SHARED CARE GUIDELINES FOR PRESCRIBING PIMECROLIMUS (ELIDEL®) AND TACROLIMUS (PROTOPIC®) FOR TREATMENT OF ATOPIC ECZEMA.

INDICATION

Pimecrolimus topical therapy is indicated for the treatment of patients aged 2 years and over with mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible. This may include:
• Intolerance to topical corticosteroids
• Lack of effect of topical corticosteroids
• Use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate.

Tacrolimus topical therapy is indicated for the treatment of patients aged 2 years and over with mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible. This may include:
• Intolerance to topical corticosteroids
• Lack of effect of topical corticosteroids
• Use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate.

NICE TA82 Tacrolimus and pimecrolimus for atopic eczema (published August 2004) states:
1.1 Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.
1.2 Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
1.3 Pimecrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2 to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
1.4 For the purposes of this guidance, atopic eczema that has not been controlled by topical corticosteroids refers to disease that has not shown a satisfactory clinical response to adequate use of the maximum strength and potency that is appropriate for the patient's age and the area being treated.
1.5 It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options.

This TA has been incorporated into the NICE Clinical Guideline 57, Atopic eczema in under 12s: diagnosis and management and the NICE Eczema Pathway.

Sometimes the consultant will recommend the 0.1% strength of Protopic® outside of licence in severe cases in younger patients. Monitoring by secondary care will continue.

AREAS OF RESPONSIBILITY FOR SHARED CARE

Patients should be at the centre of any shared care arrangements. Individual patient information and a record of their preferences should accompany shared care prescribing guidelines, where appropriate.
Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stable or predictable.
Referral to the GP should only take place once the GP has agreed to this in each individual case, and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that supply arrangements have been finalised. The secondary/tertiary provider must supply an adequate amount of the medication to cover the transition period. The patient should then be informed to obtain further prescriptions from the GP. When clinical responsibility for prescribing is transferred to general practice, it is important that the GP, or other primary care prescriber, is confident to prescribe the necessary medicines. Shared care agreements play a key role in enabling primary care prescribers to prescribe medicines with which they may not initially be familiar. Clinical responsibility for prescribing is held by the person signing the prescription, who must also ensure adequate monitoring.

**REFERRAL AND INITIATION**

Since the guidance on topical pimecrolimus and tacrolimus was issued, a safety review by the European Medicines Agency has recommended greater caution in the way these medicines are used to reduce potential risks of skin cancer and lymphoma. (MHRA guidance 2006). Patients should be appropriately counselled on the intermittent, short-term and not continuous nature of the therapies. Healthcare professionals should explain to children with atopic eczema and their parents or carers that they should only apply topical calcineurin inhibitors to areas of active atopic eczema, which may include areas of broken skin.

Shared Care is only appropriate if it provides the optimum solution for the patient.

**Specialist Responsibilities**

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<tr>
<td>1</td>
<td>To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.</td>
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| 2 | Where appropriate:  
|   | o to initiate treatment, basing choice of product on licence and NICE TA recommendations;  
|   | o assess initial response to treatment and discontinue after 6 weeks if there is no benefit from pimecrolimus or tacrolimus;  
|   | o obtain consent from the patient’s GP to continue prescribing once treatment has been stabilised (usually after 6-8 weeks);  
|   | o monitor the patient and their therapy at six monthly intervals. |
| 3 | Ensure that the child/adolescent or carer understands the management of the condition. In the long-term management of atopic eczema, treatment should begin at first appearance of signs and symptoms of atopic dermatitis to prevent flares of the disease and should be stopped when those signs and symptoms have resolved. |
| 4 | To provide the GP with appropriate prescribing information and any additional information requested. |
| 5 | To be available for advice if the patient’s condition changes. |
| 6 | To ensure that procedures are in place for the rapid re-referral of the patient by the GP. |
| 7 | To ensure the patient has given informed consent to their treatment. |
| 8 | To liaise with the GP on any suggested changes in prescribed therapy. |
### General Practitioner Responsibilities

