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# Efinaconazole: A New Topical Treatment for Onychomycosis

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Conflict of interest: Dr. Gupta has served as a clinical trials investigator for Valeant Pharmaceuticals Inc.

## ABSTRACT

*Efinaconazole is an emerging antifungal therapy for the topical treatment of onychomycosis. Efinaconazole is an inhibitor of sterol 14α-demethylase and is more effective* in vitro *than terbinafine, itraconazole, ciclopirox and amorolfine against dermatophytes, yeasts and non-dermatophyte molds. Phase II studies indicate that efinaconazole 10% nail solution is more effective than either the 5% strength or 10% solution with semi-occlusion. In duplicate Phase III clinical trials, complete cure rates of 17.8% and 15.2% were demonstrated. The mean mycological cure rate for efinaconazole is similar to the oral antifungal itraconazole and exceeds the efficacy of topical ciclopirox. Efinaconazole showed minimal localized adverse events, which ceased upon stopping treatment. Overall, efinaconazole 10% nail solution is an effective topical monotherapy for distal and lateral subungual onychomycosis (<65% nail involvement, excluding the matrix) that shows further potential use as an adjunct to oral and device-based therapies.*

**Key words:** antifungal agent, efinaconazole, fungal nail infection, onychomycosis, topical triazole

## Introduction

Onychomycosis is a fungal infection of the nail apparatus[1] caused primarily by dermatophytes, yeasts, and non-dermatophyte molds. Keratinolytic dermatophytes infect and colonize the nail plate, bed, and matrix,[2] resulting in symptoms such as onycholysis, discoloration, and thickening of the nail plate.[2] Onychomycosis warrants treatment for both cosmetic and medical purposes. Left untreated, the infection can spread to other nails and potentially cause further complications, especially in at-risk populations such as diabetic and immunosuppressed patients.[3,4]

The treatment of onychomycosis poses a number of challenges due to the nail plate's lack of intrinsic immune function and the poor accessibility of drugs into the nail plate. The current gold standard therapy for onychomycosis is oral antifungals because their systemic distribution allows them to penetrate the nail apparatus and, to a certain extent, the nail plate via the circulatory system.[5] Problematically, all of the oral drugs suffer from potential systemic adverse events and drug interactions.[6] This potential for negative side effects and drug interactions is often higher in the very populations who are at the greatest risk for onychomycosis, such as diabetics and the immunosuppressed; however, if left untreated, these individuals are the most susceptible to health complications. The existing topical antifungals are not associated with dangerous adverse events, as they rarely penetrate the systemic circulation and gain a significant concentration in the body. Topicals are less widely used for onychomycosis because their poor penetrance into the nail plate results in correspondingly poor mycological and complete cure rates.[7] Hence, the ideal scenario would be to develop topicals that have a higher nail plate penetrance compared with existing drugs, but maintain the advantage of minimal systemic uptake.[7,8]

## A Novel Topical Triazole Antifungal

Efinaconazole is a triazole antifungal that has been developed specifically for the topical treatment of distal and lateral subungual onychomycosis (DLSO).[9] Efinaconazole expands on the success of existing triazole antifungals, itraconazole and fluconazole, and is specifically formulated to more effectively penetrate the nail plate. In addition, the solution formulation avoids product build-up and removal time associated with the use of lacquers.

### In Vitro Efficacy

Efinaconazole is an inhibitor of sterol 14α-demethylase (14-DM).[10] In broth dilution tests *in vitro* against reference strains, it was more potent than terbinafine, ciclopirox, itraconazole, and amorolfine.[11] The efficacy of efinaconazole was comparable in clinical isolates of *Trichophyton mentagrophytes* (*T. mentagrophytes*) and *Trichophyton rubrum* (*T. rubrum*) from Canada, the US, and Japan (Table 1). The high *in vitro* efficacy of efinaconazole against the reference strains suggests that the agent would be effective in onychomycosis, providing the formulation renders sufficient nail penetrance.

*ALSO IN THIS ISSUE:* **Steroid-Sparing Properties of Emollients in Dermatology** *(page 5)* & **Update on Drugs** *(page 12)*

## Clinical Efficacy

The randomized, parallel-group, double-blind, vehicle-controlled Phase II clinical trial of efinaconazole was conducted at 11 sites in Mexico.[12] This initial trial compared the use of 10% solution, 5% solution, 10% solution with semi-occlusion, and placebo in a 2:2:2:1 ratio. The treatment period was 36 weeks with a four week wash-out period prior to the evaluation of the outcome measures. The efficacy variables reported were mycological cure, complete cure, clinical efficacy, and effective treatment (Table 2). Efinaconazole 10% solution without semi-occlusion was the most effective treatment for all outcomes measured.

Efinaconazole 10% nail solution (ENS) has recently completed two parallel, double-blind, randomized, controlled, Phase III trials.[9] Trial participants applied ENS daily for 48 weeks followed by a four week wash-out period. The trial outcome measures were evaluated at week 52 and results from these evaluations demonstrated that ENS was superior to vehicle for all outcome measures (Table 3). The primary outcome measure, complete cure, was 17.8% and 15.2% for efinaconazole. The mycological cure rate was 55.2% and 53.4%. Table 4 shows a comparison of the mycological cure rates for efinaconazole, itraconazole, terbinafine, and ciclopirox.[13-15] The mycological cure rate for 48 weeks of topical efinaconazole was comparable to 12 weeks of oral itraconazole.

