

# Pimecrolimus cream (Elidel) for facial atopic dermatitis

(pi-me-KRO-ly-mus)

## Summary

- Pimecrolimus 1% cream is PBS listed for treating facial atopic dermatitis in adults and children when topical corticosteroids are contraindicated or fail to control the disease with intermittent use.
- Pimecrolimus should be used intermittently for short-term treatment of signs and symptoms of atopic dermatitis.
- The efficacy of topical pimecrolimus relative to topical corticosteroids is uncertain, but the only published head-to-head comparison showed corticosteroids to be superior in adults.
- Pimecrolimus is an immunosuppressant, and long-term safety (> 2 years) is not established. There have been cases of skin cancers and lymphoma in people treated with topical pimecrolimus, but causality has not been established.
- For infants 3 months to 2 years of age there are additional safety concerns; apply pimecrolimus cream to the smallest practicable surface area and for a maximum of 3 weeks per episode of dermatitis.

## PBS listing

### Authority required

Listing 1. Treating facial (including eyelid) atopic dermatitis in patients aged over 3 months when topical corticosteroids are contraindicated.\*

Listing 2. Second-line use for facial atopic dermatitis, if intermittent topical corticosteroids fail to control the dermatitis. Three months or more must have elapsed since the initial diagnosis. This listing allows for periods of up to 3 weeks intermittent treatment with pimecrolimus, while topical corticosteroid use is interrupted.

Treatment failure is defined as:

- failure of the skin to clear despite at least 2 weeks of hydrocortisone 1% applied daily or
- failure of the skin to clear despite at least 1 week of a moderate or potent topical corticosteroid applied daily or
- significant flare within 48 hours of stopping hydrocortisone 1%, after at least 2 weeks of daily use (occurring on at least 2 consecutive occasions) or

\* Contraindications are: specific allergy to topical corticosteroids; dermal or epidermal atrophy; cataracts; raised intraocular pressure or glaucoma; rosacea; or peri-oral or peri-orbital dermatitis.

- significant flare within 48 hours of stopping a moderate or potent topical corticosteroid, after at least 1 week of daily use (occurring on at least 2 consecutive occasions).

For both listings the maximum quantity is 1 tube with 1 repeat.

NOTE: No applications for increased maximum quantities or repeats will be authorised. Only one application will be authorised per 6 months, per patient.<sup>1</sup>

## Reason for PBS listing

In November 2004 the Pharmaceutical Benefits Advisory Committee (PBAC) recommended a listing for topical pimecrolimus for children only.<sup>2</sup> The PBAC concluded that treatment was more cost effective in children than in adults.<sup>3</sup>

In July 2006 the PBAC recommended that the authority-required listing of topical pimecrolimus be extended to include adults.<sup>1</sup> The PBAC found that the efficacy and cost effectiveness was acceptable in adults under the authority restrictions (i.e. when topical corticosteroids are inappropriate), based on the results of a new study.<sup>4</sup>

Topical pimecrolimus reduced the symptoms of atopic dermatitis in placebo-controlled trials.<sup>5</sup> However, it is more expensive than topical corticosteroids, and limited comparative evidence suggests it is less efficacious (see Place in therapy).

The PBAC only considered the cost effectiveness of pimecrolimus in patients for whom topical corticosteroids are ill-advised or fail to control dermatitis with intermittent use.<sup>3</sup>

The maximum quantity of four 15 g tubes per year was considered by the PBAC to be adequate for effective intermittent treatment for most patients.<sup>3,4</sup> This limit is intended to prevent more liberal usage, for example, on skin areas other than the face or, for Listing 2, continued use beyond 3 weeks.<sup>3</sup>

Patients may use more pimecrolimus cream under Listing 1 than under Listing 2, as the length of treatment is not restricted to 3 weeks per dermatitis episode.<sup>3</sup> Nonetheless, the same annual limit on quantities applies to both listings.

