## FDA APPROVED INDICATIONS AND DOSAGE\(^1,2,11\)

<table>
<thead>
<tr>
<th>Available Products</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elidel</strong> (pimecrolimus Cream 1%)</td>
<td>Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis (AD) in nonimmunocompromised 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.</td>
<td>Apply a thin layer (minimum amount to control signs and symptoms of AD) to affected skin twice daily.</td>
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<tr>
<td><strong>Eucrisa</strong> (criaborole ointment 2%)</td>
<td>Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.</td>
<td>Apply a thin layer twice daily to affected areas</td>
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<tr>
<td><strong>Protopic</strong> (^a) (tacrolimus Ointment 0.03%, 0.1%)</td>
<td>Second-line therapy for short-term and noncontinuous chronic moderate to severe AD in nonimmunocompromised 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).</td>
<td>Apply a thin layer (minimum amount to control signs and symptoms of AD) to affected skin twice daily.</td>
</tr>
</tbody>
</table>

AD=atopic dermatitis  
\(^a\) generic available

## CLINICAL RATIONALE

### Atopic Dermatitis

Management of atopic dermatitis [AD] (also known as atopic eczema) consists of relieving symptoms and lengthening time between flare-ups. Regular, liberal use of emollients is recommended. The primary pharmacologic treatment is topical corticosteroids.\(^4\)

Recommendations for management of AD in all patients include liberal application of emollients to the entire body whether or not active symptoms are present. Topical corticosteroids are considered first-line treatment for AD flare-ups. After acute symptoms resolve, patients return to emollient use only. However, in recurrent moderate/severe AD, a maintenance regimen (e.g., twice-weekly corticosteroid application, along with an emollient) may be considered. The principal complication of prolonged application of topical corticosteroids, especially those of higher potency, is skin atrophy. Other local complications include telangiectasia, striae, hypopigmentation, and acne.\(^4\)

Pimecrolimus and tacrolimus are topical calcineurin inhibitors (TCIs) recommended as second-line treatment for persons with moderate to severe AD and who are at risk of
atrophy from topical corticosteroids. Topical steroid and TCI classes of agents act as immunomodulators, inhibiting the associated inflammatory response, through distinct mechanisms of actions.\textsuperscript{4,6} Topical corticosteroids provide effective flare control, and topical emollients may be used as daily maintenance for the xerosis associated with AD.

TCIs are reserved for short-term or intermittent long-term therapy in persons with moderate/severe AD, when there is concern that ongoing use of topical corticosteroids is causing adverse effects, such as atrophy. Because TCIs do not lead to skin atrophy, they are particularly useful for areas of thinner skin on the face, neck, and skin folds. Another benefit is that they do not demonstrate tachyphylaxis.\textsuperscript{4}

In studies comparing effectiveness, tacrolimus has been at least slightly more effective than pimecrolimus in the treatment of moderate/severe atopic dermatitis. Pimecrolimus is considered weaker than moderate or potent corticosteroids, but there have not been good studies comparing it with mild corticosteroids. Tacrolimus 0.1\% has been shown to be at least as effective as a potent corticosteroid in adults, and more effective (at 0.1\% or 0.03\%) than a weak corticosteroid in children.\textsuperscript{4}

The FDA issued a boxed warning for TCIs regarding reports of a possible link to lymphomas and skin malignancies. There also is concern about the possibility that these agents can cause systemic immunosuppression.\textsuperscript{4}

Long-term safety of TCIs has not been established. Although a causal relationship has not been determined, rare cases of malignancy have been reported in patients treated with TCIs. Therefore, continuous long-term use of TCIs in any age group should be avoided, and application should be limited to areas of AD involvement. These products should not be used in immunocompromised adults and children. If signs and symptoms do not improve within 6 weeks, patients should be re-examined by their healthcare provider and their diagnosis confirmed. The safety of these products has not been established beyond one year of non-continuous use. The safety of use under occlusion, which may promote systemic exposure, has not been evaluated. These products should not be used with occlusive dressings.\textsuperscript{1,2}

