 blocks (5 cm^2) on the forehead, central face, or scalp)	N=76 90 days with 30 day follow-up period	Primary: Investigators' global improvement index (IGII) at each post-baseline visit, target lesion number score (TLNS), and cumulative lesion number score (CLNS)	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 $\geq$75% lesion clearance was 78% at day 90 and 85% at day 120. 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 $\geq$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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Wolf et al.[40] (2001) Diclofenac 3% gel BID vs. placebo vehicle (hyaluronan gel) BID	RCT, DB, PC Patients 18 years of age or older with a diagnosis of actinic keratosis (AK) with lesions contained in 1 to 3 5-cm^2 blocks in one or more selected major body areas (forehead, central face, scalp, arms, and hands)	N=118 90 days	Primary: (1) Proportion of patients at follow-up with no lesions as rated by target lesion number score (TNLS) and cumulative lesion number score (CLNS) (both equal to 0, "no lesions"); (2) proportion of patients rated as "completely improved", with values equal to 4 on the investigator global improvement index (IGII) and the patient global improvement index (PGII)	Primary: The proportion of patients with TLNS=0 was 50% of patients in the diclofenac group compared to 20% in the vehicle group (P<0.001). The proportion of patients with CLNS=0 was 47% in the diclofenac group compared to 19% in the vehicle group (P<0.001). The proportion of patients with IGII=4 was 47% in the diclofenac group compared to 195 in the vehicle 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 vehicle group. The proportion of patients with PGII=4 was 41% in the diclofenac group compared to 17% in the vehicle 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 vehicle group.
Tanghetti et al.[113] (2007) Fluorouracil (5-FU) 5% cream twice daily for 2 to 4 weeks	RCT, SB, MC Patients >21 years of age with at least 4 actinic keratoses lesions on the face,	N=39 24 weeks	Primary: Change in AK count, complete clearance, physician's global	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. imiquimod 5% cream twice weekly for 16 weeks	forehead, or scalp		assessment, patient perception of efficacy, physician's assessment of erythema, and patient perception of discomfort associated with the treatment	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 4 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 4 and decreased post-treatment to less than mild from week 8 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
Jorizzo et al.[41] (2002) Fluorouracil 0.5% cream QD vs. vehicle cream QD	RCT, DB, PC, PG, MC Patients 18 years of age or older with at least 5 actinic keratoses (AKs) on the face or frontal scalp that are ≥4 mm in diameter	N=207 1, 2, or 4 weeks of treatment	Primary: AK lesion reduction from baseline at the post-treatment follow-up phase with final evaluation 4 weeks after treatment completion or discontinuation (determined by the Physician Global Assessment of Improvement	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 vehicle groups at week 1, 2, and 4 (P<0.001). The proportion of patients with total lesion clearance was significantly greater in the fluorouracil group compared to the vehicle group (P<0.001). The Physician Global Assessment of Improvement scores were significantly improved in the fluorouracil group compared to the placebo group at weeks 1, 2, and 4 (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			ratings), absolute reductions from baseline in AK lesion counts and proportional reductions	
Loven et al.[42] (2002) Fluorouracil 0.5% cream QD vs. fluorouracil 5% cream BID	RCT, SB, CS Patients 18 years of age and older with a diagnosis of actinic keratosis (AK) with ≥6 AK lesions (minimum of 3 on each side of treatment area); the 0.5% cream was applied to one side of the studied area (face or bald scalp) and the 5% cream to the other for the duration of the study; the severity of the AK lesions was equally matched on either side	N=21 8 weeks	Primary: Reduction in number of AK lesions compared to baseline, total clearance of AK lesions at the end of the 4-week post-treatment period, tolerability, patient preference questionnaire	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 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%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 1 patient felt their skin looked better after treatment with the 5% cream, 5 people felt that the 0.5% cream "did a better job" compared to 2 people who felt the 5% cream "did a better job", and 5 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 0.5% cream if necessary (P=0.031).
Jorizzo et al.[43] (2004) Fluorouracil 0.5% cream QD for 7 days vs. vehicle cream QD for 7 days patients with residual lesions after the 4-week follow-up period received cryosurgery	RCT, MC, DB, PC Patients 18 years of age or older with 5 or more visible or palpable actinic keratosis (AK) lesions on the face	N=144 12 months	Primary: Reduction (both absolute and percentage) in AK lesions at the 4-week follow-up visit, the proportion of patients with complete clearance of AK lesions at the 4-week follow-up visit before cryosurgery, the occurrence rate at the 6-month follow-up visit, and the clearance rate the 6-month	Primary: At 4 weeks, patients in the fluorouracil group had significantly fewer lesions compared to the patients in the vehicle 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 vehicle group (P<0.001). Complete clearance of AK lesions at the 4-week follow-up was observed in 16.7% of patients in the fluorouracil group and 0% in the vehicle 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 vehicle and cryosurgery group (P<0.001). The mean number and percentage reduction of AK lesions was significantly improved in the fluorouracil and cryosurgery

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			follow-up visit	group compared to the vehicle 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 4-week follow-up and of those, 5 remained clear at 6 months.
Shaffelburg.[114] (2009) Imiquimod 5% cream applied to one-half of the face 2 times per week vs. placebo vehicle applied to the other half of the face 2 times per week All patients received treatment with aminolevulinic acid 20% at baseline and at month 1	RCT, PC Adults with ≥10 facial actinic keratoses	N=25 12 months	Primary: Lesions	Primary: At month 12, median lesion reductions was 89.9% with imiquimod compared to 74.5% with placebo (P=0.0023). No subject discontinued for an adverse event. Severe local skin reactions occurring in the most participants were erythema (17%) and flaking/scaling/dryness (13%).
Krawtchenko et al.[121] (2007) Imiquimod 5% cream three times per week for 4 weeks (one or two courses of therapy) vs. fluorouracil (5-FU) 5% ointment twice daily for 4 weeks	RCT Patients with a minimum of five typical, visible, and histologically proven actinic keratoses lesions in one anatomical area of up to 50 cm^2 at head or neck	N=75 Treatment phase followed by a 12 month follow-up phase	Primary: Complete clearance at the test of cure (TOC), sustained clearance at 12 months, cosmetic outcome	Primary: Complete clearance at the test of cure (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. cryosurgery (one or two courses of therapy)				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.
Lebwohl et al.[44] (2004) Imiquimod 5% cream QD 2 times/week for 16 weeks vs. vehicle cream QD 2 times/week for 16 weeks	RCT, DB, PC, MC, PG Patients 18 years of age and older with 4-8 clinically diagnosed actinic keratosis (AK) lesions with a contiguous 25-cm^2 treatment area on the face or balding scalp, but not both	N=436 16 weeks of treatment with 8 weeks of post-treatment follow-up	Primary: Complete clearance rate (proportion of patients at the 8-week follow-up visit with a count of 0 clinically visible lesions) Secondary: Partial clearance rate (proportion of patients at the 8-week follow-up with at least 75% reduction in the number of clinically visible AK lesions)	Primary: The complete clearance rate was significantly higher in the imiquimod group (45.1%) compared to the vehicle group (3.2%) (P<0.001). Secondary: The partial clearance rate was significantly better in the imiquimod group compared to the vehicle group (59.1% vs. 11.8% respectively, P<0.001). At the 8-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 vehicle 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 vehicle 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stockfleth et al.[45] (2002) Imiquimod 5% cream QD 3 times/week for 12 weeks vs. vehicle cream 3 times/week for 12 weeks	RCT, DB, PC Patients 45-85 years of age diagnosed with actinic keratoses (AK) in a treatment area that did not exceed 20 cm^2	N=36 12 weeks of treatment and 1 year of follow-up	Primary: Lesion clearance rates at the end of treatment and at 14 weeks, recurrence of AK lesions in patients treated with imiquimod at 1 year post-treatment	Primary: In the imiquimod group, 84% of patients were recorded as having complete clearance of lesions (95% CI: 64%-95%, P<0.001compared to vehicle group). In the imiquimod group, 8% (2 patients) were recorded as having partial clearance (1 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 2 patients (P<0.001 compared to vehicle group). No changes in the size or number of lesions in the vehicle 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 vehicle group were not assessed at 1 year.
Stockfleth et al.[46] (2004) Imiquimod 5% cream BID 3 times/week for 12 weeks vs. vehicle cream 3 times/week for 12 weeks this study contains the results of follow-up data at 2 years in the previous Stockfleth study	RCT, DB, PC Patients 45-85 years of age diagnosed with actinic keratoses (AK) in a treatment area that did not exceed 20 cm^2	N=25 12 weeks of treatment and 2 years of follow-up	Primary: Recurrence of AK lesions in patients treated with imiquimod up to 2 years post-treatment	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 squamous cell carcinoma (SCC) after treatment with imiquimod. Ten vehicle-treated patients were observed for 1 year. In those patients, spontaneous remission of AK lesions was reported in 1 patient; all of the remaining 9 developed new AKs and 1 developed SCC.
Lee at al.[47] (2005) Imiquimod 5% cream QD 2 or 3 times/week for 16 weeks	OS Patients 45-86 years of age with AK who demonstrated complete clearance of	N=146 1 time visit 12-18 months post-original treatment	Primary: AK recurrence rate	Primary: The recurrence rate of AK lesions was lower in patients who had previously received imiquimod 3 times/week (24.7%) compared to those who had received it 2 times/week (42.6%). Patients with fair skin had a higher recurrence of AK lesions