## Safety and Adverse Events

In a Phase II trial, 76.9% of participants in the efinaconazole 10% group experienced treatment associated adverse events (TEAEs) compared with 63.6% of vehicle.[12] The main TEAEs associated with efinaconazole were blisters, contact dermatitis, erythema and ingrown nail, none of which resulted in study discontinuation. In two identical Phase III studies, the reported rates for a single adverse event during treatment with efinaconazole were comparable to vehicle (study 1: 66% vs. 61%; study 2: 64.5% vs. 58.5%).[9] The primary TEAEs reported were application site dermatitis and vesicles; however, the rates for localized skin reactions were comparable to vehicle. Discontinuation as a result of TEAEs was low, with 3.2% and 1.9% vs. 0.5% and 0% of participants in the efinaconazole groups vs. the vehicle groups, respectively. Overall, efinaconazole showed low rates of treatment emergent adverse events.

An additional study was conducted to determine if efinaconazole was associated with contact sensitization.[16] Healthy participants (n=239) were treated nine times each with efinaconazole 10% solution or its vehicle in occlusive patches over a three week period. A subsequent 48-hour challenge to a naïve site occurred three weeks later. Participants who showed signs of contact sensitization were then re-challenged and evaluated at 48, 72, and 96 hours after patch application. An additional re-challenge was evaluated on the forearm in addition to the back. These evaluations resulted in mild irritation scores of 0 or 0.5 in 67.8% and 91.6%, respectively, in efinaconazole exposures. Vehicle produced a similar result with 71% scoring 0 and 95% scoring 0.5. The highest reported score, indicating bright-red erythema with or without edema, petechiae, or papules, was observed in two efinaconazole and four vehicle treated participants. An additional 21-day cumulative irritation test was conducted in 37 individuals. Each individual was exposed to efinaconazole and vehicle solutions for three weeks. The cumulative irritation scores were comparable to the vehicle solution.

## Discussion

Efinaconazole 10% solution represents a significant advancement in improving the efficacy of topical therapy for onychomycosis. In assessing the Phase III results for existing oral therapeutics, efinaconazole exhibits a similar mycological and complete cure rate compared to oral itraconazole. Efinaconazole shows significantly improved cure rates over topical ciclopirox and does not require additional nail debridement. Furthermore, all three studies reported efinaconazole therapy was well-tolerated,

| Species | Efinaconazole | Terbinafine | Ciclopirox | Itraconazole | Amorolfine |
|---|---|---|---|---|---|
| *Trichophyton rubrum* | 0.003 | 0.009 | 0.101 | 0.037 | 0.008 |
| *Trichophyton mentagrophytes* | 0.005 | 0.010 | 0.094 | 0.063 | 0.009 |
| *Candida albicans* (24 hours) | 0.0029 | 1.409 | 0.151 | 0.014 | 0.0079 |
| *Epidermophyton floccosum* | ≤0.005 | 0.039 | 0.31 | 0.08 | 0.16 |
| *Microsporum canis* | 0.18 | 0.13 | 0.25 | 0.35 | >4 |
| *Fusarium oxysporum* | 1 | 2.5 | 1 | >4 | >4 |

**Table 1:** Minimal inhibitory concentration (MIC) geometric mean values (µg/mL) for reference strains of common causative agents of onychomycosis[11]

| Treatment | Complete Cure | Mycological Cure | Clinical Efficacy | Effective Treatment |
|---|---|---|---|---|
| Efinaconazole 10% with semi occlusion (n=36) | 22.2% | 83.3% | 67% | 61% |
| Efinaconazole 10% (n=39) | 25.6% | 87.2% | 69% | 64% |
| Efinaconazole 5% (n=38) | 15.8% | 86.8% | - | 55% |
| Vehicle (n=22) | 9.1% | - | 32% | 23% |

**Table 2:** Phase II efficacy outcomes at 40 weeks: intent-to-treat population[12] (-) = not reported

| | | Complete Cure | Mycological Cure | Complete or Almost Complete Cure | Treatment Success: % Nail Plate Involvement | | | | Unaffected Nail Growth |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 0% | ≤5% | <10% | ≤10% | |
| Study 1 | Efinaconazole (n=656) | 17.80% | 55.20% | 26.40% | 45% | 35.70% | 35% | 21% | 5.0 mm |
| | Vehicle (n=214) | 3.30% | 16.80% | 7.00% | 17% | 11.70% | 11% | 6% | 1.6 mm |
| Study 2 | Efinaconazole (n=583) | 15.20% | 53.40% | 23.40% | 40% | 31.00% | 29% | 18% | 3.8 mm |
| | Vehicle (n=202) | 5.50% | 16.90% | 7.50% | 15% | 11.90% | 11% | 7% | 0.9 mm |

**Table 3:** Efinaconazole 10% nail solution Phase III trial outcome measures at 52 weeks: intent-to-treat population[9]

| | Efinaconazole | Itraconazole | Terbinafine | Ciclopirox |
|---|---|---|---|---|
| Treatment duration | 48 weeks | 12 weeks | 12 weeks | 48 weeks |
| Assessment timepoint | 52 weeks | - | 48 weeks | 60 weeks |
| Mycological cure rate | 54% | 54% | 70% | 33% |
| Complete cure rate | 17% | 14% | 38% | 7% |

**Table 4:** Comparison of Phase III trial outcomes between efinaconazole and comparator drugs[9,13-15] (-) = not reported

therefore, demonstrating that the improved efficacy is not necessarily accompanied by an increase in complications, as is associated with oral drugs. A Phase II investigation of the 10% solution reported a treatment completion rate of 86.7%, and rates of 87.7% and 85.4% in Phase III studies.[9,12] These exceed the completion rates for vehicle, which were 81%, 87.4%, and 79.2%, respectively.[9,12] The safety profile for participants treated with efinaconazole was favorable, with minimal or transient TEAEs (e.g., contact sensitization) that resolved upon cessation of treatment.