## Place in therapy

Topical corticosteroids are the standard therapy for dermatitis that is not resolved by removal of trigger factors and use of emollients. For the face or flexures, a mild corticosteroid is generally used. Topical pimecrolimus is an alternative to topical corticosteroids, but a general advantage over the standard treatment in safety or efficacy has not been established. For patients for whom the adverse effects and limitations of corticosteroids are a problem, pimecrolimus may be useful. For patients without contraindications, topical corticosteroids of the appropriate strength, used for the recommended duration, remain first line.

### Minimise dermatitis trigger factors and encourage regular use of emollients

Managing dermatitis should always include non-drug preventive measures.

Minimise exposure to trigger factors that cause or exacerbate dermatitis. This includes eliminating soaps, shampoos and bubble baths; avoiding skin contact with woollen or acrylic fabric; minimising dust exposure; avoiding contact with sand; and washing immediately after swimming in a chlorinated pool.<sup>6</sup>

Consider allergy assessment in severe or hard-to-control dermatitis; if a particular allergen is suspected; if the dermatitis has an urticarial component; or if the dermatitis is distributed on exposed areas.<sup>6</sup>

**Table 1. Emollient strength and properties<sup>6</sup>**

Emollient type	Strength and properties
Sorbolene cream with glycerol 10%	Medium strength (greasiness), inexpensive and readily available, sticky, may cause stinging
Wool alcohols ointment	Greasy, useful in severe xerosis, rarely stings, sticky feel
Emulsifying ointment	Greasy, good patient acceptance, may sting, vary strength by adding water
Aqueous cream	Medium strength, pleasant feel, rarely stings, vary strength by mixing with white soft paraffin, liquid paraffin, peanut or olive oils
White soft paraffin	Very greasy, inexpensive, readily available, rarely stings, vary strength with aqueous cream or liquid paraffin

Dry skin is a major factor in atopic dermatitis and can be controlled with regular use of emollients. Apply an emollient at least once daily, and 2–3 times daily for severely dry skin. Children should use a dispersible bath oil.<sup>6</sup> See Table 1 for a list of emollients and their properties.

### Pimecrolimus may be useful in atopic dermatitis when topical corticosteroids are specifically contraindicated

Topical corticosteroids are contraindicated in a range of conditions, as specified in the PBS listing. These conditions may result from adverse reactions to topical corticosteroids. Pimecrolimus is available on the PBS for facial atopic dermatitis when topical corticosteroids are contraindicated.

There has only been one clinical trial of pimecrolimus specifically involving people for whom topical corticosteroids are contraindicated.<sup>7</sup> Without widespread clinical experience, pimecrolimus has an uncertain place in atopic dermatitis when rosacea, peri-oral or peri-orbital dermatitis is present. Peri-oral and peri-orbital dermatitis are rosacea-like and are associated with use of topical corticosteroids. However, there are

case reports of rosaceaform dermatitis after treatment with topical pimecrolimus.<sup>8-10</sup>

Treat each episode of atopic dermatitis with pimecrolimus for a maximum of 6 weeks (3 weeks for infants)<sup>11</sup>, although continuing treatment beyond 3 weeks probably provides little added benefit. A randomised controlled trial found similar median changes in atopic dermatitis severity at 3 weeks and at 6 weeks after starting treatment with pimecrolimus.<sup>12</sup>

### When topical corticosteroids used intermittently fail to control atopic dermatitis, pimecrolimus is an alternative

Pimecrolimus is a second-line choice.<sup>13,14</sup> It is TGA approved for first-line use to treat atopic dermatitis, but a general advantage over topical corticosteroids in safety or efficacy has not been established.<sup>13,14</sup> The PBS listing allows for second-line use of pimecrolimus for up to 3 weeks at a time for facial atopic dermatitis<sup>2</sup>, presumably with subsequent resumption of topical corticosteroids as needed. Use on all other areas of the body is also TGA approved, but not subsidised by the PBS.