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. vehicle cream QD 2 or 3 times/week for 16 weeks this study followed patients who had showed complete clearance of actinic keratosis (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	AK lesions at 8 weeks post-treatment in 4 phase III clinical trials of imiquimod vs. vehicle cream			compared to patients with Fitzpatrick type III-V skin (in the 3 times/week group: 29% vs. 14%, and in the 2 times/week group: 50% vs. 33%). The recurrence rate of AK lesions in the vehicle-treated patients was 46.7%. Statistical comparisons between groups were not reported.
Korman et al.[48] (2005) Imiquimod 5% cream QD 3 times/week for 16 weeks vs. vehicle cream QD 3 times/week for 16 weeks	MA Patients 18 years of age and older diagnosed with actinic keratosis (AK) having 4-8 AK lesions with a contiguous 25 cm^2 treatment area on the face or balding scalp	N=492 16 weeks of treatment and 8 weeks of post-treatment follow-up	Primary: Complete clearance rate (proportion of patients at the 8-week post-treatment follow-up with no clinically visible AK lesions in the treatment area) Secondary: Partial clearance rate (proportion of patients at the 8-week post-treatment follow-up with 75% reduction in the number of baseline AK	Primary: Complete clearance was observed in 48.3% of patients in the imiquimod group and 7.2% of patients in the vehicle 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 vehicle group (P<0.001). The median percentage of reduction in AK-lesion count was 86.6% in the imiquimod group and 14.3% in the vehicle 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 2 studies: complete clearance rates were 56.4% vs. 40.8% and partial clearance rates were 71.8% vs. 56.8% (P values and statistical difference not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			lesions in the treatment area), median percentage of reduction of baseline AK lesions at the 8-week post-treatment visit	
Atopic Dermatitis				
Gollnick et al.[124] (2008) Pimecrolimus 1% cream BID at the first signs/symptoms of a relapse vs. vehicle cream BID at the first signs/symptoms of a relapse patients were allowed to use moderately potent corticosteroids to treat flares	RCT, DB, PC, PG, MC Adults ≥18 years of age with mild to moderate atopic dermatitis (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	Primary: The mean number of topical corticosteroid-free days was significantly higher in the pimecrolimus cream group than in the vehicle cream group (152 days 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 vehicle cream (P=0.0014). Patients on pimecrolimus cream made 30% fewer unscheduled visits to their physician's office than patients on vehicle cream (156 vs. 223, respectively).
Sigurgeirsson et al.[125] (2008) Pimecrolimus 1% cream BID at the first signs and/or symptoms of recurring atopic dermatitis vs. vehicle cream BID at the first signs and/or symptoms of	RCT, DB, MC, PC Children and adolescents aged 2-17 years with a history of mild or moderate atopic dermatitis (AD) who were clear/almost clear of disease	N=521 26 weeks	Primary: Number of days without topical corticosteroid use for disease worsening, flares requiring topical corticosteroid use, physician office visits	Primary: The mean number of topical corticosteroid-free days was significantly higher in the pimecrolimus cream group than in the control group (160.2 days vs. 137.7 days, respectively; P<0.0001). Patients on pimecrolimus cream experienced 50% fewer flares requiring topical corticosteroids than patients on vehicle 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 vehicle cream (87 vs.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
recurring atopic dermatitis patients were allowed to use moderately potent corticosteroids to treat flares				246, respectively).
Zuberbier et al.[126] (2008) Pimecrolimus 1% cream BID used intermittently vs. vehicle cream BID used intermittently patients were allowed to use prednicarbate 0.25% cream if a flare occurred that was not controlled by study medication	RCT, DB, MC Children and adolescents aged 2-17 years with facial atopic dermatitis and mild to moderate disease after treatment of the initial flare with prednicarbate 0.25% cream	N=140 24 weeks		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 the vehicle group (P=0.0024). Fifty percent of patients in the pimecrolimus group had no flare on the face during the treatment period compared with 37.5% of patients in the vehicle group (P=0.012). The median time to first flare in pimecrolimus-treated patients was twice as long as in patients receiving vehicle (138 vs. 68 days, respectively; P=0.01).
Murrell et al.[115] (2007) Pimecrolimus 1% cream applied BID vs. vehicle cream applied BID	RCT, DB, PC Patients aged 12 years or over with mild to moderate head and neck atopic dermatitis 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 6 weeks Secondary: Head and neck Eczema Area and Severity Index (EASI), pruritus score, eyelid dermatitis, facial skin atrophy and	Primary: A significantly higher percentage of patients treated with pimecrolimus was cleared or almost cleared of facial atopic dermatitis compared with vehicle (47% vs. 16%, respectively). A statistically significant difference was also seen on head and neck EASI and pruritus score. Significantly more pimecrolimus-treated patients than vehicle-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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			telangiectasia	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.
Zuberbier et al.[25] (2007) Pimecrolimus 1% cream BID vs. vehicle cream BID patients were allowed to use prednicarbate 0.25% cream if a flare occurred that was not controlled by study medication	RCT Children and adolescents aged 2-17 years with a history of severe atopic dermatitis	N=184 24 weeks		Primary: Patients on pimecrolimus required topical corticosteroids on a mean of 29% of study days compared with 35% of patients on vehicle (P=0.1841). On the head and neck only, patients on pimecrolimus required topical corticosteroids on a mean of 10% of study days compared with 19% of patients on vehicle (P=0.0009). In patients with acute severe disease (Investigator's Global Assessment > or = 4), topical corticosteroids were used on 28% of the days in the pimecrolimus group compared to 45% in the vehicle group (P= 0.0024). In patients with acute severe disease (Investigator's Global Assessment > or = 4) on the head and neck, topical corticosteroids were used on 10% of study days with pimecrolimus versus 30% with vehicle (P< 0.0001).
Kapp et al.[49] (2002) Pimecrolimus 1% cream BID at first sign of flare until complete clearance of signs and symptoms vs. vehicle cream BID at first sign of flare until complete clearance of signs and symptoms	RCT, DB, PC, PG, MC Infants 3-23 months of age with a clinical diagnosis of atopic dermatitis (AD)	N=251 12 months	Primary: Incidence of flares of AD at 6 months Secondary: Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI), and caregiver's	Primary: There was a significantly lower number of flares in the pimecrolimus group compared to the vehicle group (67.6% of patients in the pimecrolimus group had no flare at 6 months vs. 30.4% in the vehicle 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 vehicle 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 vehicle group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patients in both groups were permitted use of moderately potent corticosteroids to help treat flares			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 7 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]).	(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 vehicle group and the proportion of study days on a corticosteroid was 3.2% in the pimecrolimus group compared to 6.2% in the vehicle 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 vehicle group (P<0.001). The maximum benefit of therapy was achieved by day 22 in the pimecrolimus group compared to 3 months in the vehicle 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 vehicle group (P=0.034). At month 6, a significantly greater proportion of patients in the pimecrolimus group had clear or nearly clear skin compared to those in the vehicle 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 vehicle group, though this difference was not statistically significant (53.9% vs. 47.8%, P value not reported). EASI mean total scores were significantly lower for patients in the pimecrolimus group compared to the vehicle group at day 43 (P<0.0001) but were not significantly different at month 6, 9, or 12 (P>0.076). Pruritus scores were significantly lower for patients in the pimecrolimus group compared to the vehicle group at day 43, month 6 and month 9 (P<0.016) but were not significantly different at month 12 (P=0.074).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 vehicle group at day 43 and month 6 (P<0.016), but the differences were not significant at month 9 or 12 (P>0.058).
Papp et al.[50] (2005) Pimecrolimus 1% cream BID at first sign of flare until complete clearance of signs and symptoms patients were permitted use of moderately potent corticosteroids to help treat flares	OL, ES Infants 3-23 months of age with a clinical diagnosis of atopic dermatitis (AD)	N=91 12 months	Primary: Proportion of patients with no flares, treatment success rates (proportion of patients with clear or almost clear skin as indicated by an Investigator's Global Assessment [IGA] of 0 or 1), Eczema Area and Severity Index [EASI], percentage of total body surface area (TBSA) affected by AD, course of disease (proportion of disease-free days without the use of any medication), adverse effects	Primary: The median number of days of pimecrolimus use during the 12 months of the present study was 99, and 27.5% of these patients required corticosteroids during this time. Seventy-six patients used pimecrolimus for 2 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 3 months of the second year to 42.3% during the last 3 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 2 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 2 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 TBSA affected by AD decreased from 11.3% to 6.6%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At the beginning of the first, double-blind year, 75% of patients treated with pimecrolimus for 2 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 TBSA 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 6 months of the second year to 50.9% during the last 2 months. The majority of adverse effects reported were conditions commonly seen in childhood such as nasopharyngitis, pyrexia, cough, diarrhea, ear infection, bronchitis, rhinitis, vomiting, and gastroenteritis. There were no reports of application site reactions.
Staab et al.[51] (2005) Pimecrolimus 1% cream BID for 4 weeks vs. placebo cream BID for 4 weeks Phase I: 4 weeks of treatment Phase II: 12 week open-label extension	RCT, DB, PC, PG, MC Patients 3-23 months of age diagnosed with atopic eczema (1) affecting some part of face (2) affecting ≥5% of body surface area (BSA), and (3) having a baseline Investigators Global Assessment (IGA) score of mild severity	N=196 4 weeks (Phase I data only)	Primary: (1) Parents' quality of as measured by the questionnaire for Parents of Children with Atopic Dermatitis (PQoL-AD); (2) pruritus and sleep loss, using the Severity Scoring of	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 2 (P=0.018) and a significant improvement in sleep observed by day 3 (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Phase II: 4 week follow-up	or greater		Atopic Dermatitis (SCOR-AD); (3) severity of disease, using Investigators Global Assessment (IGA); (4) degree of disease control, measured by the Eczema Area and Severity Index (EASI)	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 4 week treatment phase (P<0.001). The reduction in EASI was observed as early as day 4 in the pimecrolimus group and it decreased by 38.5% compared to a decrease of 17.6% in the placebo group on day 4 (P<0.001).
Kaufman et al.[52] (2006) Pimecrolimus 1% cream BID for 7 days vs. placebo cream BID for 7 days	RCT, DB, PC, PG, MC Patients 18-81 years of age with mild to moderate atopic dermatitis (AD) affecting ≥5% of total body surface area	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 with baseline Secondary: Percentage of patients achieving pruritus improvement of ≥1 point compared with baseline within 48 and/or 72 hours, percentage of	Primary: There was a significant improvement in pruritus (≥1 point) in the pimecrolimus group compared to the vehicle group over the 7 day treatment period (P=0.001). The median time to pruritus improvement (≥1 point) was 2 days in the pimecrolimus group compared with 4 days in the vehicle group. Secondary: Improvements in pruritus scores (≥1 point) were seen by day 2 (within 48 hours) in 56% if pimecrolimus patients compared to 34% of patients in the vehicle group (P=0.003). By day 3 (within 72 hours), 72% of pimecrolimus patients reported improvements in pruritus severity compared with 45% of vehicle patients (P<0.001). In the pimecrolimus group, 81% of patients sustained their pruritus relief on days 4-7 compared with 63% in the vehicle group who showed improvement by day 7 (P<0.001). For days 2-7: 42% of pimecrolimus patients recorded “mild” or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients with a pruritus response within 4,5,6, and 7 days of treatment, the percentage of patients with a pruritus severity score of 0 (absent) or 1 (mild) for treatment days 2,3,4,5,6, and 7 regardless of baseline scores, and the percentage of patients with an IGA score improvement of ≥1 point at study completion compared with baseline	"absent" pruritus scores compared to 27% in the vehicle group by day 2 (P=0.04), 55% of pimecrolimus patients recorded "mild" or "absent" pruritus scores compared to 31% in the vehicle group by day 3 (P=0.002), and 63% of pimecrolimus patients recorded "mild" or "absent" pruritus scores compared to 36% in the vehicle group by day 7 (P<0.001). Significant improvements in IGA score (≥1 point reduction) were seen in 53% of the pimecrolimus patients compared to 20% of the vehicle 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 vehicle and 76% of patients previously treated with pimecrolimus. 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.
Kempers et al.[53] (2004) Pimecrolimus 1% cream BID until clearing or for 6 weeks vs. tacrolimus 0.03% ointment BID until clearing or for 6 weeks	RCT, MC, PG, SB Patients 2-17 years of age with moderate atopic dermatitis (Investigator's Global Assessment [IGA] score of 3)	N=141 6 week treatment phase with 20 week open-label extension (only treatment-phase data presented here)	Primary: Incidence of local application-site reactions (ASRs) Secondary: Formulation attributes, safety, and efficacy (measured by IGA and patient assessment)	Primary: The incidence of ASRs decreased with time in both groups, but this was more pronounced in the pimecrolimus group. ASRs 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 ASRs 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 ASR 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 ASR lasted between 30 minutes and 12 hours (P<0.001). The difference between the 2 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). IGA response rates were slightly higher in the tacrolimus group compared to the pimecrolimus group from day 8-43, 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 body surface area (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.
Ashcroft et al.[54] (2005) Pimecrolimus 1% cream	MA Children, adolescents, and adults diagnosed with atopic dermatitis	N=6897 1 week to 12 months	Primary: For pimecrolimus: proportion of patients rated by	Primary: For pimecrolimus: In five trials evaluating pimecrolimus vs. vehicle, pimecrolimus was significantly more effective than vehicle at 3 weeks (P<0.0001), and 3 of these found that pimecrolimus retained

