

# NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

## Final Appraisal Determination

### Tacrolimus and pimecrolimus for atopic eczema

#### 1 Guidance

- 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 (see Section 1.4), 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 (see Section 1.4), 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.

## **2 Clinical need and practice**

- 2.1 Atopic eczema (synonymous with atopic dermatitis) is a chronic relapsing skin condition characterised by intense itching, dry skin, redness, inflammation and exudation. It affects mainly the flexor surfaces of the elbows and knees, as well as the face and neck.
- 2.2 The term 'atopic' refers to the association with atopy (a state of hypersensitivity to common environmental allergens that may be inherited) and differentiates atopic eczema from other forms of eczema such as irritant, allergic contact, discoid, venous, seborrhoeic and photosensitive eczema, which have different disease patterns and aetiologies.
- 2.3 Estimates of prevalence vary but suggest that the condition may affect as many as 15–20% of school-age children and 2–10% of adults. The majority of people with atopic eczema (over 80%) experience mild disease, whereas only a small proportion (around 2–4%) have a severe form of the disease. Despite the lower prevalence, the presentation of disease in adults is often more severe and chronic in nature.
- 2.4 In most people with atopic eczema, the condition begins in early childhood – often in the first year of life, when it can be particularly severe. Findings from the National Child Development Study, developed from the birth cohort of 1958, suggest an incidence of around 50 cases per 1000 in the first year of life, falling to 5 new cases per 1000 per year for the rest of childhood. In around 60% of children, the condition clears by the time they reach their teens. However, the tendency towards dry and irritable skin generally persists and later recurrences are common.
- 2.5 The aetiology of atopic eczema is complex and not fully understood. Genetic factors are important but environmental factors, such as house dust mites,

pollen, tobacco, air pollution and low humidity, may cause its onset and/or exacerbate existing symptoms. More persistent disease has been consistently linked with early disease onset, severe widespread disease in early life, concomitant asthma or hay fever, and a family history of atopic eczema. The condition is exacerbated by soap and detergents, clothes containing wool or certain synthetic fibres, and extremes of temperature.

- 2.6 The severity of atopic eczema varies enormously, from an occasional dry, scaly patch to a debilitating disease where much of the body is covered by excoriated (scratched and abraded), bleeding and infected lesions. Its course may be continuous for prolonged periods or of a relapsing–remitting nature characterised by acute flare-ups.
- 2.7 Itching skin (pruritus) is a major symptom of atopic eczema. A vicious circle can occur, where itching and scratching damage the skin and increase inflammation, which in turn increases the itch. Scratching can damage the skin and cause bleeding, secondary infection and thickening of the skin (lichenification).
- 2.8 The impact of atopic eczema on quality of life can be considerable and it has been shown to vary according to disease severity. In addition to the burden of daily treatment, studies have shown not only that the condition may affect everyday activities, such as work or school, and social relationships, but also that people with atopic eczema may experience anxiety, depression and other psychological problems. Sleep disturbance is common, especially during flare-ups, which in turn can lead to problems with irritability and lack of concentration. Severe atopic eczema in children can also have a significant impact on family life, with parents/carers having to cope with the demands associated with caring for a child with a chronic illness.
- 2.9 Historically, there have been variations in the clinical definition and diagnosis of atopic eczema. A UK Working Party has developed criteria for use in epidemiological studies, and these are now commonly used, although further

validation is required. To qualify as a case of atopic eczema using these criteria, the person must have had an itchy skin condition in the last 12 months, plus three or more of the following criteria:

- a history of flexural involvement (that is, affecting the bends of the elbows or behind the knees)
- a history of a generally dry skin
- a personal history of other atopic disease (in children under 4 years, a history of atopic disease in a first-degree relative may be included)
- visible flexural dermatitis as defined by a photographic protocol
- onset at younger than age 2 years (not used in children under 4 years).

2.10 There is uncertainty and a lack of standardisation around clinical assessment of disease severity, both in practice and in trial settings. Although a number of scoring systems have been used to categorise the disease as mild, moderate or severe, usually by aggregating scores from a range of symptoms and disease characteristics, none of these scoring systems has been accepted as a 'gold standard' and there is still general debate over their use.

2.11 Atopic eczema in childhood shows a reverse social class gradient, with higher rates in socio-economically advantaged groups and smaller families. There is also evidence of variation in prevalence by region, with the highest rates recorded in the South East and industrialised Midlands, and the lowest rates in Wales and Scotland.

2.12 Management of atopic eczema takes place predominantly in primary care, and aims to relieve symptoms and prevent complications such as infection until remission occurs. This management involves the identification and avoidance of exacerbating factors, skin care and anti-inflammatory treatment. Providing people with good-quality information about these issues is essential to successfully managing and treating atopic eczema. Referral to secondary care is only advised if the condition is severe and has not responded to appropriate therapy.

- 2.13 Emollients form a standard part of skin care and aim to retain the skin's barrier function (keeping water in and irritants or pathogens out) and prevent painful cracking. Frequent and continuous use is recommended even in the absence of symptoms. Preparations include bath oils, soap substitutes and moisturisers.
- 2.14 Topical corticosteroids are the first-line treatment for episodic worsening (flare-ups) of atopic eczema. In order to reduce exposure to topical corticosteroids, they are used only intermittently to control exacerbations. Emollients are used with the topical corticosteroids.
- 2.15 Topical corticosteroids are classified according to their potency. This is determined by the amount of vasoconstriction a topical corticosteroid produces and the degree to which it inhibits inflammation (a more potent product increases suppression to the inflammatory pathway). In the UK, four potencies are recognised: mild, moderately potent, potent and very potent. Across the different potencies, products have different formulations and different strengths (for example, 0.025%, 0.1%, 0.5%) and are available in various preparations (for example, ointment, cream, lotion, foam).
- 2.16 Treatment regimens for topical corticosteroids vary with disease severity, with clinicians usually recommending use of the mildest potency products possible to treat the condition, in order to minimise the potential adverse effects.
- 2.17 One of the potential long-term effects of topical corticosteroid treatment is skin atrophy, whereby the skin becomes thin and loses some of its function. This is more likely to occur in areas where the skin is already thin, such as the face and flexures. Although reversible in the short term, prolonged exposure can lead to permanent damage. Signs of atrophy include telangiectasia (abnormal dilation of capillary vessels and arterioles), increased transparency and shininess of the skin, and the appearance of striae (stripes or lines in the skin distinguished from surrounding tissue by colour, texture or elevation). Long-

term use of topical corticosteroids on the eyelids has also been associated with the development of glaucoma.