Although efinaconazole may primarily be intended for monotherapy, it could also serve as an excellent adjunct for oral or device-based therapies. Due to the high rate of recurrence and relapse in DLSO, even for completely cured individuals, long-term topical therapy is often recommended concurrently or following oral therapy.[17-19] Adjunctive treatment may also be desirable with newer therapeutic modalities such as lasers, in order to promote sustained cure. Thus, the addition of efinaconazole may be ideal for these situations as it demonstrates the potential for prolonged efficacy and tolerability, as well as safety for long-term use.

Efinaconazole 10% nail solution is an effective and safe emerging topical treatment of DLSO. It shows promise in comparison to the currently available topical prescription and over-the-counter options. The first regulatory approval of efinaconazole (Jublia®) as a topical monotherapy was recently granted by Health Canada in October 2013 and marketing authorization is pending in several other countries. In addition to its usefulness as a single agent therapy, efinaconazole may be a useful adjunct to oral and device-based therapies, both during the main course of treatment and as subsequent maintenance therapy to prevent reinfection.

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# Steroid-Sparing Properties of Emollients in Dermatology

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## ABSTRACT

*Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs) are very effective treatments in inflammatory dermatoses, but carry risks with long-term use. TCS are associated with cutaneous atrophy and tachyphylaxis and TCIs can be irritating and contain a black box warning of an increased risk of cancers including lymphoma and non-melanomatous skin cancers. Nevertheless, they are appropriate treatments for inflammatory conditions such as psoriasis and atopic dermatitis (AD) and should be used more often with disease flares and less as maintenance therapy. Given the associated risks of long-term continuous use with these pharmacologic agents, alternatives are needed with similar anti-inflammatory and barrier repair properties that can be used indefinitely without risk. Some over-the-counter (OTC) ingredients such as colloidal oatmeal and petrolatum, as well as anti-inflammatory prescription moisturizers (medical device creams), have demonstrated efficacy with little complications in skin barrier repair and symptom relief in steroid-responsive conditions. With regimented application, these non-drug options are safe and effective and can limit the long-term continuous use of TCS or TCIs.*

**Key words:** atopic dermatitis, emollients, eczema, skin barrier repair, moisturizers, topical corticosteroids, topical calcineurin inhibitors

## Introduction

Topical corticosteroids (TCS) are the cornerstone of treatment for inflammatory dermatoses, particularly for the swift resolution of acute flares, as TCS can calm inflamed and irritated skin due to rapid absorption and action.[1] A wide range of potencies and vehicles enables tailoring of therapy to be site-specific and considerate of patient preference. Long-term continuous therapy with TCS can lead to localized side effects such as cutaneous atrophy, telangiectasias, acne and rosacea exacerbation, and tachyphylaxis, as well as systemic absorption if used on large surface areas causing hypothalamic-pituitary-adrenal (HPA) axis suppression, growth retardation in children, and cataract and glaucoma formation in adults.[2-6] Thus, intermittent therapy should be supplemented with alternative treatments that can help limit localized side effects and provide epidermal barrier dysfunction improvement.[7]

Topical calcineurin inhibitors (TCIs; tacrolimus ointment/ Protopic®; pimecrolimus cream/Elidel®) represent second-line therapies for the short-term and non-continuous chronic treatment of moderate-to-severe atopic dermatitis (AD) in non-immunocompromised adults and children who have failed to respond adequately to or are not suitable for other topical prescription AD treatments.[8,9] TCIs inhibit calcineurin in T-cells, reducing the production of interleukin (IL)-2 and related pro-inflammatory cytokines. Clinical studies have demonstrated long-term efficacy, minimal systemic absorption, and few transient side effects, such as localized irritation, with the use of these agents.[10-12] TCIs do not induce skin atrophy or inhibit collagen synthesis, enabling their use on the face, neck and intertriginous areas.[13] In 2006 the United States Food and Drug Administration (USFDA) placed a black box warning on TCIs based on safety concerns over the possible risk of systemic absorption and on data from transplantation research reporting systemic immune suppression with oral calcineurin inhibitors (tacrolimus and cyclosporine) is associated with an increased cancer risk.[14] To date, this risk remains theoretical and is based mainly on the drug's mechanism of action, data from animal studies and a few single case reports of lymphoma and skin cancer in patients treated with TCIs.