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. tacrolimus vs. vehicle vs. topical corticosteroids			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	this efficacy at 6 weeks (P<0.0001). Another trial found no significant difference at 6 months between pimecrolimus and vehicle. In 3 vehicle-controlled trials, there were significantly fewer flares at 6 months in the pimecrolimus group compared to the vehicle 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 3 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 1 week, 3 weeks, and 6 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 6 weeks (P=0.15). One study evaluating pimecrolimus 4 times daily compared to pimecrolimus 2 times daily found no difference in the proportion of patients clear or almost clear at the end of 3 weeks. For tacrolimus: One trial compared tacrolimus 0.03%, tacrolimus 0.1%, and vehicle and found that the 0.03% strength was significantly more effective compared to vehicle when evaluating the proportion of patients clear or achieving excellent improvement

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				(P=0.006), but that the 0.1% strength did not differ from vehicle (P=0.13) at 3 weeks. When evaluating patients' assessments of improvement as better or much better, both strengths proved significantly better than vehicle. Three other trials reported the same outcomes as described above after 12 weeks and found both strengths to be significantly more effective than vehicle (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 3 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 3 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Six trials compared tacrolimus 0.1% and 0.03%. Three trials found no difference in proportion of patients clear or achieving excellent response at 3 weeks between the 2 strengths (P=0.44) and the remaining 3 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 vehicle 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 vehicle group but was significantly higher in the tacrolimus group compared to the vehicle 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 vehicle (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 vehicle (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 2 studies, parents judged quality of life to be improved in patients taking pimecrolimus compared to placebo, and 3 trials showed increases in quality of life in patients taking tacrolimus 0.03%and 0.1% compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Abramovits et al.[123] (2008) Tacrolimus 1% ointment applied BID vs. pimecrolimus 1% cream applied BID	RCT, SB, MC Adult patients with moderate atopic dermatitis	N= 6 weeks	Primary: Response rate as measured by the Eczema Area and Severity Index (EASI), Investigators' Global Atopic Dermatitis Assessment	Primary: Tacrolimus ointment-treated patients had significantly greater reduction in Eczema Area Severity Index score compared with 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 Atopic Dermatitis Assessment (P<0.02). A total of 5 pimecrolimus cream-treated patients discontinued the study early due to lack of efficacy compared with no tacrolimus ointment-treated patients (P=0.02). Reported adverse events occurred at a similar frequency for both treatment groups.
Fleischer et al.[100] (2007) Tacrolimus 1% ointment applied BID vs. pimecrolimus 1% cream applied BID	RCT, SB, MC Adult patients with moderate to very severe atopic dermatitis	N=281 6 weeks	Primary: Response rate as measured by the Eczema Area and Severity Index (EASI), treatment success rate	Primary: Tacrolimus-treated patients had significantly greater reduction in the Eczema Area Severity Index score compared with pimecrolimus-treated patients (57% vs. 39%, respectively; P=0.0002). Treatment success was significantly greater among the tacrolimus-treated patients compared with pimecrolimus-treated patients (40% vs. 22%, respectively; P=0.001). Improvement in percentage of total body surface area affected

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was significantly greater among the tacrolimus-treated patients compared with 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.
Reitamo et al.[55] (2005) Tacrolimus 0.1% ointment BID to affected areas until clear and then for 7 more days vs. hydrocortisone butyrate 0.1% ointment BID to affected areas until clear and then for 7 more days (trunk and extremities) and hydrocortisone acetate 1% ointment BID to affected areas until clear and then for 7 more days (head and neck)	RCT, DB, MC, CS Patients 18 years of age and older with a diagnosis of atopic dermatitis with a severity grading of moderate to severe	N=972 6 months	Primary: Response rate at month 3 (proportion of patients with at least 60% improvement in modified Eczema Area and Severity Index [mEASI]) Secondary: Response rate at time points other than 3 months, mEASI, Eczema Area and Severity Index (EASI), physician's global evaluation of clinical response,	Primary: At month 3, 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 6 months compared to the corticosteroid group (P<0.001). A significant improvement in mEASI was observed as early as day 8 in both treatment groups and increased up to the 6-month point. At month 6, 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patient's assessment of global response, physician's assessment of individual signs, affected body surface area (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	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 6, 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 6 months, 86.6% of patients in the tacrolimus group rated their AD as much better or better compared with 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.
Paller et al.[56] (2005) Tacrolimus 0.03% ointment or 0.1% ointment BID for 6 weeks or until 7 days after clearance vs. pimecrolimus 1% cream BID for 6 weeks or until 7 days after clearance	MA Patients 2 years of age and older with mild to severe atopic dermatitis	N=1065 6 weeks	Primary: Change from baseline in Eczema Areas and Severity Index (EASI) score at week 6 Secondary: Investigator Global Atopic Dermatitis Assessment (IGADA) where success means	Primary: The change in baseline in EASI score at week 6 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 1 (P=0.04), and a trend toward advantage with tacrolimus at week 6, but this difference was not significant (P=0.07). In all patients with moderate disease, the percentage reduction