- 2.18 Systemic adverse effects with topical corticosteroids are rare but include suppression of the pituitary–adrenal axis (which may restrict growth).
- 2.19 Absorption of topical corticosteroids is higher at certain sites such as the face and flexures, and potent topical corticosteroids are generally avoided in these areas. The more potent topical corticosteroids are also contraindicated in infants younger than 1 year and are avoided in children or used with great care and for short periods. A potent or moderately potent topical corticosteroid may be appropriate for severe atopic eczema on the limbs, but for 1–2 weeks only, followed by a weaker preparation as the condition improves.
- 2.20 In resistant severe cases, treatment with systemic corticosteroids, phototherapy and systemic use of immunosuppressants, such as ciclosporin, may be required.

### **3 The technologies**

Tacrolimus and pimecrolimus are members of a new class of topical immunomodulators and belong to the class of immunosuppressant drugs known as calcineurin inhibitors. They work mainly by reducing inflammation through the suppression of T-lymphocyte responses, a different mechanism of action to topical corticosteroids. Although tacrolimus and pimecrolimus have similar mechanisms of action, they have different licensed indications (see Sections 3.1 and 3.2).

#### **3.1 Tacrolimus**

- 3.1.1 Tacrolimus ointment (Fujisawa) is available in two strengths (0.1% and 0.03%), both of which are licensed for the treatment of moderate to severe atopic eczema in adults (16 years and above) who have not adequately responded to, or are intolerant of, conventional therapies. The lower strength is also licensed for the treatment of moderate to severe atopic eczema in

children aged 2 years and older whose condition has not responded adequately to conventional therapies.

- 3.1.2 The Summary of Product Characteristics states that tacrolimus should “be prescribed by physicians with experience in the treatment of atopic dermatitis”.
- 3.1.3 Tacrolimus is applied as a thin layer to affected areas of the skin twice daily and may be used on any part of the body, including the face, neck and flexural areas. The Summary of Product Characteristics states that the treatment of each affected region of the skin should be continued until the area is clear, and then be discontinued. It also states that treatment for adults should be started with 0.1% tacrolimus twice a day, that twice-daily treatment with 0.1% tacrolimus should be restarted if symptoms recur, and that an attempt should be made to reduce the frequency of application or to use the lower strength 0.03% tacrolimus if the clinical condition allows. For children, only the 0.03% strength is licensed, and the Summary of Product Characteristics states that the frequency of application should be reduced to once a day after a maximum of 3 weeks.
- 3.1.4 Tacrolimus can be used for short-term and intermittent long-term treatment. The net price is £21.60 for 30 g and £41.04 for 60 g (0.1% tacrolimus) and £19.44 for 30 g and £36.94 for 60 g (0.03% tacrolimus) (*British National Formulary*, 46th edition). Costs may vary in different settings because of negotiated procurement discounts.
- 3.1.5 Side effects include a burning or tingling sensation, pruritus, erythema, folliculitis, herpes simplex infection, acne, increased sensitivity to hot and cold, and alcohol intolerance. Lymphadenopathy has also been reported. The Summary of Product Characteristics states that before commencing treatment with tacrolimus, clinical infections at treatment sites should be cleared. It also states that emollients should not be applied to the same area within 2 hours of applying tacrolimus. When taken orally for other indications, tacrolimus has a

number of well-recognised adverse effects, including renal toxicity and hypertension. The Summary of Product Characteristics states that, beyond 4 years of treatment, the potential for local immunosuppression (possibly resulting in infections or cutaneous malignancies) is unknown. For full details of side effects and contraindications, see the Summary of Product Characteristics.

## **3.2 Pimecrolimus**

- 3.2.1 Pimecrolimus cream 1.0% (Novartis) is licensed in patients with mild to moderate atopic eczema aged 2 years and older, for short-term treatment of signs and symptoms and intermittent long-term treatment to prevent flare-ups.
- 3.2.2 Pimecrolimus is applied as a thin layer to affected skin twice daily and may be used on all skin areas, including the head, face, neck and intertriginous areas (where opposing skin surfaces touch and may rub, such as skin folds of the groin, axillae and breasts). The treatment of each affected region of the skin is continued until the area is clear and is then discontinued. Because of the low level of systemic absorption, there are no restrictions on the total daily dose applied, the body surface area that can be treated or the duration of treatment. The Summary of Product Characteristics states that emollients can be applied immediately after using pimecrolimus. The net price is £19.69 for 30 g, £37.41 for 60 g and £59.07 for 100 g (*British National Formulary*, 46th edition). Costs may vary in different settings because of negotiated procurement discounts.
- 3.2.3 Side effects include a burning sensation, pruritus, erythema, skin infections (including folliculitis and rarely impetigo, herpes simplex and zoster and molluscum contagiosum), papilloma (rarely) and local reactions such as pain, paraesthesia, peeling, dryness, oedema and worsening of eczema. The Summary of Product Characteristics states that pimecrolimus should not be applied to areas affected by acute cutaneous viral infections, and that before commencing treatment with pimecrolimus, clinical infections at treatment sites

should be cleared. It also states that long-term effect on the local skin immune response and on the incidence of skin malignancies is unknown. For full details of side effects and contraindications, see the Summary of Product Characteristics.

## **4 Evidence and interpretation**

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

### **4.1 Clinical effectiveness**

Ten randomised controlled trials (RCTs) of tacrolimus and eight RCTs of pimecrolimus for the treatment of atopic eczema were considered. In most of the studies, comparators were topical corticosteroids or vehicle (a placebo consisting of the base cream or ointment without the active ingredient).

