

Therapeutic Class Overview

Anti-inflammatory Agents – Misc., Topical

INTRODUCTION

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. The prevalence of atopic dermatitis is estimated to be between 15% to 30% in children and 2% to 10% in adults; approximately 18 million children and adults have atopic dermatitis in the United States (Berke et al, 2012; Eichenfield et al, 2014a; FDA presentation, 2015). Atopic dermatitis is one of the most common skin disorders in children with more than 90% of cases starting before the age of five years (Eichenfield et al, 2014a). The pathogenesis of atopic dermatitis can be explained by impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as a cutaneous inflammatory response to environmental factors. Pruritus is one of the most common symptoms of atopic dermatitis, and it is an essential feature which provokes a vicious “itch-scratch” cycle that compromises the epidermal barrier which results in water loss, xerosis, microbial colonization, and secondary infection (Castro, 2008). The clinical manifestations of atopic dermatitis vary according to age and disease activity; however, almost all patients with atopic dermatitis report dry skin. The infantile and childhood stages are characterized by pruritic, red, crusted lesions and generally involve the face, neck, and extensor skin surfaces (Eichenfield et al, 2014a). The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities (Eichenfield et al, 2014a).
- Diagnosis of atopic dermatitis is based on a constellation of clinical symptoms. There is no optimal long-term maintenance treatment for atopic dermatitis, and there is no known cure. The general approach for the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin’s abnormal barrier function, hydrating the skin and controlling active disease with topical anti-inflammatory agents (Eichenfield et al, 2014b; Schneider et al, 2013; Tollefson et al, 2014). Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents. Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized. Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation. Sedating antihistamines (e.g., diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (e.g., fexofenadine, loratadine) (Eichenfield et al, 2014b). However, evidence supporting their use is weak due to lack of controlled trials.
- Topical corticosteroids are considered to be the standard of care for the treatment of atopic dermatitis (Eichenfield et al, 2014b; Schneider et al, 2013; Tollefson et al, 2014). Low- to high-potency topical corticosteroids are utilized one or more times daily for the treatment of acute flares as well as for intermittent use to prevent relapses. One large trial showed that twice-daily application of topical corticosteroids was no more effective than once-daily application (Krakowski et al, 2008). There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents. These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck (Eichenfield et al, 2014b; Krakowski et al, 2008; Schneider et al, 2013).
- Immunosuppressive agents for atopic dermatitis include ELIDEL® (pimecrolimus) and PROTOPIC® (tacrolimus); both are approved for second-line treatment (Prescribing information: ELIDEL, 2014; PROTOPIC, 2012). The exact mechanism of action in atopic dermatitis is not known. ELIDEL and PROTOPIC inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to which is theorized to be the primary mode of inflammation reduction in atopic dermatitis (Clinical Pharmacology, 2017). immunophilin-12 (FKBP-12). PROTOPIC and ELIDEL provide immunosuppression via inhibition of T-cell activation, There are some concerns regarding the long-term safety of these agents. On January 19, 2006, the FDA approved updated labeling for the agents (FDA press release, 2006). This updated labeling was a result of cancer-related adverse events (AEs) with the use of these medications. The labeling includes a boxed warning about a possible risk of cancer and a medication guide for patients to ensure they are aware of this concern. The labeling clarifies that these medications are recommended for use as a second-line treatment and are not recommended in children under two years of age. A definitive causal link between the topical immunosuppressants and the incidence of malignancy is not yet established.
- EUCRISA™ (crisaborole) is a non-steroidal topical treatment for atopic dermatitis that works by way of phosphodiesterase (PDE)-4 inhibition (EUCRISA prescribing information, 2016). Inflammation is associated with elevated PDE-4 enzyme activity and overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis (Zane et al, 2016). Crisaborole enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cyclic adenosine monophosphate (cAMP), thereby suppressing the release of cytokines

(Paller et al, 2016). The novel boron chemistry of crisaborole additionally enables synthesis of a low molecular weight compound that facilitates effective penetration through human skin (Paller et al, 2016).