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			clear or almost clear, percent of BSA affected, patient's assessment of itch, and safety endpoints (overall incidences of all adverse events and individual incidence rates of application site adverse events)	in EASI score at week 6 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 6 was greater in the tacrolimus group compared with the pimecrolimus group (57% and 42% respectively, P=0.01). Secondary: IGADA scores were significantly better at 6 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 6 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 3 (P≤0.01). In pediatric patients with mild disease, a significant difference in favor of tacrolimus was observed at week 1 (P=0.02) but this difference was not significant at week 6 (P=0.15). At week 6 in all 3 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 1 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 1 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).
Basal Cell Carcinoma				
Gross et al.[99] (2007) Fluorouracil (5-FU) 5% cream applied BID	OL Adult patients with at least one biopsy proven superficial basal cell carcinoma on the trunk or limbs	N=29 15 weeks	Primary: Clinical evidence of cure, pain, erythema, scarring, patient satisfaction	Primary: Among the 31 lesions treated, 90% were histologically cured by the 5-FU treatment, with the mean time to clinical cure being 10.5 weeks. 5-FU 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. 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 1 (3%) lesion, mild in 5 (16%) lesions, moderate in 22 (71%) lesions, and severe in 3 (10%) lesions. The last erythema scores reported for each lesion revealed that 7 (23%) had no erythema, 19 (61%) had mild erythema, and 5 (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients were very satisfied with the study treatment at all time points.
Romagosa et al.[57] (2000) Fluorouracil 5% cream in a phosphatidyl choline carrier BID for 4 weeks vs. fluorouracil 5% cream (as Efudex®) BID for 4 weeks	RCT, DB Patients with biopsy-proven moderate thickness BCCs	N=13 (17 BCCs) 4 weeks treatment and follow-up at week 16	Primary: Cure rate	Primary: The cure rate in the phosphatidyl choline group was 90% and the cure rate in the regular fluorouracil group was 57% (P values not reported, investigators reported no statistically significant difference in outcomes detected between groups).
Marks et al.[58] (2004) Imiquimod 5% cream applied 5 times/week vs. imiquimod 5% cream applied 7 times/week	OS Patients with histologically confirmed superficial basal cell carcinoma (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	Primary: Histological clearance occurred in 161 tumors (77%). In the 5 times/week group, 100% of patients had clearance of at least 1 tumor compared with 93% in the 7 times/week regimen. Tumors cleared in 47% of patients in the 5 times/week regimen and in 58% of patients in the 7 times/week regimen. In the 5 times/week regimen, 89% of patients had 50% or more of their tumors clear compared with 84% in the 7 times/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 (statistics not reported). Lower histological clearance was noted on the lower extremities accompanied by a lower incidence of local inflammatory reactions.
Gollnick et al.[116] (2008) Imiquimod 5% cream 5 times/week on consecutive	OS, OL Patients 21-89 years of age with at least1 histologically	N=182 6 weeks of treatment, 12-week post-	Primary: Non-recurrence rate (proportion of patients who were clinically	Primary: The initial clearance rate for the intent-to-treat (ITT) population was 89.6% at the 12-week post-treatment visit. During the 5-year follow-up period, 18 clinical recurrences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days for 6 weeks	confirmed superficial basal cell carcinoma (sBCC) on the limbs, trunk, neck, or head with a minimum area of 0.5 cm^2 and a maximum diameter of 2.0 cm with a maximum tumor depth of ≤1 mm	treatment follow-up, and 5-year long-term follow-up	clear of BCC at the tumor site at the 12-week post-treatment visit and remained clear at the 5-year follow-up)	occurred at the target tumor site, 8 and 10 of which occurred during the first 6 and 12 months of follow-up, respectively. The 5-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% .
Gollnick et al.[59] (2005) Imiquimod 5% cream 5 times/week on consecutive days for 6 weeks	OS, OL Patients 21-89 years of age with at least1 histologically confirmed superficial basal cell carcinoma (sBCC) on the limbs, trunk, neck, or head with a minimum area of 0.5 cm^2 and a maximum diameter of 2.0 cm with a maximum tumor depth of ≤1 mm	N=182 6 weeks of treatment, 12-week post-treatment follow-up, and 5-year long-term follow-up (first 24 months of follow-up data are reported)	Primary: Non-recurrence rate (proportion of patients who were clinically clear of BCC at the tumor site at the 12-week post-treatment visit and remained clear at the 5-year follow-up)	Primary: The initial clearance rate for the intent-to-treat (ITT) population was 89.6% at the 12-week post-treatment visit. Fourteen subjects 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 2 had no histological evidence of recurrence. The estimated proportion of patients who were clinically clear of their treated tumor after a single 6-week treatment at 5 times/week declined from 87.3% at month 3 to 79.4% at month 24.
Peris et al.[60] (2005) Imiquimod 5% cream QD 3 times/week for 12 weeks	OS, OL Patients 45-83 years of age diagnosed with superficial or 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 of which 75 were superficial and 19 were nodular) 12 week treatment with 12 month follow-up	Primary: Assessment of clinical remission at the end of treatment and recurrences during the post-treatment observational period Efficacy rates:	Primary: Overall complete response was seen in 85.1% of the lesions. Overall 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 6 weeks of treatment, 42.9% after 2 more weeks of treatment, and 20% after the full 12 weeks of treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			1=complete response, disappearance of BCC, 2=partial response, ≥40%<100% reduction in size, 3=no response, <40% reduction in size, 4=worsening, increase in size Secondary: Adverse effects	A partial response was observed in 5.3% of superficial BCCs in 4 patients. A complete response was observed in 52.6% of nodular BCCs in 10 patients after the full 12 weeks of treatment. A partial response was seen in the remaining 36.8% of lesions. Two of the 7 patients with partial response were treated for an additional 4 weeks without further improvement. Recurrence was observed in 2.9% of successfully treated superficial BCCs 6-8 months after treatment discontinuation. No recurrence was observed in the remaining 68 superficial BCCs and in 10 successfully treated nodular BCCs after 12-34 months of follow-up. Secondary: 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%. Hyper- and hypopigmentation were each observed in 1 and 15 patients respectively 6 months after treatment discontinuation. All skin reactions were rated as mild to moderate by the patients, with the exception of 1 patient who experienced a severe local reaction on the nose.
Giesse et al.[61] (2004) Imiquimod 5% cream QD 5 times/week	MC, RCT, DB, PC, DR Patients 18 years of age or older with a	N=724 6 weeks of treatment with 12 week post-	Primary: Complete composite clearance rate, i.e., proportion	Primary: The composite clearance rates for the 5 times/week and 7 times/week imiquimod groups were 75% (95% CI: 68%-81%) and 73% (95% CI: 66%-79%) respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. vehicle cream 5 times/week vs. imiquimod 5% cream QD 7 times/week vs. vehicle cream 7 times/week	primary, histologically confirmed superficial basal cell carcinoma (sBCC) at least 0.5 cm^2 with a maximum diameter of 2 cm, located on the limbs, trunk (anogenital area excluded), neck, or head with no signs of aggressive growth patterns	treatment follow-up period	of patients at 12 weeks post-treatment who were considered complete responders, defined as those with (1) no clinical or histological evidence of BCC at target site or (2) with clinical evidence but no histological evidence of BCC, and where the false-positive clinical assessment was explained by the histological findings	Clearance rates based on histological data only for the 5 times/week and 7 times/week groups were 82% (95% CI: 76%-87%) and 79% (95% CI: 73%-85%) respectively. Composite and histological clearance rates for the vehicle groups were 2%-3%. The differences between both active groups and their corresponding vehicle groups for composite and histological clearance rates were statistically significant (P<0.001). Secondary: Adverse effects rates were higher during the treatment period compared to the post-treatment period. The percentage of patients experiencing at least 1 adverse effect during the treatment period in the 5 times/week, 7 times/week, and vehicle groups were 58%, 64%, and 36% respectively. The percentage of patients experiencing at least 1 adverse effect during the post-treatment period in the 5 times/week and 7 times/week groups were 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 5 times/week group compared to its corresponding vehicle group (P=0.027). Application site reactions possibly or probably related to treatment occurred in 29% of patients in the imiquimod 5 times/week group, and in 43% of the 7 times/week group, compared to 2.8% and 6.6% of patients in the respective vehicle groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Less than 10% of patients experienced a severe adverse effect. Local skin reactions (LSR) were more intense in the active treatment groups compared to the vehicle groups. LSRs were most intense at 3 weeks and fell back to at or below baseline by week 12. LSRs had significantly higher severity ratings in the imiquimod groups compared to their respective vehicle groups (P<0.001).Erythema was the most commonly observed LSR. Erythema, vesicles, edema, erosion, and scabbing/crusting were all significantly more severe in the imiquimod 7 times/week group compared to the 5 times/week group (P<0.05). There was a significant correlation observed between the intensity of the LSRs and clearance rates in both imiquimod groups (P<0.05).
Schulze et al.[62] (2005) Imiquimod 5% cream QD for 6 weeks vs. vehicle cream QD for 6 weeks	RCT, DB, PC, MC Patients 18 years of age or older with a histologically confirmed primary superficial basal cell carcinoma (sBCC) located on the trunk, limbs, neck, or head, with a minimum area of 0.5 cm^2 and a maximum diameter of 2 cm	N=166 6 weeks of treatment, 12 additional weeks of follow-up	Primary: Composite clearance rate based on clinical and histological clearance of sBCC Secondary: Histological clearance rate	Primary: Composite clearance rates were 77% for the imiquimod group compared to 6% for the vehicle group (P<0.001). Secondary: Histological clearance rates were 80% in the imiquimod group compared to 6% for the vehicle group (P<0.001). The prevalence sBCC in post-treatment excision histology in the imiquimod group was 16%.
Cutaneous T-Cell Lymphoma				
Heald et al.[63] (2003) Bexarotene 1% gel QD, BID,	MC, OL Patients 18 years of age and older	N=50 16 weeks with an option to	Primary: Physicians Global Assessment of	Primary: CCR or PR was observed in 44% of patients according to the PGA and in 46% of patients according to the CA.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TID, QID, escalated as tolerated all patients received active treatment	diagnosed with cutaneous T-cell lymphoma (CTCL) staged as IA, IB, or IIA according to the tumor nodes metastasis staging system for malignant tumors (TNM), and refractory or intolerant to, or have reached the 6-month or greater response plateau on at least 2 prior therapies	continue treatment	Clinical Condition (PGA), or Composite Assessment of Index Lesion Disease Severity (CA) Secondary: Overall extent of cutaneous disease determined as a percentage involvement of total body surface area (BSA), index lesion erythema, plaque elevation, scaling, pruritus, hypopigmentation or hyperpigmentation, surface area response to treatment, time to response (defined as first observation when a patient has improved by 50% or greater), duration of response, and time to disease	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% 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 1 day 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
			progression, responses to the patient Quality of Life Questionnaire	
Genital Warts				
Stefanaki et al.[122] (2008) Imiquimod 5% cream 3 times/week for 12 weeks vs. cryotherapy administered once in 3 weeks for 3 consecutive sessions.	RCT, OL HIV-negative males with anogenital warts	N=80 12 months	Primary: Clearance of treated warts, recurrence, adverse events	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 with 68.6% of patients in the imiquimod group. In the imiquimod group, 17.1% of patients did not show any signs of improvement compared with 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% 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 (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Yan et al.[98] (2006) Imiquimod 5% 3 times/week until the warts were completely cleared or for a maximum of 16 weeks vs. podophyllotoxin 0.5% applied 2-3 times/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	MA Patients with clinically visible genital warts in the genital, anal, perineal or perianal area	N=473 Up to 10 months	Primary: Clearance rate Secondary: Adverse events	Primary: <u>Imiquimod 5% versus Placebo</u> Pooled analysis across 3 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 6.05–22.44). 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%–19%. <u>Podophyllotoxin versus 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 7.06–39.48). 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%-90% . The clinical cure rates of imiquimod and podophyllotoxin were 50.34 and 56.41%, respectively, without statistically significant differences between the two (P>0.05). Secondary: 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).
Arican et al.[64] (2004) Imiquimod 5% cream 3	RTC, DB, PC Patients 18 years of age and older with a	N=45 12 week treatment, 6	Primary: Clearance of anogenital warts	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, 9 patients had 50%-90%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
times/week for 12 week vs. placebo	diagnosis of external anogenital warts	month follow-up		clearance, and 1 patient had <50% clearance. After treatment, 1 patient displayed complete clearance, 1 patient had 50%-90% clearance, and the remaining 8 patients showed no alteration in lesions. These results are statistically significant in favor of the treatment group (P<0.01).
Haidopoulos et al.[65] (2004) Imiquimod 5% cream 3 times per week at bedtime for maximum of 12 weeks or until wart clearing	OS, OL Female patients 16-52 years of age with vulvar warts with a median wart area of 55 mm^2, not treated for warts during the 6 weeks prior to entering the study	N=73 12 weeks plus a 3 month follow-up	Primary: Total or partial clearing of the warts	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 6 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).
Moresi et al.[66] (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	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 4 months to 2 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 6 patients reported clearing of lesions which remained clear 6-12 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tyring et al.[67] (1998) Podofilox 0.5% gel BID for 3 consecutive days followed by 4 days with no treatment vs. placebo gel BID for 3 consecutive days followed by 4 days with no treatment minimum of 2 and a maximum of 8 treatment cycles	RCT, DB, MC, PC Patients 18 years of age and older who were immunocompetent and had at least 2 distinct external anogenital warts	N=326 8 weeks of treatment and 8 week post-treatment follow-up	Primary: Total disappearance of treated warts (treatment success) Secondary: Number of warts, wart surface area, individual wart assessment scores, physician assessment of overall response (based on total area of treated warts remaining and overall severity of disease signs compared to baseline), patient discontinuation due to insufficient response, and recurrence rate of treated warts	Primary: Podofilox gel was significantly better than placebo at clearing anogenital and external genital warts after 4 and 8 weeks of treatment (P<0.001). With additional podofilox gel therapy (4-8 weeks), the proportion of patients with anogenital warts treated successfully increased from 62 to 81 patients (P<0.001). After 4 and 8 weeks of treatment, complete clearance was observed in 38.4% and 44.6% of patients with anogenital warts, respectively. Secondary: 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 4 and 8 weeks in the external and anogenital wart populations (P=0.001) and at 8 weeks in patients with perianal warts (P=0.03). At 4 weeks, 41.5% of baseline number of anogenital warts treated with podofilox remained, compared with 89.5% of warts remaining in the vehicle group (P=0.001). At 8 weeks, 35.9% of baseline anogenital warts treated with podofilox remained compared to 88.4% of warts in the vehicle group (P=0.001). Physician assessment of improvement was significantly better at 4 weeks in the podofilox group compared to the vehicle group (73.8% of patients had either moderate or marked improvement or complete clearance compared to 15.1% in the vehicle group, P=0.001). This trend continued at week 8 (81.1% of patients in the podofilox group compared to 17.2% in the vehicle group, P=0.001). Overall, 61.1% of patients in the vehicle group discontinued therapy due to insufficient response compared with 8.6% of patients in the podofilox group (P=0.002). At week 4, 37% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the vehicle 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 1 wart within 12 week, most occurring within the first 4 weeks. The investigators were not able to compare this to the vehicle group since only 4 patients in this group had their warts clear completely during treatment. Data for individual wart assessment scores is not reported.
Greenberg et al.[68] (1991) Podofilox 0.5% solution BID for 3 days then 4 days off vs. podofilox 0.5% cream BID for 3 days then 4 days off vs. placebo solution or cream BID for 3 days then 4 days off minimum of 2 treatment cycles, could be extended to 4 cycles if patients did not respond to the first 2	RCT, DB, PC, PG Women 18 years of age and older 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	Primary: There was a significant difference in the percentage of warts cleared in the podofilox groups compared to the vehicle group at every week of the study ($P \leq 0.042$). There was a slight increase in wart count after the week-4 study visit, especially in those patients receiving only 2 treatment cycles (P values and statistics not reported). The relapse rate was 33% in those patients achieving complete response, and time to relapse was 1-7 weeks (P values and statistics not reported). New warts appeared in untreated areas in 9 patients in the placebo group and 8 patients in the podofilox groups (P value and statistics not reported). The investigators' overall assessment of response demonstrated a statistical difference in favor of podofilox at each week ($P \leq 0.038$).
Baker et al.[69] (1990) Podofilox 0.5% solution BID for 3 days then 4 days off for minimum of 2 treatment	OL Women 18-46 years of age with a diagnosis of external anogenital warts involving an	N=37 10 weeks	Primary: Patients' subjective response to treatment (pain, burning, and	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cycles and maximum of 4 treatment cycles all patients received active treatment	area of less than 10 cm^2		itching), physicians' objective evaluation of the area (inflammation, erosion, other), and the number of warts	of the treatment period. The percentages of patients who achieved complete clearance at weeks 1, 2, 3, 4, 6, and 10 were 11.1%, 25%, 29%, 44.4%, 50%, and 50% 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 3 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.
Beutner et al.[70] (1989) Podofilox 0.5% solution BID for 3 days then 4 days off vs. placebo solution BID for 3 days then 4 days off minimum of 2 treatment cycles and maximum of 4 treatment cycles	RCT, DB, PC, MC Men 18 years of age and older with a diagnosis of genital warts	N=109 16 weeks	Primary: Change in wart count, change in wart area, and number and percentage of patients completely cleared	Primary: At the end of the active treatment phase (week 4), 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 1-6 (P=0.0001 for each). Comparisons could not be made at weeks 12 and 16 because there were no patients left in the placebo group. At week 6, 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 1 wart having evidence of recurrence. Overall, 44.6% of podofilox patients were completely clear at some point in the study compared to 0 patients in the placebo group (P<0.001). In the podofilox group, 40% of patients who completely healed did not have a recurrence.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kaposi's Sarcoma				
Walmsley et al.[71] (1999) Alitretinoin 0.1% gel TID for the first 2 weeks followed by QID for the remainder of the study vs. placebo vehicle	RCT, DB, PC, MC Patients 18 years of age and older, positive diagnosis of Kaposi's Sarcoma (KS)	N=268 12 weeks	Primary: Patient's cutaneous KS tumor response rate as evaluated by the group of 6 index lesions, responses were categorized as a clinical complete response (CCR), partial response area (PRA), partial response height (PRH), progressive disease (PD), or stable disease (SD)	Primary: CCR was observed in a significantly higher percentage of patients treated with alitretinoin 0.1% gel (35%) compared to placebo vehicle (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 vehicle 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 vehicle (P=0.002, 0.002, 0.0015, and 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, 2 achieved complete response. Time to first response was significantly faster in the alitretinoin group compared to the placebo vehicle group (P=0.0001). Overall response rates (CCR plus PR) was significantly higher in the alitretinoin group (28%) compared with the placebo vehicle group (13%) (P=0.001). Treatment with placebo vehicle was associated with less lesion pain compared to treatment with alitretinoin (P=0.007).
Bodsworth et al.[72] (2001) Alitretinoin gel 0.1% administered twice daily	RCT, DB, MC, PC Adult patients (>18 years) 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 versus 7% for the vehicle gel group (P=0.00003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. vehicle gel administered twice daily	infection and biopsy proven cutaneous Kaposi's sarcoma (KS)		rate using AIDS Clinical Trials Group (ACTG) response criteria designated as clinical complete response (CCR), partial response (PR), stable disease (SD), or progressive disease (PD) Secondary: Individual indicator lesion response, physician's subjective assessment, patient's subjective assessment	The only patient to achieve a CCR was in the alitretinoin-treated group. Incidence of progressive disease was lower for the alitretinoin gel group than for the vehicle 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 double-blind protocol were 2 of 4 (50%) for the alitretinoin group and 0 of 9 (0%) for the vehicle group. Secondary: When evaluating the response of individual lesions, 34% responded in the alitretinoin treatment group compared with 11% of indicator lesions in the vehicle control group (P≤0.00001). Both physicians and patients reported overall response rates of 40% for the alitretinoin gel group and 10% for the vehicle gel group (P=0.00004).
Psoriasis				
Rim et al.[96] (2003) Acitretin 10-20 mg/day titrated up to a maximum dose of 40mg/day plus calcipotriol ointment 50 mcg/g applied twice daily (without occlusion) up to a maximum of 60mg/week plus vs.	RCT Patients with chronic plaque type psoriasis with over 5% involvement of total body surface area	N=60 4-52 weeks	Primary: Efficacy using the Psoriasis Area and Severity Index scores (PASI)	Primary: After 12 weeks, 40% of patients in the calcipotriol + 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 + acitretin group showed faster remission at an early stage of therapy. After 52 weeks, 60% of patients in the calcipotriol + acitretin group and 40% of patients in the acitretin monotherapy group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acitretin 10-20 mg/day titrated up to a maximum dose of 40mg/day				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.
van de Kerkhof et al.[97] (1998) Acitretin 20mg QD (maximum of 70mg/day or 1mg/kg/day) plus calcipotriol ointment (50 mcg/g) applied twice daily at 12-hour intervals (maximum of 120mg/week) vs. acitretin 20mg QD (maximum of 70mg/day or 1mg/kg/day) plus placebo vehicle	RCT, DB, MC, PG, PC Patients aged 18 years and older 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 (Psoriasis Area and Severity Index) scoring system; patient assessment of overall response to treatment considering both the extent and the severity of the psoriasis	Primary: In the calcipotriol group, the mean change in PASI from baseline to the end of the double-blind treatment was – 13.2 (P<0.001). In the placebo group, the mean change in PASI from baseline to the end of the double-blind 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 double-blind 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).
Thaci et al.[73] (2001) Calcipotriol 50 mcg/mL solution BID as monotherapy or in combination with other	PRO, OS Patients aged 30- 62 years with scalp psoriasis were treated with calcipotriol	N=3,396 8 weeks	Primary: Investigator assessment of psoriasis severity based on the psoriasis scalp	Primary: There was a significant decrease in mean PSSI after 8 weeks of therapy in the group treated only with calcipotriol solution from 16.0 to 4.9 and in the patients treated with calcipotriol solution in combination with other agents from 20.7 to 6.2 (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatments	despite previous treatments received		severity index (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	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.
Reygagne et al.[74] (2005) Calcipotriol 0.005% solution BID vs. clobetasol 0.05% shampoo QD	RCT, MC, SB, PG Patients 12 years of age or older with moderate to severe scalp psoriasis having a global severity score (GSS) of at least 3 and an affected area of at least 2 cm^2	N=151 4 weeks	Primary: Global severity score (GSS) and the total severity score (TSS). 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 2 and P=0.028 at week 4) and GSS measures (P<0.001 at week 2 and P=0.016 at week 4). Secondary: Erythema, plaque thickening, adherent desquamation, and pruritus improved in both treatments groups but a greater improvement was observed in the clobetasol group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentage of scalp surface area affected showed significant difference in favor of clobetasol (P=0.02).
Veronikis et al.[75] (1999) Calcipotriene BID vs. coal tar emulsion 1% BID	SB, CS Patients 18-75 years of age with plaque-type psoriasis	N=20 12-125 days	Primary: Erythema, scaling, and plaque thickness were evaluated using a 4-point scale (0=no lesion, 2=mild, 4=moderate, 6=severe)	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.
Sharma et al.[76] (2003) Calcipotriol 0.005% ointment BID vs. coal tar 5% ointment QHS Patients applied one treatment to one side of the body and the other treatment to the other side of the body at the same time	SB, RCT Patients 16-60 years of age with nearly bilaterally symmetrical lesions of stable plaque psoriasis	N=36 12 weeks	Primary: Improvements in the erythema, scaling, and induration (ESI) of psoriatic lesions, relapse rates, and self-assessment by patient of efficacy and acceptability	Primary: At 4 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 8 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 8 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				During the 8 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.
Tosti et al.[77] (1998) Calcipotriol 50 mcg/g ointment BID vs. betamethasone 64 mg/g ointment and salicylic acid 0.03 g/g ointment BID	RCT, DB Patients 18 years of age and older with a diagnosis of nail bed psoriasis with severe subungual hyperkeratosis (>1 mm for fingernails, >2.5 mm for toenails)	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 using 5-point scale (0=nil, 1=poor, 2=fair, 3=good, 4=excellent)	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 3 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 5 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 3 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 5 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment at 3 and 5 months were not significant between groups.
Crosti et al.[78] (1997) Calcipotriol 50 mcg/g ointment BID vs. betamethasone dipropionate ointment and salicylic acid ointment BID	RCT Patients 18 years of age and older with mild stable psoriasis who have not used topical preparations for this disease in the 2 weeks prior to the study or systemic treatments 2 months prior to the study	N=160 6 weeks plus 1 month follow-up	Primary: Improvement in psoriasis area and severity index (PASI) scores, investigator assessments of efficacy using a 5 point scale (1=nil, 5=excellent)	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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.
De Jong et al.[80] (2003) Calcipotriol 50 mcg/g ointment BID plus methotrexate (MTX) vs. placebo vehicle plus MTX Phase I: Cessation of MTX and treatment initiation of blinded topical treatment with either calcipotriol or placebo vehicle for total of 30 weeks or until relapse occurs Phase II: MTX titration phase with	RCT, PC, MC, DB, PG Patients 18 years of age and older 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 modified psoriasis severity score (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	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 vehicle 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 vehicle group. Phase II: The group treated with calcipotriol required a significantly reduced dose of MTX compared with the vehicle group (3.3 mg/week compared with 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 vehicle group, who required 9.9 mg/week of MTX (P=0.002). Investigator assessments of efficacy in the intent-to-treat