Evidence from overseas is that most atopic dermatitis is well controlled with topical corticosteroids<sup>15</sup>, but daily use and use of potent agents must be limited to avoid adverse effects (see Table 2 for potencies). Consider a corticosteroid-free period of 2 weeks or more after each 2-3-week period of daily use, and use mild corticosteroids on the face or flexures.<sup>16</sup> Moderately potent to potent corticosteroids should only be used on the face or flexures under close supervision, and for a maximum of 7 days, because of the increased possibility of skin atrophy.<sup>16</sup>

### Evidence suggests pimecrolimus is less effective than topical corticosteroids

Most clinical trials of topical pimecrolimus in atopic dermatitis have compared its effect with placebo (vehicle), where it has shown efficacy in adult, child and infant populations.<sup>5</sup> Data are available from only one head-to-head trial comparing pimecrolimus with topical corticosteroids in adults: after 3 weeks of treatment 57% of patients using pimecrolimus had their dermatitis rated as moderately to completely cleared compared with 76% of those using topical corticosteroids. Patients in the topical corticosteroid arm used triamcinolone

**Table 2. Potency of topical corticosteroids<sup>6</sup>**

Potency	Generic corticosteroid
Mild	Hydrocortisone 0.5% to 1% Hydrocortisone acetate 0.5% to 1%
Moderate	Triamcinolone acetonide 0.02% Betamethasone valerate 0.02% and 0.05% Desonide 0.05%
Potent	Betamethasone dipropionate 0.05% Betamethasone valerate 0.1% Methylprednisolone aceponate 0.1% Mometasone furoate 0.1%
Very potent	Betamethasone dipropionate 0.05% in optimised vehicle

acetonide 0.1% cream (a potent preparation) on the trunk and limbs, and hydrocortisone acetate 1% cream for the face, neck and intertriginous areas. In the course of the 12-month study, 36% of patients using pimecrolimus withdrew because of unsatisfactory therapeutic effect, compared with 8% of patients using topical corticosteroids.<sup>17</sup>

### Safety issues

As with topical corticosteroids, topical pimecrolimus should not be used on areas with an uncontrolled infection. Skin areas under treatment should be protected from the sun. Pimecrolimus may be associated with a higher risk of viral skin infection and with systemic adverse effects in children. Long-term adverse effects are as yet unknown, and there are concerns that using topical pimecrolimus might be linked to skin cancer or lymphoma.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the Therapeutic Goods Administration website.

## Contraindications and precautions

Pimecrolimus should not be used if there is an existing viral skin infection, as it may be exacerbated.<sup>11</sup> Treat existing bacterial or fungal skin infections before starting pimecrolimus.<sup>16</sup>

Skin areas treated with topical pimecrolimus should be protected from the sun, and pimecrolimus should not be used by people receiving phototherapy. Sunscreen can be applied after pimecrolimus cream.<sup>11</sup> Neither phototoxicity nor photocarcinogenicity has been observed in humans, but pimecrolimus cream shortened the time to skin tumour formation in an animal study.<sup>18</sup> This effect was also seen when the cream vehicle was applied alone and so may be unrelated to any effect of pimecrolimus itself.<sup>11</sup>

Application of topical pimecrolimus to vaccination sites is not recommended.<sup>11</sup>

Topical pimecrolimus should not be used by immunocompromised patients, or applied to areas affected by pre-malignant changes (e.g. actinic keratoses) or where skin cancers have been removed.<sup>11</sup>

Pregnant women should not use pimecrolimus and it should be used with caution by breastfeeding women. Breastfeeding women should not apply pimecrolimus cream to the breast.<sup>11</sup>

## Adverse drug reactions

About 20% of patients experience irritation at the site of application.<sup>11</sup> In trials these itching or burning sensations, mostly mild to moderate in severity, started within 1–5 days of treatment and lasted no more than 5 days.<sup>18</sup> Application-site reactions, including burning, irritation and itching, were more common with pimecrolimus than with topical corticosteroid creams in one randomised controlled trial.<sup>17</sup> Local irritation may be discouraging for children, as they have poor tolerance of preparations that sting.<sup>6</sup>

Treatment with topical pimecrolimus may be associated with an increased risk of viral skin infections such as papilloma, varicella zoster, eczema herpeticum, and molluscum contagiosum.<sup>11,18,19</sup> In adults, incidence of skin infections did not differ significantly between those who used pimecrolimus and those who used a

topical corticosteroid in a 1-year trial.<sup>17</sup> Increased incidence of headache, cough, fever, upper respiratory tract infections, otitis media, gastroenteritis and diarrhoea has been seen in paediatric trials.<sup>18,20,21</sup> More participants assigned to placebo discontinued early, which may explain the greater number of systemic adverse events experienced by participants assigned to pimecrolimus.<sup>19</sup>