- Medispan Class: Immunosuppressive Agents – Topical; Phosphodiesterase 4 (PDE4) Inhibitors – Topical

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ELIDEL(pimecrolimus)	Valeant	12/13/2001	-
PROTOPIC (tacrolimus)	Astellas	12/08/2000	✓
EUCRISA (crisaborole)	Anacor	12/14/2016	✓

(DRUGS@FDA.com, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ELIDEL (pimecrolimus)	PROTOPIC (tacrolimus)	EUCRISA (crisaborole)
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, 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 adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.		✓ *	
Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older			✓

*Both 0.03% and 0.1% ointment for adults and only 0.03% ointment for children 2 to 15 years of age. (Prescribing Information: ELIDEL, 2014; **EUCRISA, 2016**; PROTOPIC, 2012)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The FDA approval of ELIDEL (pimecrolimus) cream was based on three randomized, double-blind, vehicle-controlled, Phase III studies in patients three months to 17 years of age with mild to moderate atopic dermatitis (N=589) (ELIDEL, 2014). Two of these three trials support the use of ELIDEL cream in patients two years of age and older with mild to moderate atopic dermatitis. Two other identical, six-week, vehicle-controlled, Phase III trials were conducted in pediatric patients two to 17 years of age (N=403). These two studies showed significant clinical response based on physician’s global evaluation for ELIDEL-treated patients compared to patients in the vehicle group (ELIDEL, 2014). These studies are outlined in the manufacturer product labeling.
- The FDA approval of PROTOPIC (tacrolimus) ointment was based on three randomized, double-blind, vehicle-controlled, Phase III studies in patients with moderate to severe atopic dermatitis (PROTOPIC, 2012). One of the studies was conducted in pediatric patients (N=351) ages two to 15 years, and the other two studies were conducted in adult patients (N=632). The primary efficacy endpoint was met by all three studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician’s global evaluation of clinical response in the PROTOPIC group compared to the vehicle group (P<0.001). There was some evidence that PROTOPIC 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy for the two PROTOPIC strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- ELIDEL and PROTOPIC have been directly compared in clinical trials. One trial compared ELIDEL 1% to PROTOPIC 0.03% in patients two to 17 years of age (N=141) and found no difference in the incidence of application site reactions between the two topical immunomodulators in the six week study (Kempers et al, 2004). However, itching was reported at a significantly higher rate in the PROTOPIC group. In two other clinical trials, PROTOPIC 0.1% was compared to ELIDEL in adult patients for six weeks. ELIDEL had a significantly greater improvement in the Eczema

Area Severity Index (EASI) score compared to ELIDEL (Abramovits et al, 2008; Fleischer et al, 2007). The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the PROTOPIC group in both studies (Abramovits et al, 2008; Fleischer et al, 2007). There were no differences in AEs between the groups.