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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			the MTX dose used at the end of phase II (measured by the occurrence of relapse)	population showed a non-significant trend in favor of calcipotriol (P=0.068).
Singh et al.[79] (2000) Calcipotriene 0.005% ointment BID on weeks 2 and 4 and augmented betamethasone 0.05% cream QD on weeks 1 and 3 vs. augmented betamethasone 0.05% QD for 4 weeks	RCT, SB, PG Patients 20-50 years of age with stable plaque psoriasis for more than 1 months duration	N=52 4 weeks	Primary: Proportion of patients having at least 90% reduction in baseline PASI scores at the end of the 4 week study period Secondary: PASI scores on a weekly basis, reduction in PASI scores after 2-4 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 4 weeks of therapy compared with 68% of patients in the calcipotriene/betamethasone group (P<0.001). Secondary: PASI scores were significantly lower in the calcipotriene/betamethasone group compared to the betamethasone group at different points of time except on days 0 and 7. The percentage reduction in PASI scores after 2 and 4 weeks of treatment was significantly higher in the calcipotriene/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/betamethasone group compared to the betamethasone group in both investigator and patient assessments.
Torras et al.[81] (2004) Calcipotriol cream 50 mcg/g BID plus psoralen plus ultraviolet A (PUVA) 3	RCT, MC, PC, PG Patients 18 years of age or older with skin type II or III and a diagnosis of extensive	N=120 12 weeks	Primary: Psoriasis area and severity index (PASI) scores, overall patient	Primary: Statistically significant decreases in PASI scores were observed form week 2 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
times/week vs. vehicle cream BID plus PUVA 3 times/week	psoriasis vulgaris covering 20-50% of body surface area (BSA), and who were scheduled to receive PUVA therapy on the trunk and the limbs Phase I: 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 mcg/g or vehicle 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)		assessment of skin lesions, and the total UVA dosage needed	in the calcipotriol group compared to the vehicle 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 vehicle 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 vehicle group (42 and 56 days vs. 77 and 79 days 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 vehicle group (P<0.01). The total UVA dose needed in the calcipotriol group was significantly lower compared to the vehicle group (P=0.016). The average number of irradiations needed was significantly lower in the calcipotriol group compared to the vehicle 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 vehicle group (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Parslew et al.[88] (2005) Calcipotriene plus betamethasone dipropionate combination QD vs. placebo	MA Patients 18 years of age and older with a diagnosis of psoriasis vulgaris Patients were divided into a <60 year old group and a ≥60 year old group for the meta-analysis	N=1,534 4 studies Up to 4 weeks of treatment	Primary: Percent change in Psoriasis Area and Severity Index (PASI) Secondary: PASI after 1 week of treatment (assessed in 3 of the 4 studies), Investigator's Global Assessment of Disease Severity (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 2 studies assessing Investigator's Global Assessment of Disease Severity, 52.1% of patients <60 and 52.8% of those ≥60 had controlled disease after up to 4 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. No P values were reported in this meta-analysis.
Guenther et al.[89] (2002) Calcipotriene plus betamethasone ointment QD in the evening and vehicle ointment QD in the morning vs. calcipotriene plus betamethasone ointment BID vs.	RCT, MC, PRO, DB, PC, PG Patients 18-86 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 4 Secondary: Percentage change in thickness score of a target psoriatic lesion from baseline to each treatment	Primary: The difference in PASI from baseline to week 4 in the combination treatment groups of once and twice daily 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 vehicle 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 vehicle group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriene ointment BID vs. vehicle ointment BID			visit, speed of response assessed by change in PASI from baseline to week 2, investigator's overall assessment of treatment efficacy, adverse effects	Secondary: No significant difference was observed between the once daily combined-medication group and the calcipotriene group or the once vs. twice daily combined-medication groups in lesion thickness. There was a significant difference in lesion thickness in the once and twice daily combination-medication groups compared to the vehicle group at the end of treatment (P<0.001). After 1 week of treatment, the change in PASI was greater in the combined-medication groups (45.5% for once daily and 47.6% for twice daily) compared to the calcipotriene group (33.6%) and the vehicle group (20%). (P<0.001). There was no significant difference observed in the speed of response between the once- and twice-daily 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 once- and twice-daily combination groups (once-daily: 63.3% investigators, 65.3% patients, twice-daily: 73.5% investigators, 70.1% patients) compared to the calcipotriene group (50.7% investigators, 51.5% patients), and the vehicle group (9.2% investigators, 12.6% patients) (P<0.033). According to investigators' assessments, 14% of patients receiving the once-daily and 20.1% of patients receiving the twice-daily combination products achieved clearance compared to 9.7% in the calcipotriene group and 0% in the vehicle group. A significantly lower proportion of patients experienced adverse effects in both combination groups compared to the calcipotriene group (P≤0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentage of patients with lesional or perilesional adverse reactions was less in the combination groups and the vehicle group compared to the calcipotriene group (9.9% once daily combination group, 10.6% twice daily combination group, 19.8% calcipotriene group, 12.5% vehicle group).
van de Kerkhof[90] (2004) Calcipotriene plus betamethasone ointment QD in the evening and vehicle ointment QD in the morning vs. calcipotriene plus betamethasone ointment BID vs. calcipotriene ointment BID vs. vehicle ointment BID	RCT, MC, PRO, DB, PC, PG Patients 18-86 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 Psoriasis Disability Index (PDI), EuroQOL 5D (EQ-5D), visual analogue score (VAS), and the EQ-5D vertical VAS (EQ-VAS) score from baseline to the end of the study (each of these tools measure overall quality of life [QOL])	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 vehicle 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 vehicle group (P<0.001). At baseline, pain/discomfort and anxiety/depression were the most 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 vehicle 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 vehicle group from baseline (P>0.1). There was a significant improvement observed in the EQ-VAS score between both combination groups compared to the vehicle group (P<0.001), as well as the once-daily 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 vehicle group after 1 week (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Douglas et al.[91] (2002) Calcipotriene plus betamethasone ointment BID (CB) vs. betamethasone ointment BID (B) vs. calcipotriene ointment BID (C)	RTC, PRO, DB Patients 18 years of age or older with a diagnosis of psoriasis vulgaris	N=1,106 4 weeks of treatment and an additional 4 weeks of open-label treatment with calcipotriene	Primary: Mean percent change in PASI from baseline after 4 weeks Secondary: Speed of response as assessed from percent change in PASI after 1 week, mean percentage decrease in the thickness of psoriatic lesion from baseline after 4 weeks	Primary: There was a significant reduction in mean percent change in PASI from baseline to week 4 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 1 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 4 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.
Kaufman et al.[92] (2002) Calcipotriene plus betamethasone ointment QD (CB) vs. betamethasone ointment QD (B) vs. calcipotriene ointment QD (C) vs.	RTC, PC, DB, PRO Patients 18 years of age and older 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, Patient's Global Assessment (PGA) score assessing patients with treatment success (defined as marked improvement or clearance of disease)	Primary: There was a significant decrease in PASI score in the CB group compared with 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 with 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 4 weeks in the CB group compared to the B, C, and V groups (316, 216, 137, and 15 respectively, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vehicle ointment QD (V)				
Papp et al.[93] (2003) Calcipotriene plus betamethasone ointment BID (CB) vs. betamethasone ointment BID (B) vs. calcipotriene ointment BID (C) vs. vehicle ointment BID (V)	RCT, MC, PRO, DB, PG, PC Patients 18 years of age and older 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 change in PASI from baseline after 1 week of treatment	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 1 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).
van de Kerkhof et al.[94] (2005) Calcipotriene plus betamethasone ointment QD for at least 4 weeks	MA Patients 18 years of age and older 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 1), 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 4, 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 1, 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 4 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 4 weeks according to

