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, Food and Drug Administration [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 5 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 *(Weston & Howe 2018)*. 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 (eg, diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (eg, 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 1 or more times daily for the treatment of acute flares, as well as intermittently 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). 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), which is theorized to be the primary mode of inflammation reduction in atopic dermatitis *(Clinical Pharmacology 2019)*. 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 that they are aware of this concern. The labeling clarifies that these medications are recommended for use as second-line treatments and are not recommended in children under 2 years of

age. A definitive causal link between the topical immunosuppressants and the incidence of malignancy has not been established.

- Eucrisa (crisaborole) is a non-steroidal, topical treatment for atopic dermatitis that works by way of phosphodiesterase (PDE)-4 inhibition. 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)*. Eucrisa 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 Eucrisa 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; Macrolide Immunosuppressants - Topical

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Elidel (pimecrolimus)	✔
Protopic (tacrolimus)	✔
Eucrisa (crisaborole)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

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 2017, Eucrisa 2017, Protopic 2018*)

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

CLINICAL EFFICACY SUMMARY

Elidel and Protopic

- The FDA approval of Elidel cream was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients 3 months to 17 years of age with mild to moderate atopic dermatitis (N = 589). Two of these 3 trials support the use of Elidel cream in patients 2 years of age and older with mild to moderate atopic dermatitis. Two other identical, 6-

week, vehicle-controlled, Phase III trials were conducted in pediatric patients 2 to 17 years of age (N = 403). These studies showed significant clinical response based on physician's global evaluation for Elidel-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.

- The FDA approval of Protopic ointment was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients with moderate to severe atopic dermatitis. One of the studies was conducted in pediatric patients (N = 351) ages 2 to 15 years, and the other 2 studies were conducted in adult patients (N = 632). The primary efficacy endpoint was met by all 3 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 between the 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 2 to 17 years of age (N = 141) and found no difference in the incidence of application site reactions between the topical immunomodulators in the 6-week study *(Kempers et al 2004)*. However, itching was reported at a significantly higher rate in the Protopic group. In 2 other clinical trials, Protopic 0.1% was compared to Elidel in adult patients over 6 weeks. Patients treated with Protopic had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with 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 (BSA) 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 3 randomized clinical trials showed that both adults and children in the Protopic-treated group had a significantly greater improvement in EASI score at week 6 as compared to the Elidel group *(Paller et al 2005)*. The most common AEs 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 = 6897) 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 = 7378) *(El-Batawy et al 2009)*. In terms of overall comparison, Elidel was found to be more effective than vehicle at 3 and 6 weeks. However, a long-term study that was included in this review did not find any difference between these 2 groups at 6 and 12 months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (3 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 demonstrated that Protopic was more effective than vehicle *(El-Batawy et al 2009)*. When compared to mild potency topical corticosteroids like hydrocortisone acetate, Protopic 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 = 6288) 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, 3 trials comparing Elidel to Protopic were identified. While 2 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 ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of 4 cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to Protopic and not Elidel ($p < 0.001$, $p = 0.086$, respectively) *(Hui et al 2009)*.

Eucrisa

- The safety and efficacy of Eucrisa were demonstrated in 2 identically designed, randomized, Phase III, double-blind, vehicle-controlled trials in a total of 1522 patients with mild to moderate atopic dermatitis and ≥ 5% treatable 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).
  - An open-label extension trial of AD-301 and AD-302 evaluated the safety of Eucrisa in 517 patients with mild to moderate atopic dermatitis for 48 weeks. Patients underwent an average of 6 treatment periods and used an average of 133 grams of ointment/month. Most treatment-emergent AEs were mild (51.2%) or moderate (44.6%) and were considered unrelated to treatment with Eucrisa (93.1%). The most commonly observed AEs (≥ 1% of patients) included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%). Most patients (77.8%) did not require rescue medications. Children and adolescents made up 48% of those patients that initiated rescue therapies (*Eichenfield et al 2017*).

CLINICAL GUIDELINES

- 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 the 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 (eg, 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 2 years of age. Only Protopic 0.03% ointment is indicated for use in children 2 to 15 years of age; Elidel is indicated for children 2 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 5-year, open-label, multicenter study evaluated the use of Elidel in 2418 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 0 to 5 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 5-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 Eucrisa or any component of the formulation

- Warnings/precautions:
  - Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with Eucrisa. 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, Eucrisa should be discontinued immediately and appropriate therapy initiated.
- AEs:
  - In pivotal studies AD-301 and AD-302, 1012 patients (2 to 79 years of age) with mild to moderate atopic dermatitis were treated with Eucrisa twice daily for 4 weeks. The AE reported by ≥ 1% of Eucrisa-treated patients (45/1012 [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 Eucrisa 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	Available Formulations	Route	Usual Recommended Frequency	Comments
Elidel (pimecrolimus)	Cream (1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Protopic (tacrolimus)	Ointment (0.03% and 0.1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Eucrisa (crisaborole)	Ointment (2%)	Topical	Two times daily (applied as a thin layer)	Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

See the current prescribing information for full details

CONCLUSION

- The topical calcineurin inhibitors, Elidel (pimecrolimus 1% cream) and Protopic (tacrolimus 0.03% and 0.1% ointment), are indicated 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 added 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 work by way of several mechanisms of action; 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 2019, Paller et al 2016)*.
- Several head-to-head studies comparing the efficacy of the calcineurin inhibitors have been conducted. A meta-analysis of 3 studies directly comparing Elidel and Protopic evaluated the change from baseline in EASI score at week 6 of treatment *(Paller et al 2005)*. Results favored treatment with Protopic, and AEs 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 *(Ashcroft et al 2005)*. 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 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 2 identically designed, 28-day, Phase III, 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.; 2018. Available at: http://www.clinicalpharmacology.com. Accessed February 22, 2019.

- 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: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 22, 2019.
- Eichenfield LF, Call RS, Forsha DW, et al. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. *J Am Acad Dermatol*. 2017;77(4):641-649.e5.
- 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 [package insert], Bridgewater, NJ: Valeant Pharmaceuticals North America, LLC; December 2017.
- Eucrisa [package insert], New York, NY: Pfizer, Inc.; October 2017.
- Eucrisa [product dossier], New York, NY: Pfizer, Inc.; December 2018.
- FDA presentation. Dermatologic and Ophthalmic Drugs Advisory Committee Meeting: Atopic Dermatitis. March 2015. https://wayback.archive-it.org/7993/20170114003750/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM439354.pdf. Accessed February 25, 2019.
- 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://wayback.archive-it.org/7993/20170406045051/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm153941.htm. Accessed February 25, 2019.
- 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. *J Dermatolog Treat*. 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.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 26, 2019.
- 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 [package insert], Seven Giralda Farms, Madison, NJ: LEO Pharma Inc.; October 2018.
- 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.
- Weston WL, Howe W. Atopic dermatitis (eczema): pathogenesis, clinical manifestations, and diagnosis. UpToDate Web site. https://www.uptodate.com/contents/search. Updated February 19, 2019. Accessed February 27, 2019.
- 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.

Publication Date: 11th March 2019