- A meta-analysis of three randomized clinical trials showed that both adults and children in the PROTOPIC-treated group had a significantly greater improvement in EASI score at week six as compared to the ELIDEL group (Paller et al, 2005). The most common adverse effects in all studies were local application site reactions including burning and stinging (Paller et al, 2005).
- A meta-analysis of 25 randomized controlled trials (N=6,897) showed that PROTOPIC 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis (Ashcroft et al, 2005). Additionally, ELIDEL was found to be less effective than potent topical corticosteroids (Ashcroft et al, 2005). Individual clinical trials have reported conflicting results (Bieber et al, 2007; Doss et al, 2009; Doss et al, 2010).
- A meta-analysis and systematic review assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (N=7,378) (El-Batawy et al, 2009). In terms of overall comparison, ELIDEL was found to be more effective than vehicle at three and six weeks. However, a long-term study that was included in this review did not find any difference between these two groups at six and twelve months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (three weeks) than ELIDEL in the treatment of moderate to severe atopic dermatitis. Although this meta-analysis showed that ELIDEL seems to be less effective than topical corticosteroids, ELIDEL would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds. Pooled analysis of PROTOPIC trials showed PROTOPIC was more effective than vehicle (El-Batawy et al, 2009). PROTOPIC, when compared to mild potency topical corticosteroids like hydrocortisone acetate, was more efficacious. However, when compared to moderate potency topical corticosteroids, PROTOPIC 0.03% was significantly less effective than topical corticosteroids, and PROTOPIC 0.1% was equal in effectiveness to the topical corticosteroids. Overall, PROTOPIC was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids (El-Batawy et al, 2009).
- A systematic review of 20 randomized controlled trials (N=6,288) showed that PROTOPIC was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis (Chen et al, 2010). Additionally, ELIDEL was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis. In this review, three trials comparing ELIDEL to PROTOPIC were identified. While two of the trials did find PROTOPIC to be significantly more efficacious, no significant difference was found in the third trial.
- A retrospective cohort evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure to ELIDEL or PROTOPIC was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($P < 0.001$, $P = 0.01$). However, after the exclusion of four cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to PROTOPIC and not ELIDEL ($P < 0.001$, $P = 0.086$) (Hui et al, 2009).
- The safety and efficacy of EUCRISA were demonstrated in two identically designed, randomized, Phase 3, double-blind, vehicle-controlled trials in a total of 1,522 patients with mild-to-moderate atopic dermatitis and $\geq 5\%$ treatable body surface area (BSA) (EUCRISA formulary submission dossier, 2016; Paller et al, 2016). The primary endpoint of success was defined as the proportion of subjects at Day 29 who were clear or almost clear with a ≥ 2 -grade improvement from baseline by the Investigator's Static Global Assessment (ISGA) scale. More patients receiving EUCRISA vs. vehicle achieved the primary endpoint of ISGA success (Study AD-301: 32.8% vs. 25.4%, $P = 0.038$; Study AD-302: 31.4% vs. 18.0%, $P < 0.001$), with a greater percentage achieving clear/almost clear overall (51.7% vs. 40.6%, $P = 0.005$; 48.5% vs. 29.7%, $P < 0.001$). In addition, EUCRISA-treated patients achieved greater ISGA score improvements and improvement in pruritus earlier (both $P < 0.001$). Unpublished data from an open-label safety extension trial of AD-301 and AD-302 (N=517), found that the most commonly AEs observed in $\geq 1\%$ of patients included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%) after 48 weeks of treatment (EUCRISA formulary submission dossier, 2016). Cutaneous AEs, such as application-site atrophy, telangiectasia, and hypopigmentation, did not occur during the study. Overall, 22.2% of patients used 178 concomitant medications designated as rescue medications.
- Treatment guidelines generally agree that a stepwise approach to treatment is needed. Nonpharmacological therapies (ie, lukewarm baths, skin moisturizers, etc) are followed by topical corticosteroids and/or topical calcineurin inhibitors. Low to high potency topical corticosteroids are the standard of care and strength is selected based on severity, duration of treatment, location of exacerbation, and age of patient. ELIDEL and PROTOPIC are topical calcineurin inhibitors that are recommended as second-line therapy in patients who fail or cannot tolerate corticosteroids.

EUCRISA has not yet been added to the guidelines (Eichenfield et al, 2014a; Eichenfield et al, 2014b; Schneider et al, 2013; Sidbury et al, 2014; Tollefson et al, 2014).