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<tr>
<td>1</td>
<td>Initially, to refer the patient for specialist advice.</td>
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<td>2</td>
<td>Where appropriate, to continue to prescribe pimecrolimus or tacrolimus as part of a shared care arrangement (usually after 6-8 weeks).</td>
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<td>3</td>
<td>To reinforce to the patient or carer of the intermittent nature of the treatment and that it is not intended for long-term continuous use.</td>
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<td>4</td>
<td>To deal with general health issues of the patient and to advise the patient/carer of appropriate sun protection measures, such as minimisation of the time in the sun, use of sunscreen product and covering the skin with appropriate clothing.</td>
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<td>5</td>
<td>To monitor concordance with therapy</td>
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### Responsibility of community pharmacies

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<tr>
<td>1</td>
<td>To provide support and advice to the patient and/or family regarding concordance, adverse effects and over the counter therapies.</td>
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<tr>
<td>2</td>
<td>To advise the patient/carer about appropriate sunscreen products.</td>
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<tr>
<td>3</td>
<td>To monitor concordance with therapy and refer the patient to their GP if any concern arises.</td>
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### Patient's role (or that of carer)

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<td>1</td>
<td>Report to the specialist or GP if he or she does not have a clear understanding of the treatment.</td>
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<td>2</td>
<td>Attend appropriate GP and other follow up appointments</td>
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<td>3</td>
<td>Share any concerns in relation to treatment with pimecrolimus or tacrolimus.</td>
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<td>4</td>
<td>Use written and other information on the medication.</td>
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<td>5</td>
<td>Seek help urgently if side effects are suspected, or if otherwise unwell.</td>
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### SUPPORTING INFORMATION

**Dosage and Administration**

**TACROLIMUS (PROTOPIC ®)**

Topical tacrolimus (Protopic ®) is available in two strengths, 0.03 % and 0.1 % ointment. Tacrolimus can be used for short-term and intermittent long-term treatment. Treatment should not be continuous on a long-term basis. Sometimes the consultant will recommend the 0.1% strength of Protopic® outside of licence in severe cases in younger patients. Monitoring by secondary care will continue in these cases.

Tacrolimus treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with tacrolimus until lesions are cleared, almost cleared or mildly affected. Thereafter, patients are considered suitable for maintenance treatment (see below). At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.

**Treatment of flares**

Adults and adolescents (16 years of age and above)

Treatment should be started with tacrolimus 0.1% twice a day and treatment should be continued until the lesions are cleared, almost cleared or mildly affected, treatment should be reduced to use of the 0.1% ointment once daily OR switch to twice daily use of the lower strength (0.03%)
ointment. If symptoms recur, twice daily treatment with the 0.1% ointment should be restarted. Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further treatment options should be considered.

Children (age of 2 to 16 years).
Tacrolimus 0.03% ointment should be applied to affected skin twice daily for up to three weeks until the lesions are cleared, almost cleared or mildly affected, then treatment should be reduced to use of the 0.03% ointment once daily. The higher strength tacrolimus ointment (0.1%) is not suitable for use in children.

In adults and children, if no signs of improvement are seen after two weeks of treatment, other treatment options should be considered.

**Maintenance treatment**

Patients who are responding to treatment with tacrolimus ointment (lesions cleared, almost cleared or mildly affected) are suitable for maintenance treatment.

Adults and adolescents (16 years of age and above)
Adult patients should apply tacrolimus 0.1% ointment once a day twice a week to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without tacrolimus treatment (e.g. apply ointment on Monday and Thursday each week).

During maintenance treatment, patients should be monitored for response to therapy and the need for continued treatment should be evaluated. After 12 months treatment, a review of the patient’s condition should be conducted by the consultant and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

Children (age of 2 to 16 years).
Tacrolimus 0.03% ointment should be applied to affected skin twice a week to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without tacrolimus treatment (e.g. apply ointment on Monday and Thursday each week). The higher strength tacrolimus ointment (0.1%) is not suitable for use in children.