Effectiveness was assessed in different ways across the trials, but common measures included the following:

- changes in severity using the Eczema Area Severity Index (EASI) or modified Eczema Area Severity Index (mEASI), which are well established assessment tools that account for individual symptoms and disease severity in four predefined regions of the body
- the Investigator's Global Assessment (IGA), a physician's rating scale based on interpretation of signs of eczema
- the Physician's Global Evaluation (PGE) of treatment success, which estimates the percentage change in the condition since the person was last seen
- the physician's evaluation of reduction in affected body surface area (BSA)
- patient-based measures such as number of flare-ups, pruritus and use of alternative treatments, such as topical corticosteroids.

The main quality-of-life measure used in the trials was the Dermatology Life Quality Index (DLQI), which is a 10-item, self-administered questionnaire designed to measure the impact of skin diseases on patients' lives over the previous week.

#### **4.1.1 Tacrolimus**

- 4.1.1.1 Of the ten RCTs of tacrolimus, four were conducted in children and six in adults, all in populations with moderate to severe disease, reflecting the licensed indications.
- 4.1.1.2 Two of the studies in children compared tacrolimus with mild topical corticosteroids (n = 374 and n = 417 ['n' refers to overall study size]) and two compared it with vehicle (n = 180 and n = 352). Results were considered for 0.03% tacrolimus only, as 0.1% tacrolimus is not licensed for use in children. No trials in children have compared tacrolimus to potent or moderately potent topical corticosteroids.
- 4.1.1.3 Three of the RCTs in adults used potent topical corticosteroid regimens as a comparator (n = 181, n = 570 and n = 975) and three used vehicle (n = 14, n = 215 and n = 632).
- 4.1.1.4 For children, a pooled analysis of two studies that compared 0.03% tacrolimus with mild topical corticosteroids showed 0.03% tacrolimus to be more effective at 3 weeks, as measured by an improvement of at least 90% ('cleared' to 'excellent improvement') in the PGE (relative risk [RR] 2.56, 95% confidence interval [CI] 1.95 to 3.36). Based on the median improvement in mEASI score, both studies also showed 0.03% tacrolimus to be statistically significantly more effective than mild topical corticosteroids.
- 4.1.1.5 Both studies in children comparing 0.03% tacrolimus and vehicle found tacrolimus to be more effective using the PGE categories of 'cleared' to 'marked improvement' (56.5% vs 15.7% in the larger study [ $p < 0.001$ ] and

69.0% vs 38.0% in the smaller study [ $p < 0.01$ ] for 0.03% tacrolimus vs vehicle). Statistically significant differences were also demonstrated for a number of other measures, including changes in EASI score, pruritus score and patient reports of 'feeling better'. Loss to follow-up was higher in the vehicle arms of the trials (56.0% vs 17.0% in the larger study and 15.9% vs 8.1% in the smaller study).

- 4.1.1.6 For adults, a pooled analysis of two studies ( $n = 181$  and  $n = 570$ ) comparing 0.1% tacrolimus and potent topical corticosteroids found no statistically significant difference in the proportions of people with an improvement of at least 75% on the PGE ('cleared' to 'marked improvement') at 3 weeks (RR 1.08, 95% CI 0.97 to 1.21).
- 4.1.1.7 The pooled analysis did not include the largest study ( $n = 975$ ), which compared 0.1% tacrolimus with mild topical corticosteroids on the face and with potent topical corticosteroids on the body. Overall, this study found a greater improvement on the PGE with tacrolimus (62.9% vs 40.7% at 3 months, difference = 22.2%, 95% CI 16.1 to 28.4). This study reported other statistically significant differences favouring tacrolimus compared with a topical corticosteroid regimen. This included a higher proportion of people achieving an improvement in mEASI by at least 60% at 3 months (the primary outcome), a greater median improvement in mEASI (83.3% vs 76.9% at 3 months,  $p < 0.001$ ; also statistically significant at 4 and 6 months, 95% CIs not stated), a greater reduction in the affected BSA, and a greater proportion of people 'feeling better'. However, there was a high loss to follow-up (25.5% with tacrolimus and 42.1% with topical corticosteroids).
- 4.1.1.8 The other two studies that compared 0.1% tacrolimus and potent topical corticosteroids in adults did not report any statistically significant differences, although the larger of the two ( $n = 570$ ) found smaller improvements in median mEASI score with 0.03% tacrolimus compared with potent topical corticosteroids (71% vs 83%,  $p < 0.05$ ). Loss to follow-

up in this study was 11.5% with tacrolimus and 9.1% with topical corticosteroids.

- 4.1.1.9 Compared with vehicle, treatment of adults with tacrolimus was shown to be statistically significantly more effective using a number of outcome measures, including the PGE categories of 'cleared' to 'marked improvement', reduction in BSA affected, and improvement in EASI score. Loss to follow-up was noticeably high in the vehicle arms of the trials (68.4% vs 26.7% and 38.9% vs 13.2% in the two largest trials).
- 4.1.1.10 Quality of life measures were reported by one study with an active comparator (n = 975) and one vehicle-controlled study in which participants were drawn from subsets of the largest studies of adults and children (n = 985). Both studies measured quality of life using the DLQI. Compared with a topical corticosteroid regimen (potent topical corticosteroid on the body and mild topical corticosteroid on the face), greater percentage improvements were found with 0.1% tacrolimus (66.7% vs 58.5% at 3 months and 74.3% vs 69.2% at 6 months, statistical significance was not reported), although the results for the different dimensions of 'quality of life' were not reported separately. Compared with vehicle, both strengths of tacrolimus were associated with greater improvements across all measurement dimensions in adults (symptoms and feelings, daily activities, leisure, work/school, personal relations, treatment [p = 0.0001]). In children (using the Children's DLQI [CDLQI] completed by children with help from parents/guardians), greater improvements were found with 0.03% tacrolimus than with vehicle across all measurement dimensions except one (the personal relationships dimension [p < 0.0001 to p = 0.02]) and across all dimensions for toddlers (using the CDLQI for toddlers completed by parents/guardians [p < 0.0001 to p = 0.001]).
- 4.1.1.11 For adverse effects, pooled analyses showed no statistically significant differences in skin infection rates between tacrolimus and topical

corticosteroids. However, there was more skin burning in children with 0.03% tacrolimus compared with mild topical corticosteroids (RR 1.97, 95% CI 1.25 to 3.11) and in adults with 0.1% tacrolimus compared with potent topical corticosteroid regimens (RR 4.17, 95% CI 3.36 to 5.18). Withdrawal because of adverse effects was similar for tacrolimus and topical corticosteroids (1.6% to 3.9% of the tacrolimus group vs 1.6% to 3.3% of those using topical corticosteroids) but was consistently higher in the vehicle arms of the trials (4.5% to 12.3% with vehicle vs 2.9% to 5.7% with tacrolimus).