SAFETY SUMMARY

ELIDEL and PROTOPIC

- **Boxed warning:** Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
 - Avoid continuous long-term use, in any age group, and limit application to areas of involvement with atopic dermatitis.
 - Both agents are not indicated for use in children less than two years of age. Only PROTOPIC 0.03% ointment is indicated for use in children two to 15 years of age; ELIDEL is indicated for children two years and older and adults.
- **Key Warnings/Precautions:**
 - Do not use on malignant or pre-malignant skin conditions.
 - Resolve bacterial or viral infections at the treatment site.
 - While using avoid exposure to sunlight.
 - Do not use in immunocompromised patients.
- **AEs:** Application site irritation and reactions such as skin burning, itching, redness, and rash. Hypersensitivity reactions can also occur.
- A five-year, open-label, multicenter study evaluated the use of ELIDEL in 2,418 infants compared to topical corticosteroids (Sigurgeirsson et al, 2015). The primary endpoint was safety; the secondary endpoint was long-term efficacy defined as a score of zero to five on the Investigator's Global Assessment (IGA). Topical corticosteroids included low potency such as hydrocortisone 1% or medium potency such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More ELIDEL patients reported bronchitis (P=0.02), infected eczema (P<0.001), impetigo (P=0.045), and nasopharyngitis (P=0.04). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the ELIDEL-treated group. Over the five year period, 88.7% and 92.3% of the ELIDEL- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of ELIDEL- and corticosteroid-treated patients completing the study.

EUCRISA

- **Contraindications:** Known hypersensitivity to crisaborole or any component of the formulation
- **Warnings/precautions:**
 - Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with crisaborole. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, crisaborole should be discontinued immediately and appropriate therapy initiated.
- **Adverse effects:**
 - In pivotal Studies AD-301 and AD-302, 1,012 patients (two to 79 years of age) with mild-to-moderate atopic dermatitis were treated with crisaborole twice daily for four weeks. The AE reported by ≥1% of crisaborole-treated patients (45/1,012 [4%] vs. 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common (<1%) AEs in patients treated with crisaborole included contact urticaria.
 - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study (EUCRISA formulary submission dossier, 2016; Paller et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ELIDEL (pimecrolimus)	Cream: 1% 30, 60 and 100 gram tubes	Apply a thin layer of cream to the affected skin twice daily.	Do not use in children less than two years of age. If signs and symptoms persist beyond six weeks, patients	Patients should stop use when signs and symptoms resolve and instructions on what actions to take

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			<p>should be re-examined by their health care provider to confirm the diagnosis.</p> <p>Continuous long-term use should be avoided, and application should be limited to areas of involvement.</p>	<p>if symptoms recur.</p> <p>Do not use with occlusive dressings. Occlusion may promote systemic exposure. Safety has not been evaluated.</p>
PROTOPIC (tacrolimus)	Ointment: 0.03% and 0.1% 30, 60 and 100 gram tubes	Apply a thin layer of cream to the affected skin twice daily.	<p>Do not use in children less than two years of age.</p> <p>Patients two to 15 years: Use 0.03% ointment twice daily.</p> <p>If signs and symptoms persist beyond six weeks, patients should be re-examined by their health care provider to confirm the diagnosis.</p> <p>Continuous long-term use should be avoided, and application should be limited to areas of involvement.</p>	<p>Do not use with occlusive dressings.</p> <p>Occlusion may promote systemic exposure. Safety has not been evaluated.</p>
EUCRISA (crisaborole)	Ointment: 2% 60 and 100 gram tubes	Apply a thin layer of ointment twice daily to affected areas.	--	EUCRISA is for topical use only and not for ophthalmic, oral, or intravaginal use.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ELIDEL (pimecrolimus)	Clinical studies did not include sufficient numbers of patients aged 65 years and older to assess efficacy and safety.	Do not use in <2 years of age.	Dose adjustment should not be needed because >80% of drug excreted in feces.	nd	Pregnancy Category C* Unknown if excreted in human milk.
PROTOPIC (tacrolimus)	AE profile consistent with younger adults.	<p>Ages 2 to 15 years: Use 0.03% ointment twice daily.</p> <p>Do not use in <2 years of age.</p>	Use caution especially if applying to large body surface areas.	nd	Pregnancy Category C* Unknown if excreted in human milk.
EUCRISA (crisaborole)	Clinical studies did not include sufficient numbers of subjects age 65	Age: ≥2 years: Use ointment twice daily. Safety and	nd	nd	No available data in pregnant women to