Recently, medical device creams (Table 1), which are non-steroidal agents with emollient, anti-inflammatory and anti-pruritic properties, have entered the marketplace for the treatment of inflammatory dermatoses to help treat epidermal barrier dysfunction as well as limit potential long-term use of TCS and TCIs. Atopiclair® is a hydrolipidic cream containing *Butyrospermum parkii* (shea tree), glycyrrhetinic acid (licorice), *Vitis vinifera* (grapevine) extract, bisabolol (German chamomile), hyaluronic acid and tocopheryl acetate (vitamin E), and is thought to have moisturizing, anti-inflammatory and antioxidant properties.[15] It also contains telmesteine, which inhibits elastase, collagenase and matrix metalloproteinases, helping to prevent epidermal breakdown. MimyX™ contains lipid components that mimic the normal skin barrier (triglycerides, phospholipids, and squalene) along with the anti-inflammatory cannabinoid N-palmitoylethanolamine (N-PEA), an endogenous fatty acid amide thought to target the peroxisome proliferator-activated receptor-alpha (PPAR-$\alpha$).[16] Other added ingredients such as purified water, olive oil, glycerin, pentylene glycol, vegetable oil, and hydrogenated lecithin have humectant and emollient effects. EpiCeram® is a microencapsulation system emulsion of ceramide, conjugated linoleic acid, cholesterol and palmitic acid formulated with *Euphorbia cerifera* (candelilla) wax, corn syrup solids, squalene, glycerin, petrolatum, and dimethicone.[17,18] Eletone® has a high lipid content dispersed in an outer aqueous phase (Hydrolipid Technology™) in petrolatum, purified water, and mineral oil.[19] Hylatopic Plus® is an emollient cream and foam containing *Theobroma grandiflorum* seed butter (a skin conditioning butter made from the fruit of a the Cupuaçu tree

| Product Name | Main Active Ingredients | Other Important Ingredients | Year of Approval | Indication | Dosage Forms (grams) |
|---|---|---|---|---|---|
| Atopiclair® (Sinclair Pharma) | Glycyrrhetinic acid (licorice), hyaluronic acid | *Butyrospermum parkii* (shea tree), glycine, bisabolol, tocopheryl acetate, *Vitis vinifera* (grape vine) | 2003 | Relieve the burning, itching and pain experienced with various types of dermatoses including atopic and allergic contact dermatitis; relief of dry skin | 100 cream |
| MimyX™ (Stiefel Laboratories) | Palmitoyl ethanolamide, olive oil, glycerin, vegetable oil | Palm glycerides, hydrogenated lecithin, squalane | 2005 | Manage the burning and itching experienced with various types of dermatoses including atopic dermatitis, allergic contact dermatitis and radiation dermatitis | 70, 140 cream |
| EpiCeram® (PuraCap Pharmaceutical) | Ceramide, capric acid, conjugated linolenic acid, cholesterol | Purified water, *Euphorbia cerifera* (candelilla) wax, glyceryl stearate, squalane, glycerin, hydroxypropyl bispalmitamide MEA (ceramide), petrolatum, dimethicone, cholesterol, conjugated linoleic acid, palmitic acid | 2005 | To treat dry skin conditions and to manage and relieve the burning and itching associated with various types of dermatoses including atopic dermatitis, irritant contact dermatitis and radiation dermatitis; relief of dry and waxy skin | 50, 90 cream |
| Eletone® (Mission Pharmacal) | Petrolatum | Mineral oil | 2009 | Management and relief of burning, itching and redness associated with atopic dermatitis | 100 cream |
| HylatopicPlus®* (Onset Dermatologics) | Hyaluronic acid | Glycerin, ethylhexyl palmitate, propylene glycol, *Theobroma grandiflorum* seed butter, petrolatum, dimethicone, tocopheryl acetate | 2009 | To manage and relieve the burning, itching and pain experienced with various types of dermatoses including atopic dermatitis, allergic contact dermatitis and radiation dermatitis; relief of dry and waxy skin | 100, 450 cream; 100, 150 foam |
| Promiseb™ (Promius Pharma) | Piroctone olamine | *Butyrospermum parkii*, ethylhexyl palmitate, cera alba (beeswax), bisabolol, tocopheryl acetate, hydrogenated castor oil, acifructol complex, *Vitis vinifera*, glycyrrhetinic acid (licorice), telmesteine | 2009 | To manage and relieve the signs and symptoms of seborrhea and seborrheic dermatitis such as itching, erythema, scaling and pain; helps to relieve dry waxy skin | 30 cream |
| Tetrix™ (Coria Laboratories/ Valeant Pharmaceuticals) | Cyclomethicone, dimethicone | Aluminum magnesium hydroxide stearate | 2008 | To manage the burning and itching experienced with various types of dermatoses including atopic dermatitis, allergic contact dermatitis and irritant contact dermatitis; helps to relieve dry waxy skin | 56.7 cream |
| Bionect® (Innocutis Holdings) | Hyaluronic acid | Oleic acid, emulsifying wax, sorbitol | 2012 | Dressing and management of partial to full thickness dermal ulcers (pressure sores, venous stasis ulcers, arterial ulcers, diabetic ulcers) and wounds including cuts, abrasions, donor sites, and post-operative incisions, irritations of the skin, and first and second degree burns | 25, 50, 100 cream; 30, 60, 100 gel; 20 ml spray |
| Biafine® (Valeant Pharmaceuticals) | Paraffin | Stearic acid, squalane, avacado oil, trolamine/ sodium alginate, cetyl palmitate, sorbic acid | 2006 | Full thickness wounds, pressure sores, dermal ulcers including lower leg ulcers, superficial wounds, first and second degree burns including sunburns, dermal donor and graft site management, radiation dermatitis and minor abrasions | 45, 90 cream |
| Neosalus™ (Quinnova Pharmaceuticals) | Dimethicone | Carbomer, glycerin, polysorbate 20, povidone, propylene glycol, sodium hydroxide, stearic acid, trolamine | 2009 | For the management of various types of dermatoses including atopic dermatitis and allergic contact dermatitis | 60, 100 cream; 70, 200 foam; 236 ml bottle |

**Table 1:** Prescription medical device creams on the market

*Emollient foam formulation has glycerin (humectant), dimethicone (occlusive) and petrolatum (occlusive)

that is native to Brazil), hyaluronic acid, glycerin, dimethicone, petrolatum, and tocopheryl acetate (vitamin E).[20] All of the medical device creams are indicated for the treatment of various dermatoses such as AD, allergic contact dermatitis, and radiation dermatitis, which are associated with symptoms of itching, burning, and pain.