- 4.1.1.12 Overall, tacrolimus is more effective in treating moderate to severe disease in adults and children than vehicle alone. In children, a number of measures of treatment effect suggest that tacrolimus is also more effective than mild topical corticosteroids but no trials have compared it with more potent topical corticosteroids. In adults, compared with topical corticosteroids, 0.1% tacrolimus was statistically significantly more effective in one study (n = 975) but not statistically significantly different in the other two studies (n = 570 and n = 181).

#### **4.1.2 Pimecrolimus**

- 4.1.2.1 Of the eight RCTs of pimecrolimus, three were conducted in children and five in adults. Three of the studies were provided by the manufacturer as commercial in confidence (two studies in adults and one study in children).
- 4.1.2.2 None of the RCTs in children compared pimecrolimus with topical corticosteroids. Two studies used vehicle as a comparator (n = 403 and n = 713 ['n' refers to overall study size]) and one compared pimecrolimus with 0.03% tacrolimus (provided in confidence by the manufacturer [n = 141]).
- 4.1.2.3 Two of the RCTs in adults used potent topical corticosteroids as a comparator (n = 260 and n = 658); the larger of these two RCTs was provided in confidence by the manufacturer. Three studies used vehicle as

a comparator (n = 34, n = 192 and n = 260). A further vehicle-controlled study was provided in confidence by the manufacturer (n = 200).

- 4.1.2.4 One of the studies in children (n = 713) and one in adults (n = 192) permitted the use of moderately potent topical corticosteroids to treat flare-ups in the treatment and control groups.
- 4.1.2.5 Three of the studies in adults were conducted in people with moderate to severe disease, which does not match the licensed indication (see Section 3.2.1). They were included in the review for pragmatic reasons – firstly, on the basis of expert advice that there is considerable overlap between categories of eczema severity and, secondly, because of the limited evidence available from studies comparing pimecrolimus with an active treatment.
- 4.1.2.6 Compared with potent topical corticosteroids, evidence from the smaller study suggests that pimecrolimus is less effective in treating moderate to severe atopic eczema. This study included four strengths of pimecrolimus (0.05%, 0.2%, 0.6% and 1.0%) but only the results for 1.0% pimecrolimus are presented, reflecting the product licence (see Section 3.2.1). Fewer people treated with pimecrolimus were judged to have ‘clear’ or ‘almost clear’ eczema at 3 weeks using the IGA score (11.1% vs 50.0%, difference = 38.9%, 95% CI 21 to 56). The study also reported a smaller percentage reduction in EASI for those using pimecrolimus (47.0% vs 78.0%, statistical significance was not reported) and that fewer people treated with pimecrolimus had mild or absent pruritus (46.7% vs 81.0%, difference = 34.3%, 95% CI 15.5 to 53.1,  $p < 0.05$ ). The risk of skin burning was greater with pimecrolimus (RR 5.26, 95% CI 1.97 to 14.0). However, almost a quarter of participants were lost to follow-up (23.5%).
- 4.1.2.7 Compared with vehicle, pooled analyses of studies in children with mild to moderate disease and in adults with moderate to severe disease showed that treatment with pimecrolimus resulted in better IGA scores at 3 and

6 weeks (RR 4.47, 95% CI 1.40 to 14.27 [3 weeks]; RR 1.87, 95% CI 1.26 to 2.76 [6 weeks]) and fewer flare-ups at 6 months (RR 1.78, 95% CI 1.10 to 2.86). People using pimecrolimus were less likely to use additional treatment with topical corticosteroids (RR 1.82, 95% CI 1.51 to 2.21) and pruritus was more often absent or mild at 3 and 6 weeks among the pimecrolimus group (RR at 3 weeks 1.99, 95% CI 1.53 to 2.58).

- 4.1.2.8 Results from individual studies showed that pimecrolimus was statistically significantly more effective than vehicle using other measures of treatment effect, such as changes in EASI score and reduction in BSA affected.
- 4.1.2.9 Quality of life for people treated with pimecrolimus was reported by one comparison with vehicle in adults (n = 192) and for a subset of participants from the smaller study in children (n = 241). The study in adults reported changes in two quality of life measures (the Quality of Life Index – Atopic Dermatitis [QoLIAD] and the DLQI) and found greater improvements among patients using pimecrolimus compared with those using vehicle for both measures (25.6% vs 7.4%, p = 0.002 and 22% vs 6.7%, p = 0.01). The study in children, which used the Parent’s Index of QOL in Atopic Dermatitis, also reported a higher quality of life with pimecrolimus (p = 0.023).
- 4.1.2.10 For adverse effects, a pooled analysis showed no statistically significant differences in rates of bacterial infection and skin burning between pimecrolimus and vehicle, but there was a greater risk of viral skin infection with pimecrolimus (12% vs 6%, RR 1.97, 95% CI 1.21 to 3.19).
- 4.1.2.11 Overall, studies found pimecrolimus to be more effective at treating atopic eczema in adults and children than was vehicle alone. There is limited evidence on the effectiveness of pimecrolimus compared with topical corticosteroids.

## 4.2 *Cost effectiveness*

The Committee considered economic analyses submitted by the manufacturers of both products and a model developed by the Assessment Group. There was only one relevant published economic analysis and this was conducted from the perspective of the US healthcare system and had methodological problems that limited its value. The Assessment Group analysis consisted of eight separate models, each relating to different cohorts of people with atopic eczema.