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	and over to determine whether they respond differently from younger subjects.	effectiveness in pediatric patients <2 years have not been established.			inform the drug-associated risk for major birth defects and miscarriage. No information available on the presence of EUCRISA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production after topical application of EUCRISA to women who are breastfeeding.

nd=no data

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The two topical calcineurin inhibitors, ELIDEL (pimecrolimus 1% cream) and PROTOPIC (tacrolimus 0.03% and 0.1% ointment), are FDA approved as second-line therapies for the short-term and non-continuous chronic treatment of atopic dermatitis (ELIDEL: mild-to-moderate atopic dermatitis; PROTOPIC: moderate-to-severe atopic dermatitis) in non-immunocompromised adults and children (ELIDEL: ≥ 2 years of age; PROTOPIC: 0.03% and 0.1% in adults, 0.03% in patients 2 to 15 years of age) who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. The FDA approved another agent to the atopic dermatitis armamentarium with the approval of EUCRISA (crisaborole) ointment for the topical treatment of mild-to-moderate atopic dermatitis in patients ≥ 2 years of age.
- The topical anti-inflammatory agents have a variety of mechanisms in which therapy is administered; however, the exact mechanism of action in atopic dermatitis is not known. ELIDEL and PROTOPIC inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12). PROTOPIC and ELIDEL provide immunosuppression via inhibition of T-cell activation, which is theorized to be the primary mode of inflammation reduction in atopic dermatitis. EUCRISA is a non-steroidal treatment option with a novel mechanism of action. In patients with atopic dermatitis, PDE-4 activity increases circulating inflammatory cells resulting in increased cytokine production. It is believed that EUCRISA enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cAMP, thereby suppressing the release of cytokines (Clinical Pharmacology, 2017; Paller et al, 2016).
- Several head-to-head studies comparing the efficacy of these two calcineurin inhibitors have been conducted. A meta-analysis of three studies directly comparing ELIDEL and PROTOPIC evaluated the change from baseline in EASI score at week six of treatment (Paller et al, 2005). Results favored treatment with PROTOPIC, and adverse effects between the groups were similar. Another meta-analysis evaluating ELIDEL, PROTOPIC, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in EASI score in patients using

PROTOPIC compared to patients using ELIDEL in addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease, though only one direct comparison of these agents was represented in the meta-analysis (Ashcroft et al, 2005). A meta-analysis and systematic review showed ELIDEL was found to be more effective than vehicle (El-Batawy et al, 2009). A long-term study did not find any difference between these two groups at six and 12 months. A pooled analysis of PROTOPIC trials showed PROTOPIC was more effective than vehicle. PROTOPIC was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids (El-Batawy et al, 2009).

- Concerns regarding the long-term safety of the topical calcineurin inhibitors have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the potential risk of cancer of these two products to healthcare providers and patients. The FDA has advised that ELIDEL and PROTOPIC be used only as labeled and asked providers and patients to consider these agents only as second-line therapies; new labeling was approved in early 2006 (FDA press release, 2006). Topical calcineurin inhibitors may be associated with immunosuppression or malignancy.
- EUCRISA demonstrated short-term efficacy over vehicle ointment in two identically designed, 28-day, Phase 3, randomized, double-blind trials; more patients receiving EUCRISA vs. vehicle achieved the primary endpoint of ISGA success, with a greater percentage of EUCRISA-treated patients achieving clear/almost clear overall. Over 28 days, application site pain was the most commonly reported AE. Unpublished data gleaned from the 48-week, long-term study revealed no significant safety signals.
- Current guidelines for the treatment of atopic dermatitis recommend the use of topical corticosteroids as first-line treatment and recommend the use of topical ELIDEL or PROTOPIC in those patients intolerant or unresponsive to corticosteroids or in whom corticosteroids are contraindicated or when corticosteroid-sparing measures may be desired. EUCRISA has not yet been added to the guidelines (Eichenfield et al, 2014a; Eichenfield et al, 2014b; Schneider et al, 2013; Sidbury et al, 2014; Tollefson et al, 2014).