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	patient's 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 4 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 4 weeks, 53.0% in patients with moderate disease, and 69.3% in patients with mild disease.
Kragbale et al.[95] (2004) Calcipotriene plus betamethasone ointment QD for 8 weeks followed by calcipotriene ointment QD for 4 weeks (Group 1) vs. calcipotriene plus betamethasone ointment QD for 4 weeks followed by 8 weeks of calcipotriene ointment QD on weekdays and calcipotriene plus betamethasone ointment QD on weekends (Group 2) vs. calcipotriene ointment BID for 12 weeks (Group 3)	RCT, PRO, DB, PG Patients 18 years of age and older with a diagnosis of psoriasis	N=971 12 weeks	Primary: Mean percent change in PASI from baseline to week 8, proportion of patients with absent or very mild disease according to the IGA at the end of 8 weeks Secondary: Mean percent change in PASI 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	Primary: There was a significant reduction in the mean percent change in PASI from baseline to week 8 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
Menter et al.[102] (2009) Clobetasol propionate 0.005% spray vs. calcipotriene 0.005%-betamethasome diproprionate 0.064% ointment	RCT Patients with moderate to severe plaque psoriasis	N= 8 weeks	Primary: Overall disease severity (ODS), adverse events	Primary: In the ODS assessment, 75% of patients treated with clobetasol achieved a rating of clear or almost clear after 4 weeks of treatment compared to 45% of calcipotriene/betamethasone treated patients (P=0.003). Adverse events were 31% in the clobetasol treatment group and 33% in the calcipotriene/betamethasone treatment group.
van de Kerkhof et al.[103] (2009) Calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g vs. betamethasone dipropionate 0.5mg/g vs. calcipotriol 50mcg/g	RCT, DB, MC, PG Adult 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 8 was significantly higher in the calcipotriol/betamethasone group (68.4%) than the betamethasone dipropionate (61.0%, P=0.0079) or calcipotriol (43.4%, P<0.0001) groups. The proportion of patients rating their scalp psoriasis as 'clear' or 'almost clear' was significantly higher in the calcipotriol/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/betamethasone and betamethasone dipropionate groups than the calcipotriol group.
Luger et al.[104] (2008) Calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g vs. calcipotriol 50mcg/g	RCT, DB, MC Patients with moderate-to-severe scalp psoriasis	N=869 52 weeks	Primary: Efficacy and safety	Primary: Disease was satisfactorily controlled in 92.3% of visits in the calcipotriol/betamethasone group versus 80.0% in the calcipotriol group (P< 0.001). Adverse drug reactions were less frequent in the calcipotriol/betamethasone group compared with the calcipotriol group (17.2 vs. 29.5%; P < 0.001). Incidences of adverse events possibly associated with long-term

