Atopic Dermatitis (Elidel [pimecrolimus], Eucrisa, Protopic [tacrolimus]) Step Therapy Program Summary

This program applies to Medicaid.

The BCBS MN Step Therapy Supplement also applies to this program for Medicaid.

FDA APPROVED INDICATIONS[1-3]

Agents	Indication
Elidel® (pimecrolimus) Cream 1%[a]	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis (AD) 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.
Eucrisa™ (crisaborole) Ointment 2%	Topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older.
Protopic® (tacrolimus) Ointment 0.03%, 0.1%[a]	Second-line therapy for short-term and non-continuous chronic moderate to severe AD in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable. (0.03% and 0.1% for adults; 0.03% only for children ages 2-15).

[a] generic available

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that follows a relapsing course. AD occurs most frequently in children, but also affects many adults. Topical agents are the mainstay of AD therapy, with topical corticosteroids being the .first-line treatment for mild-to-severe dermatitis in all skin regions.(4,8) Continuous application of topical corticosteroids for long periods of time should be avoided to limit the occurrence of negative changes. Cutaneous side effects include purpura, telangiectasia, striae, focal hypertrichosis, and acneiform or rosacea-like eruptions. Of greatest concern is skin atrophy, especially through use of higher-potency agents, use on thinner skin, and older patient age.[4]

Topical calcineurin inhibitors (TCI) such as topical pimecrolimus and topical tacrolimus, are approved as second-line agents for the short-term and noncontinuous chronic treatment of AD in non-immunocompromised individuals who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable. TCIs do not carry the risk of skin atrophy with little effect on collagen synthesis and skin thickness. Use of TCIs have been studied in long-term studies to 12 months and have shown to reduce the need for topical corticosteroid use. TCIs may be preferable over corticosteroids in certain situations:

- Recalcitrance to steroids
- Use in sensitive areas (e.g., face, anogenital, skin folds)
- Steroid-induced atrophy
- Long-term uninterrupted topical steroid use[4]

Crisaborole 2% ointment is a topical nonsteroidal treatment for mild to moderate AD. It is well tolerated by most patients. It has shown superiority to emollient treatment alone. There is no data on long-term effectiveness because studies lasted for only 28 days. Crisaborole has not been compared directly with other treatments for atopic dermatitis.[6]

Psoriasis
The 2023 American Academy of Dermatology (AAD) Guidelines state that although corticosteroids remain the mainstay of topical therapy for psoriasis, the most potent and efficacious of these agents are approved for only short-term treatment (2-4 weeks). Consideration should be given to use of medications that have been developed to either replace potent topical corticosteroids in longer term treatment, or to be used in combination to provide greater efficacy with lesser exposure to steroid containing agents. Pursuit of these goals with agents including vitamin D analogues, topical retinoids, and TCIs has shown benefit.[7] Although tacrolimus and pimecrolimus have not been found beneficial for plaque psoriasis, these agents have shown some benefit for intertriginous and facial psoriasis.[8]

A review (2013) on treatment of psoriasis suggests tacrolimus and pimecrolimus generally improve symptoms with less skin atrophy than topical corticosteroids, and are considered first-line treatments for facial and flexural psoriasis. Tacrolimus is superior to pimecrolimus in reducing psoriasis symptoms.[7]

Efficacy
Protopic/Elidel
A meta-analysis (2016; 12 RCTs) compared calcineurin inhibitors (n=3492) vs. corticosteroids (n=3462) in treatment of atopic dermatitis. Calcineurin inhibitors and corticosteroids had similar rates of improvement of dermatitis (81% vs. 71%; p=0.01) and treatment success (72% vs. 68%; p=0.04). Calcineurin inhibitors were associated with higher costs and had more adverse events (74% vs. 64%; p=0.02) including a higher rate of skin burning (30% vs. 9%; p less than 0.00001) and pruritus (12% vs. 8%; p less than 0.00001). There were no differences in atrophy, skin infections, or adverse events that were serious or required discontinuation of therapy.(5)

Though comparative data are limited in regard to high (i.e., betamethasone dipropionate 0.05%) and very high (clobetasol 0.05%) potency steroids, they appear to be more effective than pimecrolimus 1% cream. The comparative data with medium potency steroids are less clear. While they do appear to be more effective than pimecrolimus in terms of change in severity and itch reduction, not all studies reached significance. There does not seem to be a difference in infection risk between pimecrolimus and medium potency TCS. Although tacrolimus 0.1% ointment appears to be more effective than pimecrolimus 1% cream, it may be similarly as effective as medium potency TCS.(8)

Eucrisa
Four randomized trials comparing crisaborole ointment to vehicle in adult AD were included for analysis. Crisaborole ointment use led to a small but significant improvement in dermatitis in all 4 studies. Across 2 identical trials, 1016 AD patients (aged 2-79 years) were randomized to crisaborole 2% ointment twice daily and 506 to vehicle for 28 days.66 On day 29, significantly more crisaborole-treated patients achieved Investigator's Static Global Assessment success (clear or almost clear with 2-grade or greater improvement

from baseline): 326 (32.1%) vs 110 (21.7%) (RR: 1.80, 95% CI: 1.48-2.18, P < .0001). Crisaborole has also demonstrated efficacy in the pruritus of AD in 3 studies.