## Epidermal Barrier Dysfunction

Defects in skin barrier function and stratum corneum hydration have been identified in a variety of inflammatory dermatoses.[21] A functioning stratum corneum consists of corneocytes surrounded by ceramides, cholesterol, and free fatty acids – the so-called "bricks and mortar" model.[22] Topical balms containing lipids and lipid-like substances have been shown to restore the barrier function of an impaired stratum corneum by replacing the deficient lipids, thereby improving skin hydration through decreasing transepidermal water loss (TEWL).[23] Further, epidermal barrier disruption results in greater density of epidermal Langerhans cells (antigen-presenting immune cells), enhanced inflammatory responses by increased foreign antigen presentation, and decreased anti-microbial proteins (AMPs), which play a role in innate skin defense (first-line skin protection).[24]

In AD, the disturbed epidermal barrier is explained by nonsense mutations in the gene encoding filaggrin (FLG) and subsequent affect on the pro-inflammatory cascade, such as abnormal elevation in IL-1 cytokine profile in the stratum corneum.[25,26] FLG is a structural protein essential in the cornified envelope and is expressed as pro-FLG, which functions to secure keratinocytes together in the stratum corneum. Dysfunction or loss of FLG heavily influences keratinocyte adhesion, enhances TEWL, and causes dysregulation of skin pH, resulting in increased skin permeability.[27] Overall, this can induce persistent, recalcitrant and/or severe disease, increase the risk of cutaneous infections caused by microbes such as herpesvirus (eczema herpeticum) and *Staphylococcus aureus*, as well as increase the risk of sensitization to allergens and asthma.[28] Thus, the importance of an uncompromised skin barrier in improving inflammatory conditions cannot be over-emphasized and should be a major consideration in the treatment of acute flares as well as in long-term disease management.

It is important to note that despite the acknowledged contributions of a defective epidermal permeability barrier [i.e., FLG mutations, decreased AMPs such as human tissue kallikreins and cathelicidins (LL-37)] and dryness of eczematous skin, immunologic abnormalities such as T-helper type 2 (Th2) cytokines [i.e., IL-4 and IL-13 that influence immunoglobulin E (IgE) synthesis and adhesion molecule expression] also contribute to the pathogenesis of AD.[29] This suggests the development of inflammatory disorders is likely due to underlying immune dysregulation as the primary cause and epidermal dysfunction may be a secondary consequence.

## Over-The-Counter Options and Clinical Studies

### Petrolatum

Petrolatum – a mixture of long-chain hydrocarbons that is pale yellow in color, translucent, odorless, and hydrophobic – has been used for over 100 years as a healing ointment. Originally thought to be an occlusive moisturizer that forms a hydrophobic layer on the skin surface, petrolatum can penetrate and restore the stratum corneum by filling the spaces between desquamating corneocytes. This can reduce the appearance of fine lines and impart a soft, silky feel to the skin. Increased skin hydration is a consequence of epidermal lipogenesis and production of free sterols, sphingolipids, and free fatty acids.[30-32] Occlusives are generally not appealing to patients, due to their greasy feel, but can be very beneficial directly as a moisturizer and indirectly by reducing TEWL. A recently published study demonstrated the clinical efficacy and cost-effectiveness of a petrolatum-based moisturizer (Aquaphor® Healing) in treating mild-to-moderate AD as compared to two commonly prescribed medical device creams; one glycyrrhetinic acid-containing barrier repair cream (Atopiclair™) and another a ceramide-dominant barrier repair cream (EpiCeram®).[33] Some barrier repair creams contain petrolatum as their primary ingredient (Eletone®) and one study demonstrated comparable efficacy to a TCI (i.e., Elidel®) in the treatment of AD.[34]

### Dimethicone

Dimethicone – a mixture of polydimethylsiloxanes and silicon dioxide sometimes called simethicone – is another occlusive (insoluble in water) used in many OTC moisturizers and found to be safe and effective at skin moisturizing, though it is not as effective as petrolatum at reducing TEWL.[35,36] Dimethicone is the first ingredient in a foam formulated for the relief of irritation from inflammatory dermatoses such as AD and allergic contact dermatitis (Neosalus™). A combination of cyclomethicone (a cyclic higher-viscosity silicone) and dimethicone are used in barrier creams designed to prevent skin sensitization to allergens and can be useful in patients with itching and burning associated with contact dermatitis (Tetrix™).[37,38] Additionally, a recent study showed significant reduction in the incidence of incontinence-associated dermatitis in patients using dimethicone-impregnated clothes.[39]