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				corticosteroid use were low in both the two-compound (2.6%) and the calcipotriol (3.0%) groups.
Jemec et al.[105] (2008) Calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g applied once daily vs. betamethasone dipropionate 0.5mg/g applied once daily vs. calcipotriol 50mcg/g applied once daily vs. vehicle applied once daily	RCT, DB, MC Adult patients with scalp psoriasis	N=1505 8 weeks	Primary: Patients with ‘‘absence of disease’’ or ‘‘very mild disease’’ according to Investigator’s Global Assessment of disease severity at week 8 Secondary: Total Sign Score at week 8, 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 8 was significantly greater in the calcipotriol/betamethasone group (71.2%) compared with the betamethasone dipropionate group (64.0%, P=0.011), the calcipotriene group (36.8%, P<.0001), and the vehicle group (22.8%, P<0.0001). At week 8, the percentage change in Total Sign Score was significantly larger for the calcipotriol/betamethasone group (-70.8%) than for calcipotriene (-49.0%; P<0 .0001) and for vehicle (-35.6%; P<0.001). The difference versus 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 8 was 68.6% for the calcipotriol/betamethasone group, 62.5% for betamethasone dipropionate, 38.3% for calcipotriene, and 20.7% for the vehicle alone. The calcipotriol/betamethasone group was significantly more effective than calcipotriene (P<0.0001) and the vehicle alone (P<0 .0001). The difference versus betamethasone dipropionate was not statistically significant (P=0.2).
Saraceno et al.[106] (2007) Calcipotriol 50 mcg/g and betamethasone dipropionate 0.5 mg/g applied once daily for 4 weeks, followed by maintenance of calcipotriol 50 mcg/g cream applied twice daily for 8 weeks	RCT, MC Patients aged >18 years with mild-to-moderate plaque psoriasis	N=150 12 weeks	Primary: Changes in the Psoriasis Area and Severity Index (PASI) after 4 weeks of treatment Secondary:	Primary: A significant improvement of PASI score was demonstrated in patients receiving once-daily treatment with calcipotriol/betamethasone dipropionate compared with twice-daily treatment with calcipotriol at week 2 (P<0.001). These results were confirmed and maintained at week 4 (P<0.001). Secondary: Treatment with calcipotriol from week 5 to week 12 was associated with a further clinical improvement and treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. calcipotriol 50 mcg/g cream applied twice daily for 12 weeks.			Maintenance of the PASI score with calcipotriol as a sequential therapy in the following 8 weeks; safety of the study drugs; patients' quality of life, as assessed by the Skindex-29	with calcipotriol/betamethasone dipropionate was associated with maintenance of the results. At week 12, no significant differences of PASI score were seen between the two groups. The quality of life assessment showed a marked improvement in terms of Skindex-29 in both groups at weeks 2 and 4 as compared to baseline. Similarly to the clinical improvement, the quality of life results were significantly superior in the calcipotriol/betamethasone dipropionate group compared with 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.
White et al.[107] (2006) Calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g ointment for 4 weeks followed by calcipotriol cream 50mcg/g for 8 weeks (cream group) vs. calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g ointment for 4 weeks followed by calcipotriol cream 50mcg/g on weekdays and the combination of calcipotriol/ betamethasone on weekends for 8 weeks (alternating group) vs.	RCT, SB (4 weeks), DB (8 weeks) Patients had to be >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 Psoriasis Area and Severity Index (PASI), investigators' global assessment of disease severity on a 6-point scale (disease absent, very mild, mild, moderate, severe, or very severe), and adverse events	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g ointment for 4 weeks followed by vehicle cream for 8 weeks (vehicle group)				
Kragballe et al.[108] (2006) Calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g for 52 weeks vs. calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g for 4 weeks followed by calcipotriol 50mcg/g for 4 weeks (alternating for 52 weeks) vs. calcipotriol 50mcg/g and betamethasone dipropionate 0.5mg/g for 4 weeks followed by calcipotriol 50mcg/g for 48 weeks	RCT, DB Patients aged 18 years or older with a clinical diagnosis of psoriasis vulgaris of the trunk and/or limbs	N=634 52 weeks	Primary: Adverse drug reactions	Primary: Adverse drug reactions (ADRs) occurred in 21.7% of patients in the calcipotriol/betamethasone group, 29.6% in the alternating group and 37.9% in the calcipotriol group (P<0.001). The odds ratio (OR) for an ADR in the calcipotriol/betamethasone group relative to the calcipotriol group was 0.46 (95% CI 0.3-0.7; P<0.001). The OR for the alternating group relative to the calcipotriol group was 0.69 (95% CI 0.46–1.04; P=0.073), and for the calcipotriol/betamethasone group relative to the alternating group 0.66 (95% CI 0.42–1.03; P=0.066). ADRs of concern associated with long-term topical corticosteroid use occurred in 4.8% of patients in the calcipotriol/betamethasone group, 2.8% of patients in the alternating group and 2.9% of patients in the calcipotriol group. Those ADRs with the highest incidence were skin atrophy and folliculitis.
Rigopoulos et al.[118] (2007) Tazarotene 0.1 % cream applied at bedtime for 12 weeks vs.	RCT, DB Patients with psoriasis including nail involvement	N=23 24 weeks	Primary: Assessment of pitting, onycholysis, subungual hyperkeratosis and salmon patches using the	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clobetasol propionate 0.05% cream applied at bedtime for 12 weeks			nail psoriasis severity index (NAPSI)	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.
Angelo et al.[119] (2007) Tazarotene 0.1% cream on one side of the body for 12 weeks vs. clobetasol 0.5% cream 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	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 2 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 2, 4, 6 and 8. 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 2, 4, 10 and 12. The difference was statistically significant at week 2. Both were equally effective at weeks 6 and 8. During the 12-week treatment period both tazarotene and clobetasol creams were associated with reduction in desquamation scores from baseline except at week 2 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 2, 4, 6, 8, 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Clobetasol produced higher success rates than tazarotene over the 12-week treatment period. Statistically significant differences favored clobetasol over tazarotene at weeks 2 and 4. Treatment success rate was 100% at Week 6 with clobetasol and was 73% with tazarotene. At week 12, it was 100% with clobetasol and 88% with tazarotene.
Tzung et al.[82] (2005) Tazarotene 0.1% gel QHS plus petrolatum QAM vs. calcipotriol 0.005% ointment BID both treatments were used in each patient on opposite sides of the body	RETRO, IB, CS Patients 12-80 years of age with a diagnosis of psoriasis and a total of 50 target lesion pairs	N=19 12 weeks of treatment and 4 weeks of post-treatment evaluation	Primary: Severity scores for scaling, plaque elevation, erythema, overall lesion severity, and patient self-reported efficacy	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 1 and reduction of erythema on this side was first observed in week 2. The difference in erythema between sides was not significant after 8 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 ($P\geq0.46$).
Guenther et al.[83] (2000) Tazarotene 0.1% gel QHS plus mometasone 0.1% cream QAM vs. calcipotriene 0.005% BID	MC, IB, PG Adult patients with chronic, stable plaque psoriasis affecting 5%-20% of total body surface area	N=120 8 weeks of treatment with 12 week post-treatment follow-up phase	Primary: Physician-rated measures of efficacy including global improvement, plaque elevation, scaling, erythema, and percentage of body surface area	Primary: Physician-rated assessments: After 2 weeks of treatment, the percentage of patients achieving marked improvement ($\geq$75% global improvement) was significantly higher in the tazarotene and corticosteroid group compared to the calcipotriene group (45% and 25% respectively, $P\leq0.05$). There was no significant difference in the percentage of patients achieving complete or almost complete clearance between the 2 treatment groups at any time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			involvement; patient-rated assessments including efficacy of study treatment compared with previous therapies, comfort of treated skin, outlook for long-term control, and overall impression of treatment	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 4 of the post-treatment phase ($P \leq 0.05$) 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 4 of treatment and at week 4 of the post-treatment phase ($P \leq 0.05$). 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 4 of treatment and at the end of treatment ($P \leq 0.05$). 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 body surface area involvement was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group after 2 and 4 weeks of treatment ($P \leq 0.01$), 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 body surface area involvement after 2 and 4 weeks of treatment compared to the calcipotriene group ($P \leq 0.05$ at 2 weeks and $P \leq 0.01$ at 4 weeks). No significant differences were observed during the post-treatment phase between groups. For lower limb lesions, significance was only achieved for patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				admitted to the post-treatment phase and only at the end-of-treatment visit (P≤0.001). Patient-rated assessments: 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 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).
Bowman et al.[84] (2002) Tazarotene 0.05% gel plus calcipotriene 0.005% ointment QAM and calcipotriene ointment QHS vs.	PRO, OL, CS Patients 18 years of age and older with psoriasis vulgaris that was chronically stable for at least 1 month prior to screening with at least 1 bilateral mirror image plaque	N=15 (28 lesion pairs) 2 weeks of treatment, 4 weeks of post-treatment follow-up	Primary: Severity scores for erythema, scaling, and plaque elevation	Primary: At the end of the 2 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clobetasol 0.05% ointment BID both treatments were used in each patient on opposite sides of the body	on the trunk, arms, or legs			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.
Schiener et al.[85] (2000) Tazarotene 0.05% gel QD plus total body narrowband ultraviolet B (UVB) irradiation QD 4 times per week vs. calcipotriene 0.005% ointment QD plus total body narrowband ultraviolet B (UVB) irradiation QD 4 times per week both treatments were used in each patient on opposite sides of the body	IB, CS Patients with widespread symmetrical psoriasis	N=10 Minimum duration of 4 weeks	Primary: Psoriasis Area and Severity Index (PASI)	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Skin Graft Adherence				
Griswold et al.[117] (2008) Fibrin sealant (Artiss®) vs. staples	RCT, MC, SB Burn patients with wounds measuring ≤40% of total body surface requiring wound excision and skin grafting	N=138 28 days	Primary: Wound closure at day 28 Secondary: Hematoma/seroma on day 1, engraftment on day 5, wound closure on day 14, investigator-assessed outcomes, patient-assessed outcomes	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. 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 1 occurred at significantly fewer fibrin-treated sites (29.7%) compared with stapled sites (62.3%; P<0.0001). Engraftment on day 5 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).
Wound Care				
Wieman et al.[86] (1998) Becaplermin gel 30 mcg or 100 mcg	MA Patients 19 years of age and older, type I or II diabetes with at	N=922 20 weeks or until complete ulcer healing	Primary: Incidence of complete wound healing defined as ulcers without	Primary: In Study 1, the incidence of complete healing was significantly higher in the becaplermin group compared to the placebo group (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. good ulcer care vs. placebo gel in study 1 patients received placebo or becaplermin 30 mcg gel, in study 2 patients received becaplermin 30 mcg, 100 mcg, or placebo, in study 3 patients received becaplermin 100 mcg, placebo, or good ulcer care (undefined), and in study 4 patients received becaplermin 30 mcg or 100 mcg	least 1 but no more than 3 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)	was achieved	draining and with no dressing required Secondary: Time to complete healing (study 2 only)	In study 2, the incidence of complete healing was 50% in the becaplermin 100 mcg group, 36% in the becaplermin 30 mcg group, and 35% in the placebo group and was only significant when comparing the 100 mcg group to placebo (P=0.01). In study 3, the incidence of complete healing was 44% in the becaplermin 100 mcg 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 vehicle 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.
Embil et al.[87] (2000) Becaplermin 100 mcg QD all patients received active treatment	OL, MC Patients 18 years of age and older with type I or II diabetes, having at least 1 but no more than 2 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	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%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			each visit, and rate of target ulcer recurrence during the 6-month period following healing	
Burgos et al.[109] (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.	RCT, MC, OL, PG Hospitalized or institutionalized patients aged 55 years and older presenting with stage III pressure ulcers for <1 year	N=102 8 weeks	Primary: Efficacy, 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 with 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 relative risk of non-healing among the 48-hour interval group as compared with 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 intention-to-treat 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 relative risk of adverse reaction occurrence was 1.02 (95% CI, 0.21 to 4.80).
Palmieri et al.[110] (1998) Collagenase ointment vs. placebo	RCT, DB, PC 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	Primary: Collagenase was significantly more effective than placebo for debridement, granulation, epithelization, and inflammation (P<0.01). Differences reached statistical significance after 6 days of treatment for both debridement and inflammation, and after 4, 5 and 8 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.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=3 times daily, QID=4 times daily, QAM= every morning, QHS=every bedtime
Study abbreviations: CI=confidence interval, CS=comparative study, DB=double-blind, DR=dose response study, ES=extension study, IB=investigator-blinded, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind
Miscellaneous abbreviations: ACTG=AIDS Clinical Trials Group, AD=atopic dermatitis, AK=actinic keratosis, ALT=alanine aminotransferase , ASR=application-site reaction, AST=aspartate aminotransferase, BCC=basal cell carcinoma, BSA=body surface area, CA=Composite Assessment of Index Lesion Disease Severity, CCR=clinical complete response, CTCL=cutaneous T-cell lymphoma, EASI=Eczema Area and Severity Index, EBT=electron beam radiation therapy, ECOG=Eastern Co-operative Oncology Group, ESI=erythema, scaling, and induration, CLNS=Cumulative Lesion Number Score, GSS=Global Severity Score, HIV=human immunodeficiency virus, IGA=Investigator's Global Assessment, IGADA=Investigator Global Atopic Dermatitis Assessment, IGII=Investigators' Global Improvement Index, KS=Kaposi's Sarcoma, mEASI=Modified Eczema Area and Severity Index, MPSS=Modified Psoriasis Severity Score, PASI=Psoriasis Area and Severity Index, PD=progressive disease, PGA=Physicians Global Assessment of Clinical Condition, PGII=Patient Global Improvement Index, PR=partial response, PRA=partial response area, PRH=partial response height, PQoL-AD=Quality-f-Life Questionnaire for Parents of Children with Atopic Dermatitis, PSSI=Psoriasis Scalp Severity Index, PUVA=psoralen ultraviolet A, QoL=quality of life, sBCC=superficial basal cell carcinoma, SCOR-AD=Severity Scoring of Atopic Dermatitis, SD=stable disease, TBSA=total body surface area, TLNS=Target Lesion Number Score, TNM=tumor nodes metastasis, TSS=Total Severity Score, ULN=upper limit of normal, UVA=ultraviolet A, UVB=ultraviolet B