In 40 adults with AD, 2 AD lesions of identical severity were randomized to crisaborole 2% ointment or vehicle twice daily or 14 days. The mean change from baseline in lesion itch NRS at day 15 was greater for crisaborole-treated than vehicle-treated lesions (−3.9 vs −2.0, P < .0001). Crisaborole appears to have a favorable safety profile (i.e., small percentage of patients with application burning, stinging, and/or pain) and discontinuation rate comparable to placebo. Current 2023 AAD guidelines strongly recommends its use for mild-to-moderate AD, based on high certainty evidence.(8)

Safety

Elidel is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream. Elidel also carries the following black box warning:[2]

- Long-term safety of topical calcineurin inhibitors has not been established
- Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including Elidel Cream, 1%. Therefore:
    - Continuous long-term use of topical calcineurin inhibitors, including Elidel Cream, 1%, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis
    - Elidel Cream, 1% is not indicated for use in children less than 2 years of age

Eucrisa is contraindicated in individuals with known hypersensitivity to crisaborole or any component of the formulation.[3]

Protopic is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the ointment. Protopic also carries the following black box warning:[1]

- Long-term safety of topical calcineurin inhibitors has not been established
- Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including Protopic Ointment. Therefore:
    - Continuous long-term use of topical calcineurin inhibitors, including Protopic Ointment, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
    - Protopic Ointment is not indicated for use in children less than 2 years of age. Only 0.03% Protopic Ointment is indicated for use in children 2-15 years of age.

References

1. Protopic prescribing information. LEO Pharma Inc. April 2019.
2. Elidel prescribing information. Bausch Health US, LLC. September 2020.
3. Eucrisa prescribing information. Pfizer, Inc. April 2023.
4. Eichenfield LF, Tom WL, Berger TG, et. al. Guidelines of care for the management of atopic dermatitis. J Am Acad Dermatol. July 2014;71(1) 116-132. https://www.jaad.org/article/S0190-9622(14)01257-2/fulltext
5. Broeders JA, Ali UA, Fischer, G. Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience. Journal of the American Academy of Dermatology. 2016;75(2):410-419.e3.
6. Castelli G and Schaffer M. Crisaborole (Eucrisa) for Mild to Moderate Atopic Dermatitis. Am Fam Physician. 2018 Sep 15;98(6):379-380. https://www.aafp.org/afp/2018/0915/p379.html

7. Weigle N, Mc Bane S. Psoriasis. Am Fam Physician. 2013;87(9):626-633. https://www.aafp.org/afp/2013/0501/p626.html
8. Sidbury MD, MPH, Robert, Eichenfield MD, Lawrence, et. al. Guidelines of care for the management of atopic dermatitis in adults with topical therapies. J Am Acad Dermatol. July 2023;89(1) E1-E20. https://www.jaad.org/article/S0190-9622(23)00004-X/fulltext

Atopic Dermatitis (Elidel [pimecrolimus], Eucrisa, Protopic [tacrolimus]) Step Therapy

TARGET AGENTS
Elidel® (pimecrolimus cream)[a]
Eucrisa™ (crisaborole ointment)
Protopic® (tacrolimus ointment)[a]
[a] generic available, targeted in the step therapy program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target Agents will be approved when ONE of the following is met:

1. The requested agent is for use on the face (including eyelids), neck, or skin folds (e.g., groin, armpit/under arm)
   OR
2. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   A. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   C. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR
3. The patient's medication history includes use of any topical corticosteroid or topical corticosteroid combination preparation in the past 999 days
   OR
4. The prescriber has stated that the patient has tried a topical corticosteroid or topical corticosteroid combination preparation AND ONE of the following:
   A. The topical corticosteroid or topical corticosteroid combination preparation was discontinued due to lack of effectiveness or an adverse event
      OR
   B. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over a topical corticosteroid or topical corticosteroid combination preparation

   OR
5. The patient has an intolerance or hypersensitivity to a topical corticosteroid or topical corticosteroid combination preparations
   OR
6. The patient has an FDA labeled contraindication to ALL topical corticosteroids and topical corticosteroid combination preparations
   OR
7. The prescriber has provided documentation that ALL topical corticosteroids and topical corticosteroid combination preparations cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: 12 months