An evidence update (2013) suggested epidemiologic and clinical data fail to demonstrate a causal relationship between TCI use and malignancy or lymphoma risk, especially for pimecrolimus cream. The observed number of malignancies and lymphomas observed both in post-marketing surveillance and reported to the FDA using its adverse events reporting system is much lower among TCI-exposed patients than the expected number for the general population. Among children enrolled in post-marketing pediatric registry studies for both tacrolimus and pimecrolimus followed for up to 5.5 years [10,724 patient-years (PY)] or 6.5 years (16,219 PY)], respectively, the observed number of malignancies and lymphomas is very low and similar to the number expected for a sample of similar size in the general population.\textsuperscript{7}

Updated American Academy of Dermatology (2014) recommendations for the use of TCIs include the following.\textsuperscript{9}

- TCIs are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with AD, and are particularly useful in selected clinical situations. TCIs may be preferable to topical steroids in the following situations: recalcitrance to steroids, sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use.
- TCIs are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of AD.
For patients with AD <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended.

Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with AD using topical corticosteroids should be considered to minimize TCI application site reactions. Patients with AD should be counseled about the possibility of these reactions.

Proactive, intermittent use of TCIs as maintenance therapy (2-3 times/week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids, and is more effective than the use of emollients alone. The concomitant use of a topical corticosteroid with a TCI may be recommended for the treatment of AD.

No consistent increases in prevalence of cutaneous viral infections have been seen with continuous or intermittent use of TCIs for up to 5 years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time. Clinicians should be aware of the black-box warning on the use of TCIs for patients with AD and discuss as warranted.

Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with AD who are applying these agents is not recommended at this time.

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<0.00001) and pruritus (12% vs. 8%; p<0.00001). There were no differences in atrophy, skin infections, or adverse events that were serious or required discontinuation of therapy.10

Psoriasis (off-label use)
The American Academy of Dermatology Guidelines (2009-2011) 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.5 Although tacrolimus and pimecrolimus [off-label] have not been found beneficial for plaque psoriasis, these agents have shown some benefit for intertriginous and facial psoriasis.3,5

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.8

For additional clinical information see the Prime Therapeutics Formulary Chapter 14.5Y: Topical Immunomodulators.

References
Atopic Dermatitis (Elidel®, Eucrisa™, Protopic®, tacrolimus ointment) Step Therapy

OBJECTIVE
The intent of the Atopic Dermatitis Step Therapy program is to encourage the use of topical corticosteroid or topical corticosteroid combination preparations prior to, or concurrent with, Elidel, Eucrisa, Protopic, tacrolimus ointment. The program allows use of Elidel, Eucrisa, Protopic, tacrolimus ointment when the patient has had a trial, documented intolerance, FDA labeled contraindication, or hypersensitivity to a topical corticosteroid or topical corticosteroid combination preparation, or when the requested agent is for use on the face, neck or skin folds. The program allows continuation of therapy when there is documentation that the patient is receiving the requested agent. Requests for Elidel, Eucrisa, Protopic, tacrolimus ointment will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS
- Elidel® (pimecrolimus cream)
- Eucrisa™ (crisaborole ointment)
- Protopic® (tacrolimus ointment)*
  *generic available, targeted in criteria

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target agents will be approved when ONE of the following is met:
1. The patient is requesting the requested agent for use on the face (including eyelids), neck, or skin folds (e.g. groin, armpit/under arm)
   OR
2. The patient’s medication history includes use of any topical corticosteroid or topical corticosteroid combination preparation in the past 120 days
   OR
3. There is documentation that the patient is currently using the requested agent
   OR
4. The prescriber states the patient is currently using the requested agent AND is at risk if therapy is changed
   OR
5. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to topical corticosteroids or topical corticosteroid combination preparations

Length of approval: 12 months