### 4.2.1 **Tacrolimus**

4.2.1.1 For the analysis of cost effectiveness in children, the Assessment Group model was run over 14 years to incorporate the possibility of disease resolution. All patients were assumed to be aged 2 years on entering. The model estimated that the costs per additional quality-adjusted life year (QALY) of first- and second-line treatment of eczema on the body were £9100 and £14,200, respectively, relative to the standard practice of using topical corticosteroids alone. For eczema in sensitive areas (on the face or in areas such as the armpits or groin where the treatment options are more limited because of concerns about skin atrophy), the costs per additional QALY were higher. First-line treatment cost £35,700 per additional QALY and second-line treatment was dominated by topical corticosteroids (that is, tacrolimus was both less effective and more costly than topical corticosteroids).

4.2.1.2 In adults, the cost per additional QALY of first-line treatment of eczema on the body with tacrolimus was £37,400 relative to standard treatment with topical corticosteroids. Second-line treatment of 'body' eczema with tacrolimus cost less than topical corticosteroids alone but also conferred fewer QALYs. For eczema in sensitive areas (see Section 4.2.1.1), the cost per additional QALY of first-line treatment with tacrolimus was £11,900, and second-line treatment with tacrolimus was dominated by topical corticosteroids.

- 4.2.1.3 Using a lower estimate of the amount of tacrolimus ointment used (2.3 g per day rather than 6.8 g per day) for adults reduced the incremental cost effectiveness ratio (ICER) for the treatment of 'body' eczema with tacrolimus (first-line) to £30,300 per QALY. Second-line treatment of 'body' eczema with tacrolimus still cost less than topical corticosteroids alone whilst also conferring fewer QALYs. The ICER for first-line treatment of eczema in sensitive areas (see Section 4.2.1.1) was also lower (£7000 per QALY), but tacrolimus as a second-line treatment continued to be dominated by topical corticosteroids.
- 4.2.1.4 Overall, tacrolimus (first- and second-line) was estimated to be more costly than topical corticosteroids alone in all cases except one (second-line treatment of 'body' eczema in adults), whilst absolute differences in QALYs were very small. The Assessment Group also performed probabilistic analyses. The base-case results of all the Assessment Group's models were shown to be associated with considerable uncertainty, due mainly to the very small incremental benefits predicted.
- 4.2.1.5 The manufacturer provided a cost-effectiveness analysis, in terms of disease-controlled days (DCDs), and compared treatment with tacrolimus (0.1% in adults, and 0.1% and 0.03% in children) after topical corticosteroids (potent topical corticosteroids as comparator for 0.1% tacrolimus, mild topical corticosteroids as comparator for 0.03% tacrolimus) with treatment with tacrolimus before topical corticosteroids in a hospital outpatient setting. The model adopted a semi-Markov approach, organised in four arms (topical corticosteroids in moderate or severe disease and tacrolimus in moderate or severe disease), and each one included four states of progression of atopic eczema (cleared or virtually cleared, moderately controlled, uncontrolled and flare-up). Each arm was run for 27 weeks (adults) or 15 weeks (children), corresponding to the duration of follow-up in the RCTs from which the effectiveness estimates were derived (scenario 1). In a second scenario, the model was run for

51 weeks on the basis of effectiveness estimates obtained from experts, and ciclosporin was included as a comparator for adults with severe eczema. A modified NHS and Personal and Social Services perspective was adopted, including work days lost.

- 4.2.1.6 The results were presented as average cost-effectiveness ratios rather than ICERs. The Assessment Group calculated ICERs using the data provided by the manufacturer.
- 4.2.1.7 For children with moderate disease, results from scenario 1 showed that 0.03% tacrolimus was dominated by both topical corticosteroids and 0.1% tacrolimus (that is, it produced fewer DCDs and was more costly than topical corticosteroids and 0.1% tacrolimus) and that 0.1% tacrolimus produced more DCDs than topical corticosteroids but was also more costly (the cost per additional DCD with 0.1% tacrolimus relative to topical corticosteroids was £16.40). In contrast, for children with severe disease, 0.1% tacrolimus was dominated by 0.03% tacrolimus and topical corticosteroids, and 0.03% tacrolimus produced more DCDs than topical corticosteroids but was also more costly (the cost per additional DCD with 0.03% tacrolimus relative to topical corticosteroids was £18.10). In scenario 2, where the model was run over 51 weeks, the cost per additional DCD with tacrolimus relative to topical corticosteroids was £3.30 (moderate eczema) and £16.10 (severe eczema). Overall, differences in the costs and effectiveness of tacrolimus compared with topical corticosteroids were very small and the results were sensitive to a number of cost and effectiveness variables.
- 4.2.1.8 For adults, results from scenario 1 showed that tacrolimus dominated topical corticosteroids in those with moderate or severe atopic eczema. In scenario 2, where the model was run over 51 weeks, tacrolimus produced more DCDs compared with topical corticosteroids but was also more costly; the cost per additional DCD with tacrolimus was £6.20 (moderate eczema) and £26.80 (severe eczema). However, patients with severe

atopic eczema treated with ciclosporin achieved more DCDs than did those treated with tacrolimus, although ciclosporin was more expensive (the cost per additional DCD with ciclosporin was £4.80). These patterns were reflected in further analyses excluding work days lost. The results were sensitive to a number of variables.

#### **4.2.2 Pimecrolimus**

- 4.2.2.1 The Assessment Group's base-case results showed that, compared with topical corticosteroids, first-line use of pimecrolimus cost more and conferred slightly fewer QALYs for children and adults with atopic eczema both on the body and in sensitive areas (see Section 4.2.1.1). Using pimecrolimus as a second-line rather than first-line treatment was less expensive but was still dominated by topical corticosteroids. However, the probabilistic analyses showed that these results were associated with considerable uncertainty.
- 4.2.2.2 The Assessment Group developed subsidiary models (one for adults and one for children) to evaluate the cost effectiveness of pimecrolimus compared with emollients, with moderately potent topical corticosteroids used as a 'rescue therapy' for all patients with uncontrolled 'problem' eczema. The basic structure of these models was the same as that of the models used to compare active treatments, although no distinction was made between eczema on sensitive areas and eczema on the rest of the body. Compared with emollients alone, the ICERs for treatment with pimecrolimus were £9700 per QALY in children and £16,600 per QALY in adults. Again, the results were associated with a high degree of uncertainty.
- 4.2.2.3 The manufacturer developed a cost–utility model comparing pimecrolimus with emollients. A Markov approach was used, based on four states of progressive severity (remission, mild, moderate and severe). The use of topical corticosteroids was permitted as a rescue therapy in patients with

severe disease. The model was run for 1 year. An NHS perspective was adopted and 2003 was the base year for estimating costs.