### Colloidal Oatmeal

Colloidal oatmeal has a long-standing history of benefit in dermatologic conditions associated with itch and irritation because of the ability to soothe and protect inflamed skin.[40] It contains a variety of active components including polysaccharides, proteins, lipids, saponins, enzymes, flavonoids, vitamins and avenanthramides (polyphenol).[41] In 2003, colloidal oatmeal became an approved OTC monograph ingredient.[40] Current, ready-to-use oatmeal preparations are the concentrated starch-protein fraction of the oat grain mixed with emollient. Fine particles disperse on the skin and form a protective, occlusive barrier that retards water loss and moisturizes to improve the epidermal barrier. Further, oatmeal saponins help to solubilize dirt, oil and sebaceous secretions, which may normalize the skin pH.[42] Oats have important antioxidant, ultraviolet (UV) absorbent and anti-inflammatory properties attributed to the ferulic, caffeic and coumaric acids, as well as flavonoids and α-tocopherol (vitamin E) components.[43,44] Recent research has identified avenanthramides (phenolic compounds) as a minor component of oat grains and *in vitro* work has demonstrated anti-inflammatory and anti-pruritic properties by decreased production of Nuclear Factor-kappaB (NF-κB) in

| Product Name | Main Active Ingredients | Average Cost ($) | Size |
|---|---|---|---|
| Cetaphil® Restoraderm® (Galderma) | Glycerin, caprylic/capric triglyceride, *Helianthus annuus* (sunflower) seed oil, *Butyrospermum parkii* (shea tree), sorbitol, cyclopentasiloxane, tocopheryl acetate, hydroxypalmitoyl sphinganine (ceramide precursor), niacinamide, allantoin, panthenol, caprylyl glycol, dimethiconol, sodium hyaluronate, arginine and sodium PCA (filaggrin breakdown products) | 12 | 10 fl oz |
| CeraVe® Cream (Valeant Pharmaceuticals) | Glycerin, capric/caprylic/stearic triglyceride, ceramides, hyaluronic acid, cholesterol, petrolatum, dimethicone, sodium lauroyl lactylate (milk/coconut oil), phytosphingosine | 15 | 16 oz |
| Curel® Advanced Ceramide Therapy (Kao) | Mineral oil, petrolatum, glycerin, microcrystalline wax, hydrogenated castor oil, paraffin, dimethicone, *Eucalyptus globulus* leaf extract | 13 | 16 oz |
| SkinMedica® TNS Ceramide Treatment Cream™ (SkinMedica) | Cetyl ethylhexanoate, hyroxypropyl bispalmitamide MEA, human fibroblast conditioned media, dimethicone, *Olea europaea* (olive) fruit oil, *Glycine soja* oil, palmitoyl oligopeptide, palmitoyl tetrapeptide-7, tetrahexyldecyl ascorbate, *Avena sativa* (oat) kernel extract, *Glycine soja* sterols, retinyl palmitate, tocopheryl acetate, sodium carboxymethyl beta-glucan, squalane, allantoin, bisabolol, panthenol, sodium hyaluronate, glycerin | 64 | 2 oz |
| DHC Ceramide Cream (DHC Corporation) | Caprylic/capric triglyceride, squalane, stearic acid, *Olea europaea* fruit oil, lanolin, hydrogenated lecithin, cholesteryl hydroxystearate, dimethicone, tocopherol, allantoin, *Pyrus cydonia* seed extract, dipotassium glycyrrhizate (licorice), phospholipids, ascorbyl tetraisopalmitate, sodium hyaluronate, hydrolyzed rye phytoplacenta extract, sphingolipids, *Glycine soja* seed extract | 38 | 1.4 fl oz |
| Elizabeth Arden® Ceramide Premiere Activation Cream SPF 30 (Elizabeth Arden) | Octinoxate (7.5%), octisalate (5%), oxybenzone (4%), octocrylene (3%), avobenzone (2%), dimethicone, glycerin, petrolatum, caprylic/capric triglyceride, *Butyrospermum parkii*, hydrogenated lecithin, ceramide, *Fucus serratus* extract, retinyl linoleate, tocopheryl acetate, cetearyl dimethicone crosspolymer, soy amino acids, hydrolyzed soy protein, phytosphingosine, cholesterol | 92 | 1.7 oz |
| Elizabeth Arden® Time Complex Moisture Cream SPF 15 (Elizabeth Arden) | Octyl methoxycinnamate/octinoxate (6%), cyclopentasiloxane, glycerin, cetyl dimethicone, urea, ceramides, algae extract, *Avena sativa* (oat) bran, sodium hyaluronate, hydroxycaprylic acid, sodium lactate, ascorbyl palmitate, tocopheryl acetate, *Carum petroselinum* (parsley) seed oil, *Santalum album* (sandalwood) seed oil | 28 | 1.7 oz |
| Only YouRx™ Soothing Barrier Repair Moisturizer (Only YouRx Skin Care) | *Butyrospermum parkii*, algae extract, *Artemisia vulgaris* extract, dimethicone, ceramide NP, *Glycine soja* seed extract, *Camellia sinensis* (green tea) leaf extract, alpha lipoic acid, decyl olive esters, squalene, panthenol, bisabolol, allantoin, tocopheryl acetate, linoleic acid, palmitic acid, oleic acid, stearic acid, cholesterol, glycerin | 53 | 60 ml (2 oz) |
| Mario Badescu Alpha Hydroxy Acid (AHA) and Ceramide Moisturizer (Mario Badescu) | *Aloe vera* gel, lemon extract, squalane, glyceryl stearate, dimethicone, myristyl lactate, lemongrass extract | 20 | 2 oz |
| First Aid Beauty® Daily Face Cream (First Aid Beauty) | Gylceryl stearate SE, glycerin, squalane, caprylic/capric triglyceride, dimethicone, ceramide, caprylyl glycol, *Camellia sinensis* leaf extract, *Chrysanthemum parthenium* (feverfew) extract, *Glycyrrhiza glabra* (licorice) root extract | 20 | 2 fl oz |
| AKTA® Moisturizer with Ceramides (Gunilla of Sweden) | Whole leaf *Aloe vera* concentrate, ceramide lipids, squalene, beeswax, jojoba oil, panthenol, seaware, organic extracts of (hops, horse tail, rosemary, pine tree, lemon, arnica, cucumber, elder, ivy, mallow, Pellitory-of-the-wall), rose oil, tocopherol, retinol, ascorbic acid | 37 | 2.1 oz |