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 15. Relative Cost of the Skin and Mucous Membrane Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Acitretin	kit	Soriatane® CK	$$$$$	N/A
Alitretinoin	gel	Panretin®	$$$$$	N/A
Becaplermin	gel	Regranex®	$$$$$	N/A
Betamethasone and calcipotriene	ointment, suspension	Taclonex®, Taclonex Scalp®	$$$$$	N/A
Bexarotene	gel	Targretin®	$$$$$	N/A
Calcipotriene	cream, solution	Dovonex®*	$$$$$	$$$$
Collagenase	ointment	Santyl®	$$$	N/A
Diclofenac	gel	Solaraze®	$$$$-$$$$$	N/A
Fluorouracil	cream, kit, solution	Carac®, Efudex®*, Efudex® Occlusion Pack, Fluoroplex®	$$$$-$$$$$	$$$$$
Formaldehyde	solution	Formalaz®*, Lazerformalyde®*	$$$	$$$
Imiquimod	cream	Aldara®	$$$$$	N/A
Phenylephrine, shark liver oil, glycerin, and white petrolatum‡	rectal cream	N/A	N/A	$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Phenylephrine, shark liver oil, mineral oil, and white petrolatum‡	rectal ointment	Preparation H®*	$	$
Pimecrolimus	cream	Elidel®	$$$$	N/A
Podofilox	gel, solution	Condylox®*	$$$-$$$$$	$$$
Podophyllum resin	liquid	Podocon-25®	$$$	N/A
Sodium phosphate (monobasic/dibasic), potassium phosphate (monobasic/dibasic), zinc, and urea	spray	Constant- Clens®	$	N/A
Tacrolimus	ointment	Protopic®	$$$$$	N/A
Tazarotene	cream, gel	Tazorac®	$$$$-$$$$$	N/A
Thrombin, fibrinogen, aprotinin, and calcium chloride	kit, syringe	Artiss®, Artiss® Duploject	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
N/A=Not available

X. Conclusions

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, genital/perianal warts, hemorrhoids, Kaposi's sarcoma, psoriasis, and wounds.

There are many topical treatments available for patients with actinic keratoses (AK), including diclofenac, fluorouracil and imiquimod. Guidelines for the management of AK state that all of these treatments are effective and do not give preference to one agent over another.[33,35] Several clinical trials have demonstrated a significant reduction in AK lesions with diclofenac, fluorouracil and imiquimod compared to placebo.[40-41,43-48,114] Recently, three head-to-head studies have been published. Diclofenac and imiquimod were found to be equally effective in a 12-week study.[120] Two studies evaluated the effects of fluorouracil and imiquimod in reducing AK lesions. Fluorouracil was found to be more effective than imiquimod in a 24-week study.[113] A second study demonstrated similar 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.[121] With the limited number of head-to-head studies, it is difficult to make comparisons between these agents.

Two topical calcineurin inhibitors, pimecrolimus and tacrolimus, are FDA-approved for the treatment of atopic dermatitis. Guidelines for the treatment of atopic dermatitis state that topical corticosteroids are considered first-line therapy.[30-32] Topical calcineurin inhibitors are second-line therapy for the short-term and non-continuous chronic treatment of atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.[16,19] Numerous clinical trials have demonstrated greater efficacy with pimecrolimus and tacrolimus compared to placebo.[25,49,51-52,54,115,124-126] Several studies have found tacrolimus to be more effective than pimecrolimus.[54,56,100,112,123] However, it should be noted that pimecrolimus is only indicated for the treatment of mild to moderate atopic dermatitis; whereas, tacrolimus is indicated for the treatment of moderate to severe atopic dermatitis. The long-term safety of topical calcineurin inhibitors has not been established.[16,19] Although a causal relationship has not been established, rare cases of malignancy have been reported in patients treated with topical calcineurin inhibitors.[16,19] Therefore, the long-term use of these agents should be avoided.[16,19]

Fluorouracil and imiquimod are FDA-approved for the treatment of superficial basal cell carcinoma (sBCC). Guidelines recommend the use of these agents in patients with low-risk squamous cell carcinoma in situ, where surgery or radiation is contraindicated or impractical; however, cure rates may be lower.[35] Guidelines do not give preference to one topical treatment over another.[35] There are limited clinical trials evaluating the efficacy and safety of fluorouracil and imiquimod in the treatment of sBCC.[57-62,99,116] Imiquimod has been shown to be effective in both

open-label and placebo-controlled studies.[58-62,116] Fluorouracil has been shown to be effective in two studies; however, there are no placebo-controlled studies with this agent.[59,99] There were no head-to-head studies found in the medical literature directly comparing fluorouracil and imiquimod in the treatment of sBCC. Therefore, it is difficult to make comparisons between these agents.

Bexarotene is the only miscellaneous topical agent indicated for the 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. According to guidelines published by the Joint British Association of Dermatologists and United Kingdom Cutaneous Lymphoma Group, topical bexarotene may be appropriate for patients with early stages of mycosis fungoides (stage IA-IIA); however, patients with later stages (stage IIB or higher) will require systemic therapy.[34] Bexarotene has been shown to be effective in one open-label clinical trial, which evaluated its use in patients who were refractory to, intolerant to, or reached a response plateau for at least six months on at least two prior therapies.[63]

Imiquimod, podofilox, and podophyllum resin are FDA-approved for the treatment of external genital and perianal warts. Imiquimod and podofilox are patient-administered treatments and podophyllum resin is applied by health care professionals. Guidelines state that there is no definitive evidence to suggest that any of the available treatments are superior to any other, and no single treatment is ideal for all patients or all warts.[37] Several clinical trials have demonstrated that both imiquimod and podofilox are effective treatments for external anogenital warts.[64-70,122] A meta analysis of 12 placebo-controlled trials demonstrated similar clinical cure rates with imiquimod and podofilox (50.3% and 56.4%, respectively).[98] However, no study has directly compared the efficacy and safety of these two agents. No clinical trials evaluating the use of podophyllum resin were found in the medical literature.

Guidelines for the treatment of hemorrhoids state that the cornerstone of therapy is adequate fiber intake and water.[38] Topical corticosteroids and analgesics may bring symptomatic relief of local pain, itching and inflammation.[38] Over-the-counter topical agents and suppositories are often used in the empirical treatment of hemorrhoids, however data supporting their use are lacking.[38] A literature search did not reveal any published studies evaluating the use of rectal products containing phenylephrine, shark liver oil, glycerin, mineral oil, and white petrolatum for the treatment of hemorrhoids.

Alitretinoin is the only miscellaneous agent indicated for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS). It has been shown to be more effective than placebo in two clinical trials.[71-72] Alitretinoin should not be used when systemic anti-KS therapy is required (e.g., more than 10 new KS lesions in the prior month, symptomatic lymphedema, symptomatic pulmonary KS, or symptomatic visceral involvement).[2] There are no published guidelines available discussing the role of alitretinoin compared to other modalities in the treatment of KS.

There are four miscellaneous agents indicated for the treatment of psoriasis: acitretin, betamethasone/calcipotriene, calcipotriene, and tazarotene. Acitretin is an oral formulation that is packaged with an emollient foam. The other agents are topical formulations. Guidelines for the management of psoriasis state that topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis, particularly those with limited disease.[26,28] However, when topical corticosteroids are used to treat psoriasis, it is recommended that a gradual reduction in the frequency of usage following clinical response be instituted.[26,28-29] Calcipotriene is an effective and safe treatment for the long-term management of psoriasis, as demonstrated in several clinical trials.[28,73-78,80] Numerous clinical trials have also demonstrated that the combination product containing betamethasone/calcipotriene was more effective than monotherapy with betamethasone or calcipotriene [26,28-29,79,89,95,91-93,103-106] However, no studies have been published which directly compare the betamethasone/calcipotriene combination product with dual use of betamethasone and calcipotriene as separate formulations. Several clinical trials have demonstrated similar efficacy with calcipotriene and tazarotene.[82-83,85] Acitretin is an effective systemic agent for the treatment of psoriasis; however, it is teratogenic and its use is limited in female patients of childbearing potential.[27,96-97]

Collagenase is indicated for debriding chronic dermal ulcers and severely burned areas; however, there are few published studies available comparing its use with other agents or debridement techniques.[109-110]

Becaplermin is indicated for the treatment of lower extremity diabetic ulcers which extend into subcutaneous tissue or beyond and have adequate blood supply. Guidelines on diabetic foot wound care state that becaplermin shows a modest benefit if used with adequate off-loading, debridement, and treatment of infection, but is not a substitute for

comprehensive wound care.[36] There are limited clinical trials assessing the efficacy and safety of becaplermin.[86-87] Wieman et al. described the results of 4 clinical trials; two studies demonstrated a significantly higher incidence of complete wound healing in patients receiving becaplermin compared to placebo.[86] A third study found no difference between becaplermin and placebo.[86] The fourth study was not adequately powered to detect a difference between the treatment groups.[86]

At this time, there is not a role for the miscellaneous skin and mucous membrane agents 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.

There is insufficient data to support that one brand miscellaneous skin and mucous membrane agent is safer or more efficacious than another. Therefore, all brand miscellaneous skin and mucous membrane products within the class reviewed are comparable to each other and to the generics and OTC products 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

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