- 4.2.2.4 For all parts of the body, the estimated cost per additional QALY was £24,500 in children and £27,400 in adults and, for head and neck only, £4668 in children and £21,766 in adults. The results were sensitive to a number of variables. Probabilistic analyses of the model for children showed that, when £30,000 is considered to be an acceptable amount to pay for an additional QALY, the probability of pimecrolimus being most likely to be cost effective is 60%, the probability that it will dominate vehicle is 20% and the probability that the cost for an additional QALY will be greater than £100,000 is 17%. In patients with mainly head and neck atopic eczema, the probabilities were 75%, 35% and 20%, respectively. Probabilistic analyses were not presented for adults.

### **4.3 Consideration of the evidence**

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of tacrolimus and pimecrolimus, having considered evidence on the nature of the condition and the value placed on the benefits of tacrolimus and pimecrolimus by people with atopic eczema, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee was persuaded that tacrolimus and pimecrolimus have both been shown to be effective in treating atopic eczema when compared with vehicle. They noted, however, that vehicle is not the most appropriate comparator in the majority of cases.
- 4.3.3 The Committee observed that no studies had compared 0.03% tacrolimus in children with moderate to severe disease with potent or moderately potent topical corticosteroids, but that there was evidence from two RCTs of greater effectiveness compared with mild topical corticosteroids. It also noted that the two largest RCTs in adults that compared tacrolimus and potent topical

corticosteroid regimens had produced inconsistent results: 0.1% tacrolimus was statistically significantly more effective than topical corticosteroids in the larger study, whereas no statistically significant differences were reported in the smaller study, although potent topical corticosteroids were found to be more effective than 0.03% tacrolimus. The Committee concluded that the available evidence suggested that tacrolimus was similar in effectiveness to topical corticosteroids for the treatment of moderate to severe atopic eczema.

- 4.3.4 The Committee noted that there is limited evidence on the effectiveness of pimecrolimus compared with topical corticosteroids. No studies had compared pimecrolimus with topical corticosteroids in children, and the results of the studies in adults favoured topical corticosteroids.
- 4.3.5 Consideration was given to the results of the economic models developed by the Assessment Group and the manufacturers of tacrolimus and pimecrolimus. The Committee acknowledged that the base-case results of the Assessment Group's model were associated with very considerable uncertainty, reflecting the closeness of the utility estimates for all the strategies, coupled with the necessity to estimate a number of parameters in the model in the absence of good-quality evidence, and of the need to combine treatment and disease states in order to address the different potential uses of the new immunomodulators. The Committee concluded that, because of the significant parameter uncertainty, the base-case ICERs could not, in themselves, provide the sole basis for a decision. It was agreed, however, that similar benefits accrue to patients with atopic eczema with tacrolimus as with the use of topical corticosteroids but at a greater cost.
- 4.3.6 The Committee considered that the Fujisawa economic model of tacrolimus did not provide any evidence to override their conclusion in 4.3.5. The analysis was limited in that results were expressed only in terms of DCDs rather than QALYs; and it only compared tacrolimus treatment after the use of topical corticosteroids with tacrolimus treatment before topical corticosteroids, and not with topical corticosteroids alone.

- 4.3.7 On the basis of the Assessment Group's economic model of pimecrolimus, the Committee agreed that pimecrolimus was not cost effective compared with topical corticosteroids. Although the Assessment Group's model and the manufacturer's model suggested that pimecrolimus was cost effective relative to emollients alone, the Committee was not convinced that this was the most clinically appropriate comparator in the majority of cases.
- 4.3.8 The Committee was concerned by the possibility that immunomodulators might increase the risk of skin malignancy in the long term – there is some evidence that tacrolimus may reduce the time to development of ultraviolet-induced tumours in experimental animals, although this was associated with much higher systemic levels of tacrolimus than would be seen in clinical use, and it is known that systemic use of tacrolimus and related drugs is associated with the development of skin cancers. For this reason, the Committee believed that topical immunomodulators should not be used without careful discussion of the potential risks and benefits with the patient.
- 4.3.9 The Committee heard from the clinical experts that topical corticosteroids provide effective first-line management of atopic eczema and that, because of the higher cost of tacrolimus and pimecrolimus and their potential unknown long-term adverse effects, the experts would not recommend either of these products as first-line treatments.
- 4.3.10 The Committee heard from the clinical experts that topical immunomodulators are useful in cases where continual use of potent topical corticosteroids is required and there is a serious risk of skin atrophy. The experts also agreed that topical immunomodulators are useful alternatives to systemic treatments in severe resistant atopic eczema.
- 4.3.11 The Committee heard from the clinical experts that concern about long-term adverse effects, particularly the risk of skin atrophy, causes significant anxiety about the use of topical corticosteroids in people with atopic eczema. The clinical experts were in agreement, however, that anxiety around steroid use

should not be an indication for treatment with topical immunomodulators, but that this anxiety should be addressed through effective patient information and education.

4.3.12 Taking into account the evidence on the cost and effectiveness of topical immunomodulators, and the views of the clinical experts, the Committee agreed that topical immunomodulators should not be recommended for mild atopic eczema or as first-line treatments for atopic eczema of any severity. The risk of skin atrophy associated with topical corticosteroid use was relevant only to the moderate and severe end of the disease spectrum and to continual and high-dose use. The Committee, however, did recognise the need for second-line treatments in patients with moderate to severe disease 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.