During maintenance treatment, patients should be monitored for response to therapy and the need for continued treatment should be evaluated. After 12 months treatment, a review of the patient’s condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

**PIMECROLIMUS (ELIDEL®)**

**Children and adolescents (2-16 years)**

A thin layer of cream should be applied to the affected skin twice daily and rubbed in gently. The cream should be used until clearance of the skin occurs, and treatment of the skin with pimecrolimus should then be discontinued.

Pimecrolimus cream may be used on all areas of skin on the head, face and neck (including intertriginous areas), **except** on mucous membranes.

Emollients can be applied immediately after using pimecrolimus cream.

If there is no response to the pimecrolimus after 6 weeks, or there is a worsening of the eczema during treatment, the pimecrolimus should be discontinued.
The use of pimecrolimus cream in adults, or in children on skin other than the face and neck, is not covered by this guideline.

Contraindications

Pimecrolimus cream and Tacrolimus ointment is contraindicated:
- in patients with a known hypersensitivity to the drug, other macrolactams or any of the excipients
- in pregnancy or breastfeeding women.

Special Warnings

Pimecrolimus cream and Tacrolimus ointment should not be used in:
- congenital or acquired immunodeficiencies
- patients on therapies that cause immunosuppression.
- potentially malignant or pre-malignant skin lesions.
- acute cutaneous viral infections (herpes simplex, chicken pox).
- clinical infections at treatment sites
- patients with Netherton’s syndrome
- patients requiring occlusive dressings.

Treatment with pimecrolimus or tacrolimus may be associated with an increased risk of folliculitis and herpes viral infections (herpes simplex dermatitis, herpes simplex, Kaposi’s varicelliform eruption). In the presence of these infections, the balance of risks and benefits associated with tacrolimus use should be evaluated.

Use of pimecrolimus cream may cause mild and transient reactions at the site of application, such as a feeling of warmth and/or burning sensation. If the application site reaction is severe, the risk-benefit of treatment should be re-evaluated.

Topical pimecrolimus should not be used under occlusion (bandages and dressings) for treating atopic eczema in children without specialist dermatological advice.

Tacrolimus is extensively metabolised in the liver and although blood concentrations are low following topical therapy, the ointment should be used with caution in patients with hepatic failure.

Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the cream should be thoroughly wiped off and/or rinsed off with water.

Physicians should advise patients on appropriate sun protection measures, such as minimisation of the time in the sun, use of sunscreen product and covering the skin with appropriate clothing.

Pimecrolimus cream contains cetyl alcohol and stearyl alcohol which may cause local skin reactions. It also contains propylene glycol, which may cause skin irritation.

Care should be exercised if applying Tacrolimus to patients with extensive skin involvement over an extended period, especially in children.

Cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported in patients using tacrolimus ointment or pimecrolimus cream. However, patients with atopic dermatitis treated with topical tacrolimus or pimecrolimus have not been found to have significant systemic pimecrolimus levels.

Lymphadenopathy present at initiation should be investigated and kept under review. Patients who receive tacrolimus ointment or pimecrolimus cream and who develop lymphadenopathy should be monitored to ensure that it resolves. In case of persistent lymphadenopathy, aetiology needs to be investigated. In the absence of a clear aetiology or in the presence of acute infectious mononucleosis, discontinuation of Tacrolimus ointment or the pimecrolimus cream should be considered.
If no improvement occurs after 6 weeks, or in case of disease exacerbation, the tacrolimus ointment or pimecrolimus cream should be stopped. The diagnosis of atopic dermatitis should be re-evaluated and further therapeutic options considered.