People using pimecrolimus may develop swollen lymph nodes. In all cases, monitor to ensure the lymphadenopathy resolves; if there is no clear cause, or if infectious mononucleosis is diagnosed, consider discontinuing pimecrolimus. In clinical trials of pimecrolimus, a small number of cases of swollen lymph nodes (0.9% of study participants) were reported, but these were mostly related to infections.<sup>11</sup>

## Adverse effects may be more likely in infants under 2 years old

Pimecrolimus is approved for use in infants (3 months to 2 years old), but the likelihood of adverse effects in this group may be higher than in older children. As safety data are limited, minimise the exposure to pimecrolimus (see Dosing issues). In the USA and UK, registration was only granted for use in children 2 years and older. For most individuals in adult populations the plasma concentration of pimecrolimus was undetectable (< 0.5 ng/mL) after repeated topical application. In contrast, an increased proportion of children and infants had plasma concentrations above this level<sup>18,22</sup>, indicating a higher level of systemic exposure.

## There are concerns that pimecrolimus may be associated with malignancies

In early 2006, warnings relating to malignancies were added to the approved product information for pimecrolimus in Australia, Europe and the USA.<sup>18,23,24</sup> Clinical trials of topical pimecrolimus of up to 2 years have not shown an increased incidence of malignancy; however, the manufacturer reported that a number of cases of malignancies, including lymphoma and skin cancers, had been reported worldwide in people who had used pimecrolimus.<sup>24</sup> It has not been established whether pimecrolimus was the cause.<sup>11</sup>

Increased incidence of malignancy has been seen with long-term exposure to high topical and oral doses of pimecrolimus in animal studies.<sup>11,18</sup> Like tacrolimus, pimecrolimus is an immunosuppressant of the calcineurin inhibitor class.<sup>16</sup> High levels of systemic exposure to orally administered tacrolimus, which are routine in organ transplant recipients, have been associated with an increased risk of malignancy.<sup>25</sup> There are also case reports of benign and malignant neoplasia in areas treated with topical tacrolimus.<sup>26–28</sup>

## Dosing issues

Apply twice a day in a thin film to the affected areas and rub in gently and completely. Wash hands after application.<sup>11</sup>

Apply emollients or sunscreen immediately after topical pimecrolimus.<sup>11</sup>

Initiate treatment at the first sign of itching and/or erythema and/or thickening of the skin, to prevent progression to flares of atopic dermatitis. Discontinue when there is no longer evidence of the disease apart from dry skin, and resume at the first signs of recurrence. If no improvement occurs after 6 weeks or the condition worsens, topical pimecrolimus should be stopped.<sup>11</sup>

For infants (3–23 months old), treat each episode of atopic dermatitis for a maximum of 3 weeks. Apply pimecrolimus cream to the smallest practicable body surface area.<sup>11</sup>

Experience with topical pimecrolimus is too limited to allow assessment of the safety of its use during pregnancy. Pregnant women should not use it<sup>11</sup> and should avoid exposure (e.g. by wearing gloves) when applying it to others.

## Information for patients and carers

Advise the patient or carer:

- when to stop and start treatment in order to control dermatitis symptoms with intermittent usage
- that the cream may cause a temporary feeling of warmth or burning, which is only of concern if the reaction is severe or if it lasts more than a week
- to protect treated skin areas from the sun with sunscreen and hat or protective clothing
- that the long-term safety of pimecrolimus is not known and, although a link remains uncertain, that rare cases of skin cancer and lymphoma have been reported
- to contact the doctor if they notice a lump, or a new spot, freckle or mole, or a change to an existing one
- that pregnant women should avoid exposure to pimecrolimus
- to contact the doctor if they notice swollen lymph nodes
- that in rare cases, pimecrolimus may cause facial flushing or skin irritation if they drink alcohol.

For more detailed information, suggest or provide the Elidel consumer medicine information (CMI) leaflet.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.