REFERENCES

- Abramovits W, Fleischer Jr AB, Jaracz E, et al. Adult patients with moderate atopic dermatitis: Tacrolimus ointment versus pimecrolimus cream. *J Drugs Dermatol*. 2008;12(7):1153-8.
- Ashcroft D, Dimmock P, Garside R, et al. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. *BMJ*. 2005;330(7490):516-24.
- Berke R, Singh A, Guralnick M. Atopic dermatitis: an overview. *Am Fam Physician*. 2012;86(1):35-42.
- Bieber T, Vick K, Fölster-Holst R, et al. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. *Allergy*. 2007;62(2):184-9.
- Castro AP. Calcineurin inhibitors in the treatment of allergic dermatitis. *J Pediatr (Rio J)*. 2006;82(5):166-72.
- Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. *J Dermatolog Treat*. 2010;21:144-56.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: <http://www.clinicalpharmacology.com>. Accessed January 18, 2017.
- Doss N, Kamoun M-R, Dubertret L, et al. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate to severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs. fluticasone 0.005% ointment. *Pediatr Allergy Immunol*. 2010;21:321-329.
- Doss N, Reitamo S, Dubertret L, et al. Superiority of tacrolimus 0.1% ointment compared with fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. *Br J Dermatol*. 2009;161:427-34.
- DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed January 25, 2017.
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014b;71:116-32.
- Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014a;70(2):338-51.
- El-Batawy MM, Bosseila MA, Mashaly HM, et al. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Science*. 2009;54(2):76-87.
- ELIDEL prescribing information. Valeant Pharmaceuticals North America, LLC. Bridgewater, NJ. August 2014.
- EUCRISA formulary submission dossier. Pfizer, Inc. New York, NY. December 2016.
- EUCRISA prescribing information. Anacor Pharmaceuticals, Inc. Palo Alto, CA. December 2016.
- FDA presentation. Dermatologic and Ophthalmic Drugs Advisory Committee Meeting: Atopic Dermatitis. March 2015. <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm439354.pdf>. Accessed January 25, 2017.
- FDA press release. FDA approves updated labeling with boxed warning and medication guide for two eczema drugs, Elidel and Protopic. January 19, 2006. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108580.htm>. Accessed January 18, 2017.
- Fleischer Jr AB, Abramovits W, Breneman D, et al. Tacrolimus ointment is more effective than pimecrolimus cream in adult patients with moderate to very severe atopic dermatitis. *Journal of Dermatological Treatment*. 2007;18:151-7.
- Hui RL, Lide W, Chan J, et al. Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother*. 2009;43:1956-63.
- Kempers S, Boguniewicz M, Carter E, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *J Am Acad Dermatol*. 2004;51(4):515-25.

- Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics*. 2008;122(4):812-24.
- Paller AS, Lebwohl M, Fleischer AB Jr, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. *J Am Acad Dermatol*. 2005;52(5):810-22.
- Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. 2016;75(3):494-503.e4.
- PROTOPIC prescribing information. Astellas Pharma US, Inc. Northbrook, IL. May 2012.
- Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131(2):295-9.e1-27.
- Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Derm*. 2014;71:327-49.
- Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics*. 2015;135(4):597-606.
- Tollefson MM, Bruckner AL; Section on Dermatology. Atopic dermatitis: skin-directed management. *Pediatrics*. 2014;134:e1735-e1744.
- Zane LT, Chanda S, Jarnagin K, et al. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy*. 2016;8(8):853-66.

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