4.3.13 Only tacrolimus is licensed for severe atopic eczema, and so consideration was given to the relative benefits of pimecrolimus compared with tacrolimus for the second-line treatment of moderate atopic eczema. The Committee noted the considerably weaker evidence base for pimecrolimus compared to tacrolimus in adults and agreed that pimecrolimus should not therefore be recommended for use in adults.

4.3.14 The Committee further considered the effectiveness of pimecrolimus and tacrolimus in children for whom the only licensed tacrolimus strength is 0.03%. The Committee noted the results of the study that compared pimecrolimus and 0.03% tacrolimus in children, and was persuaded by the views of some of the clinical experts that pimecrolimus is a useful treatment option for moderate facial atopic eczema in children because of its different formulation and tolerability to tacrolimus.

4.3.15 The Committee therefore concluded that tacrolimus should be recommended as an option for the second-line treatment of moderate to severe atopic

eczema in adults and children aged 2 years and older in the circumstances outlined in Section 4.3.12. The Committee also concluded that pimecrolimus could be recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2 to 16 years, but that it should not be recommended for use on other parts of the body.

4.3.16 It was agreed that, for the purposes of this guidance, atopic eczema that has not been controlled by topical corticosteroids would refer to disease that has not shown a satisfactory clinical response to adequate use of the maximum strength and potency of topical corticosteroid that is appropriate for the patient's age and the area being treated.

4.3.17 Finally, the Committee considered how and by whom tacrolimus and pimecrolimus should be prescribed. Given the uncertainties around the long-term effects of the immunomodulators, the Committee agreed that it would be appropriate to recommend that they be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient of the potential risks and benefits of all appropriate second-line treatment options.

## **5 Recommendations for further research**

5.1 Given that 0.03% tacrolimus in children with moderate to severe atopic eczema has only been compared to mild topical corticosteroids, the Committee recommends that high-quality studies be undertaken using moderately potent topical corticosteroids as a comparator.

5.2 The Committee recommends that high-quality RCTs of pimecrolimus compared with appropriate potencies of topical corticosteroids be undertaken in children and adults with mild to moderate atopic eczema.

5.3 The Committee recommends that additional head to head studies of tacrolimus and pimecrolimus be conducted to enable further direct comparisons of efficacy to be made.

- 5.4 The Committee emphasises the need for careful and long-term surveillance for adverse effects of tacrolimus, including skin and other types of malignancy.
- 5.5 To achieve greater consensus among researchers and clinicians on how to measure treatment success in studies of atopic eczema, the Committee recommends that further research be conducted into the reliability of methods of measurement.
- 5.6 The Committee recommends that observational studies be conducted to provide basic information about the treatment patterns and health service utilisation by people with atopic eczema in England and Wales.

## **6 Implications for the NHS**

- 6.1 The guidance will affect only a small proportion of people with atopic eczema who have moderate or severe forms of the disease (see Section 2.3). It is not clear what proportion of people with moderate or severe disease currently experience an unsatisfactory clinical response to adequate use of the maximum strength and potency of topical corticosteroid that is appropriate for their age and the area being treated and who are at serious risk of developing important adverse effects from further topical corticosteroid use such as permanent skin atrophy. It is therefore unclear what proportion of people with moderate or severe atopic eczema would use tacrolimus or pimecrolimus under this guidance. For pimecrolimus, this is further complicated by the lack of information on the number of children with moderate atopic eczema that has not been controlled by topical corticosteroids and who are affected by the disease on the face and neck.
- 6.2 The cost per gram of topical corticosteroids (3–14p) is small compared with the cost per gram of tacrolimus (62–68p) and the cost per gram of pimecrolimus (59p). By varying estimates around the cost of topical corticosteroids and the quantity used, a crude calculation suggests that the

additional cost per year per patient compared with topical corticosteroids would lie between £538 and £1192 for tacrolimus and between £511 and £1117 for pimecrolimus. However, these estimates assume that all other treatment costs, such as the number of visits to physicians, the incidence of adverse effects such as infections and the quantity of the topical immunomodulators required compared with topical corticosteroids, would remain the same.

6.3 Using the above estimates, the additional spending in a Primary Care Trust (PCT) with a population of 100,000 people was calculated crudely, assuming different levels of uptake with tacrolimus and pimecrolimus. The calculations assumed the point prevalence of atopic eczema to be 13.4% (based on a prevalence study in the UK in 1996), that 14% of people with atopic eczema have moderate disease and that 2% of people with atopic eczema have severe disease. On the basis of these assumptions, the estimated additional annual spending in a PCT this size would be:

- between £11,500 and £25,600 if 1% of people currently using topical corticosteroids with moderate or severe disease need to switch to tacrolimus, and between £9600 and £21,000 if 1% of people with moderate disease need to switch to pimecrolimus (in this case, children with atopic eczema on the face or neck)
- between £23,100 and £51,100 if 2% of people currently using topical corticosteroids with moderate or severe disease need to switch to tacrolimus, and between £19,200 and £41,900 if 2% of people with moderate disease need to switch to pimecrolimus (in this case, children with atopic eczema on the face or neck)
- between £57,700 and £127,800 if 5% of people currently using topical corticosteroids with moderate or severe disease need to switch to tacrolimus, and between £47,900 and £104,800 if 5% of people with moderate disease

need to switch to pimecrolimus (in this case, children with atopic eczema on the face or neck).

Given the number of assumptions involved in the calculations, these estimates should be interpreted cautiously. In addition, it is known that 610,000 prescriptions for tacrolimus with a total net ingredient cost of £2,260,300 and 21,650 prescriptions for pimecrolimus with a total net ingredient cost of £652,900 were issued in England during 2003. It has therefore been estimated that a PCT with a population of 100,000 would have spent around £4500 on prescriptions for tacrolimus and around £1300 on prescriptions for pimecrolimus during this time.

## **7 Implementation and audit**

- 7.1 All clinicians who care for people with atopic eczema should review their current practice and policies to take account of the guidance set out in Section 1.
- 7.2 Local guidelines or care pathways for people with atopic eczema should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
  - 7.3.1 Topical tacrolimus and pimecrolimus are not prescribed for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.
  - 7.3.2 Topical tacrolimus is considered, within its licensed indications, as an option for the second-line treatment of moderate or 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.