**Table 2:** Ceramide-containing non-prescription creams on the market

keratinocytes and reduced pro-inflammatory cytokine (such as IL-8) production.[45] Avenanthramides have also been reported to inhibit prostaglandin synthesis.[46] As a result, many studies have substantiated the anti-inflammatory, hydrating and anti-pruritic properties of colloidal oatmeal and their use in the management of common inflammatory dermatoses.

## Ceramides

As discussed previously the ceramides – which are a family of lipid molecules composed of sphingosine and a fatty acid, and found in high concentrations within the membrane of cells in the stratum corneum – are an essential component of the normal stratum corneum and function to help maintain the integrity of the skin barrier.[47] They serve as important water-holding molecules in the extracellular space, linking corneocytes and creating a waterproof barrier. In ceraminde-deficient skin there is enhanced TEWL, dryness, and increased permeability to environmental irritants and allergens. A recent study found that the mechanisms of ceramide changes in atopic skin are due to both Th1 (accentuate) and Th2 (attenuate) cytokines, as both IL-4 and IL-6, as well as interferon (IFN)-γ and tumor necrosis factor (TNF)-α influenced ceramide content in the stratum corneum.[48] This further solidifies that immune dysregulation in AD has a multitude of pathophysiological effects on the skin.

Newer moisturizers/topical skin care products (Table 2) targeted to improve epidermal barrier dysfunction by replenishing the amount of ceramides in the skin – with ceramide and pseudoceramide products mimicking the natural physiological skin barrier – are a mainstay of adjunctive therapy for patients with AD. Although evidence on their efficacy compared to older, less expensive traditional therapies, such as occlusives and humectants, remains to be validated.[49] It is known that proper moisture therapy can reduce the frequency of flares and limit the need for TCS or TCIs, likely a result of barrier recovery, including restoration of proper permeability function and increased levels of AMPs. In one study, a ceramide-hyaluronic acid emollient foam (Hylatopic Plus®) and pimecrolimus both showed equivalent improvement in the signs and symptoms of AD.[50] In another study, a ceramide-dominant, physiologic lipid-based, barrier repair emollient (TriCeram®) showed improvement when substituted for other OTC moisturizers in 24 children also receiving standard therapy (TCS or TCIs) for recalcitrant AD, thereby demonstrating the use of a ceramide-dominant moisturizer as compared to traditional agents can elicit significant improvement in symptoms of AD.[51] TriCeram® has been discontinued by the manufacturer and is no longer available on the market.

EpiCeram® (a prescription device) consists of a specific combination of ceramides, cholesterol and fatty acids (in the ratio of 3:1:1) that mimics those naturally found in the skin and is reported to have similar efficacy to a mid-potency topical corticosteroid.[1,52,53] It contains capric acid, cholesterol, conjugated linolenic acid, candelilla and petrolatum. In a five-center, investigator-blinded, randomized trial, EpiCeram® was compared to fluticasone (Cutivate®) cream in 121 patients with moderate-to-severe AD and showed reduced clinical disease severity, decreased pruritus and improved sleep habits at both 14 and 28 days after initiation of therapy. The fluticasone group improved faster – greater improvement by day 14 – but by day 28, both interventions showed equal efficacy.[17] A more recent study established improvement in clinical dryness scores and skin hydration and reduction in TEWL with the use of a new moisturizer (Cetaphil® Restoraderm® Body Moisturzier; CRM) containing FLG breakdown products [natural moisturizing factor (NMF)], a ceramide precursor pseudoceramide 5 or N-(2-hydroxyhexadecanoyl) sphinganine and niacinamide (vitamin B3), at week 4 as compared to the untreated areas.[54] A significantly higher level of ceramide and a trend toward increased water content were observed in the stratum corneum of CRM-treated skin when compared to the control.

## Additional Ingredients

Additional ingredients such as glycerin or glycerol, urea, hydroxy acids and propylene glycol are common humectants added to OTC ingredients to help increase the ability of the skin to absorb water; although they are typically combined with an occlusive to prevent upward migration of water from the dermis and inadvertent increased TEWL. Glycerol or glycerin are the most effective as they have the ability to activate transglutaminase activity in the stratum corneum, accelerating the maturation of corneocytes as well as increasing water channels called aquaporins (particularly aquaporin-3) in diseased skin, which ultimately increases cutaneous hydration and reduces TEWL.[55,56]

## Clinical Studies

Several studies have directly examined the steroid-sparing potential of OTC emollients in patients with AD. Daily hydrocortisone 2.5% cream in the morning combined with a once daily water-in-oil emollient cream in the evening (Eucerin® Creme) was equally efficacious as twice daily hydrocortisone 2.5% cream in children.[57] Similarly, once daily betamethasone diproprionate cream with Eucerin® Creme was equally efficacious as twice daily betamethasone diproprionate cream in patients with plaque psoriasis.[58] As well, in infants under 12 months of age with AD, the addition of an emollient containing water, petrolatum, shea butter, evening primrose oil, glycerin, paraffin oil, niacinamide, butylene glycol, benzoic acid, carbomer and also specific active Rhealba® oat extracts (flavonoids and saponins) (Exomega® Emolient Lotion) significantly reduced the use of topical corticosteroids (desonide 0.1% cream).[59]