**Side Effects**

**Pimecrolimus Cream**

The most common adverse effects are: burning sensation, pruritus, erythema, skin infections (including folliculitis and less commonly impetigo, herpes simplex and zoster, molluscum contagiosum); rarely papilloma, skin discoloration, local reactions including pain, paraesthesia, peeling, dryness, oedema, and worsening of eczema. Post marketing cases of malignancy, including cutaneous and other types of lymphoma and skin cancers have been reported in patients using pimecrolimus cream.

**Tacrolimus Ointment**

The most common adverse effects are: application-site reactions including rash, irritation, pain and paraesthesia; herpes simplex infection, Kaposi’s varicelliform eruption; application-site infections and alcohol intolerance. Less common side effects include acne; also reported rosacea. Post marketing cases of malignancy, including cutaneous and other types of lymphoma and skin cancers have been reported in patients using tacrolimus ointment.

**Drug Interactions**

**Pimecrolimus Cream**

Pimecrolimus is exclusively metabolised by CYP 450 3A4. Based on its minimal extent of absorption, interactions of pimecrolimus cream with systemically administered medicinal products are unlikely to occur.

The present data indicate that pimecrolimus cream can be used simultaneously with antibiotics, antihistamines and corticosteroids (oral/nasal/inhaled).

Based on the minimal extent of absorption, a potential systemic interaction with vaccination is unlikely to occur. However, this interaction has not been studied. Therefore, in patients with extensive disease, it is recommended to administer vaccinations during treatment-free intervals.

There is no experience with concomitant use of immunosuppressive therapies given for atopic eczema such as UVB, UVA, PUVA, azathioprine and cyclosporin. Pimecrolimus cream has no photocarcinogenic potential in animals. However, since the relevance to man is unknown excessive exposure of the skin to ultraviolet light including light from a solarium, or therapy with PUVA, UVA or UVB should be avoided during treatment with pimecrolimus cream.

**Tacrolimus Ointment**

Systemically available tacrolimus is metabolised via the hepatic Cytochrome P450 3A4 (CYP3A4). Systemic exposure from topical application of tacrolimus ointment is low (< 1.0 ng/ml) and is unlikely to be affected by concomitant use of substances known to be inhibitors of CYP3A4. However, the possibility of interactions cannot be ruled out and the concomitant systemic administration of known CYP3A4 inhibitors (e.g. erythromycin, itraconazole, ketoconazole and diltiazem) in patients with widespread and/or erythrodermic disease should be done with caution.

There is no experience with concomitant use of immunosuppressive therapies given for atopic eczema such as UVB, UVA, PUVA. Excessive exposure of the skin to ultraviolet light including light from a solarium, or therapy with PUVA, UVA or UVB should be avoided during treatment with tacrolimus ointment.

The manufacturer’s summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.
References
- Protopic (Leo Pharmaceuticals Ltd) Summary of Product Characteristics. Accessed 8th November 2018
- BNF online (accessed October 2018)
- NICE TA 82

Current prices of Elidel® (pimecrolimus cream) (Drug Tariff Nov 18):
- 30g - £19.69
- 60g - £37.41
- 100g - £59.07

Current prices of Protopic® (tacrolimus ointment) (Drug Tariff Nov 18)
Tacrolimus Ointment 0.1%
- 30g – £25.92
- 60g - £47.28

Tacrolimus Ointment 0.3%
- 30g - £23.33
- 60g - £42.55

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<th>Single agent documents written by</th>
<th>Medicines Management Team</th>
<th>March 2013</th>
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<tr>
<td>Considered by</td>
<td>Dermatology Working Group</td>
<td>March 2013</td>
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<tr>
<td>Approved By</td>
<td>Bournemouth, Dorset and Poole Health Technologies Forum</td>
<td>April 2013</td>
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<tr>
<td>Dual agent document reviewed by</td>
<td>Dermatology Working Group</td>
<td>November 2018</td>
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<tr>
<td>Approved by</td>
<td>Dorset Medicines Advisory Group</td>
<td>March 2019</td>
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<td>Review Date</td>
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