## Prescription Alternatives: Medical Device Creams

Prescription medical device creams are not classified as drugs, but rather as medical devices that have received 510(k) FDA clearance based on a demonstrated reduction in TEWL, which is a less extensive regulatory process that focuses on safety and less on efficacy. Each device cream has ingredients with proposed moisturizing, anti-inflammatory and anti-pruritic properties that may be useful as adjunctive or maintenance therapy in inflammatory dermatoses and, thereby, may help to limit the use of TCS or TCIs. Whether these device creams are equivalent in efficacy and long-term maintenance as compared to their OTC counterparts remains to be seen. Financial burden and supply limitation (insurance approval required in the US) may create difficulty in initiating and continuing therapy, especially in cases of severe disease.

## Conclusion

Epidermal barrier dysfunction is a consequence of a combination of genetic factors influenced by immune dysregulation and abnormal structural proteins. Inflammatory dermatoses require treatment with TCS and/or TCIs to control acute flares, but also necessate appropriate and adequate moisturization to mitigate structural dysfunction and insufficient skin hydration. High predisposition to recurrent and recalcitrant disease, as well as infections and sensitization to allergens, makes long-term management with the goal to prolong periods of remission and reduce the severity of flares of utmost importance. As TCS can induce long-term complications and some patients are concerned with the black box warning of TCIs, non-drug options such as OTC and/or prescription medical device creams containing active ingredients known to have moisturizing, anti-inflammatory and anti-pruritic properties, are important therapeutic adjuncts that can be used daily without the risks associated with pharmacologics. Further studies are needed to determine the long-term efficacy of these products in treating chronic inflammatory dermatoses and validate their role through the development of management guidelines.

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# Update on Drugs

| Name/Company | Approval Dates/Comments |
|---|---|
| **Hyaluronic acid gel dermal filler**<br>*Juvéderm Voluma™XC*<br>Allergan, Inc. | The US FDA approved this first and only crosslinked hyaluronic acid gel filler in October 2013 for the temporary correction of age-related volume loss in the cheek area in adults >21 years of age. Treatment is indicated for deep (subcutaneous and/or supraperiosteal) injection into facial tissue to temporarily restore volume and fullness to the areas of the mid-face, which include the cheeks and nearby regions confined to the middle portion of the face. In clinical trials, 86% of subjects demonstrated an improvement in their cheek fullness at 6 months, and results lasted up to 2 years in a majority of subjects. Most subjects experienced moderate tenderness, swelling, firmness and/or lumps and bumps at the injection site that generally lasted 2-4 weeks. Juvéderm Voluma™ XC is formulated using the proprietary Vycross™ technology, which allows the gel to be injected smoothly and consistently through a needle or microcannula. It also contains the local anesthetic, lidocaine, to limit discomfort. |
| **Methotrexate injection**<br>*Otrexup™*<br>Antares Pharma, Inc. | The FDA approved subcutaneous (SC) methotrexate (MTX) in October 2013 for symptomatic control of severe recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy in adults. The FDA also approved the use of Otrexup™ for treating adults with active, severe rheumatoid arthritis who have shown an insufficient therapeutic response to or are intolerant of first-line therapy, including full dose non-steroidal anti-inflammatory agents (NSAIDs), or children with active polyarticular juvenile idiopathic arthritis. It is the first FDA-approved SC MTX for once-weekly self-administration delivered with a single-dose, disposable auto injector. |
| **Luliconazole 1% cream**<br>*Luzu®*<br>Valeant Pharmaceuticals International | The FDA approved luliconazole, a novel imidazole drug, in November 2013 for the topical treatment of athlete's foot (interdigital tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis) caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients ≥18 years of age. This is the first topical, broad-spectrum, azole antifungal agent approved to treat tinea cruris and tinea corporis with a one-week, once-daily treatment regimen. All other approved treatments require two weeks of therapy. Interdigital tinea pedis is approved with a two-week, once-daily regimen. This US approval is the first regulatory approval in North America. Luliconazole has been sanctioned in Japan since 2005. |
| **Polidocanol 1% injectable foam**<br>*Varithena™*<br>BTG plc | The FDA approved this sclerosing agent in November 2013 for the treatment of patients with incompetent veins and visible varicosities of the great saphenous vein (GSV) system. Varithena™ (formerly known as Varisolve® PEM) is a pharmaceutical-grade, low-nitrogen, polidocanol foam dispensed from a proprietary canister device. Treatment is administered by intravenous injection using ultrasound guidance. It is a minimally invasive, non-surgical procedure that does not require tumescent anesthesia or sedation, and improves symptoms and appearance for a range of varicose veins, including incompetent GSV, accessory saphenous veins and visible varicosities of the GSV system both above and below the knee. |
| **Smallpox vaccine**<br>*Imvamune®*<br>Bavarian Nordic A/S | Health Canada granted a Notice of Compliance in November 2013 approving Imvamune® for active immunization against smallpox in a public health emergency. Treatment is indicated for persons ≥18 years of age who are contraindicated to replicating smallpox vaccines, including individuals with immune deficiencies and skin disorders. |

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Articles are indexed by drug names, trade names and disease terms. Bold entries refer to major references.