7.3.3 Pimecrolimus is considered, 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.

7.3.4 Treatment with tacrolimus or pimecrolimus is initiated only by a physician with a special interest and experience in dermatology.

7.3.5 Treatment with tacrolimus or pimecrolimus is initiated only after careful discussion between the prescribing physician and the patient about the potential risks and benefits of all appropriate second-line treatment options.

7.4 Local clinical audits could also include measurement of compliance with recognised guidelines for the management of atopic eczema and the effectiveness of patient education on the use of treatments for atopic eczema.

## **8 Related guidance**

8.1 The frequency of application of topical corticosteroids for atopic eczema is currently being appraised by NICE and guidance is due to be published in July 2004, subject to any appeals.

## **9 Review of guidance**

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide

whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology will be reviewed in September 2007.

Andrew Stevens

Chair, Appraisal Committee

June 2004

## **Appendix A. Appraisal Committee members**

**NOTE** The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice-chair and a number of other members between them attending meetings of all branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **Dr Darren Ashcroft**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences,  
University of Manchester

### **Professor David Barnett**

Professor of Clinical Pharmacology, University of Leicester

### **Mr Brian Buckley**

Vice Chairman, InContact

### **Professor John Cairns**

Professor of Health Economics, Health Economics Research Unit, University of  
Aberdeen

### **Professor Mike Campbell**

Statistician, Institute of General Practice & Primary Care, Sheffield

National Institute for Clinical Excellence  
Final Appraisal Determination  
Tacrolimus and pimecrolimus for atopic eczema  
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**Dr Mark Chakravarty**

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd, Egham, Surrey

**Dr Peter I Clark**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Wirral, Merseyside

**Dr Mike Davies**

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

**Mr Richard Devereaux-Phillips**

Public Affairs Manager, Medtronic Ltd

**Professor Jack Dowie**

Health Economist, London School of Hygiene

**Professor Gary A Ford (Vice-Chair)**

Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

**Dr Fergus Gleeson**

Consultant Radiologist, The Churchill Hospital, Oxford

**Ms Sally Gooch**

Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

**Professor Trisha Greenhalgh**

Professor of Primary Health Care, University College London

**Miss Linda Hands**

Clinical Reader in Surgery, University of Oxford

**Professor Peter Jones**

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

National Institute for Clinical Excellence

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Issue date: June 2004

**Professor Robert Kerwin**

Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

**Ms Joy Leavesley**

Senior Clinical Governance Manager, Guy's and St Thomas' NHS Trust

**Ms Rachel Lewis**

Staff Nurse (Nephrology), Hull Royal Infirmary

**Dr Ruairidh Milne**

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology Assessment, University of Southampton

**Dr Neil Milner**

General Medical Practitioner, Sheffield

**Dr Rubin Minhas**

General Practitioner with a Special Interest in Coronary Heart Disease, Primary Care CHD Lead, Medway PCT & Swale PCT

**Mr Miles Scott**

Chief Executive, Harrogate Health Care NHS Trust

**Professor Mark Sculpher**

Professor of Health Economics, University of York

**Dr Ken Stein**

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Professor Andrew Stevens (Chair)**

Professor of Public Health, University of Birmingham

## **B. NICE Project Team**

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

### **Zoe Charles**

Technical Lead, NICE project team

### **Dr Sarah Cumbers**

Project Manager, NICE project team

## Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was produced by:

- Peninsula Technology Assessment Group, Peninsula Medical School, Universities of Exeter and Plymouth
- School of Pharmacy and Pharmaceutical Sciences, University of Manchester
- Wessex Institute for Health Research and Development, University of Southampton.

Garside R, Stein K, Castelnovo E, et al. *The effectiveness and cost effectiveness of pimecrolimus and tacrolimus for atopic eczema*, January 2004.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Fujisawa Ltd
- Novartis Pharmaceuticals Ltd

II Professional/specialist and patient/carer groups:

- British Association of Dermatologists
- Department of Health
- Kensington and Chelsea Primary Care Trust
- National Eczema Society
- Royal College of General Practitioners
- Royal College of Nursing

- Royal College of Physicians
- Royal Pharmaceutical Society
- Skin Care Campaign
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- Centre of Evidence-Based Dermatology, University of Nottingham
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Skin Treatment & Research Trust

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on tacrolimus and pimecrolimus for atopic eczema by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Ms Margaret Cox, Chief Executive, National Eczema Society, nominated by the National Eczema Society.
- Dr John English, Consultant Dermatologist, Queens Medical Centre, Nottingham, nominated by the Centre of Evidence-Based Dermatology.
- Professor John Harper, Consultant Paediatric Dermatologist, The Hospital for Sick Children, Great Ormond Street, nominated by the British Association of Dermatologists.

- Dr Celia Moss, Consultant Dermatologist, Birmingham Children's Hospital, West Midlands NHS Trust, nominated by The National Eczema Society and The Centre of Evidence-Based Dermatology.
- Dr Catherine H Smith, Consultant Dermatologist, Lewisham University Hospital, nominated by the British Association of Dermatologists.

## **Appendix C. Detail on criteria for audit of the use of tacrolimus and pimecrolimus for atopic eczema**

### ***Possible objectives for an audit***

An audit could be carried out to ensure that pimecrolimus and tacrolimus are prescribed appropriately.

### ***Possible patients to be included in the audit***

An audit could be carried out on all children and adults seen for atopic eczema in a reasonable period for audit, for example, 6 months.

### ***Measures that could be used as a basis for an audit***

The measures that could be used in an audit of the appropriateness of prescription of tacrolimus and pimecrolimus for atopic eczema are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. Topical tacrolimus or pimecrolimus are prescribed for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity</p>	<p>0% of people with atopic eczema</p>	<p>None</p>	<p>The diagnosis of atopic eczema is established by the individual having an itchy skin condition in the last 12 months, plus three or more of the following criteria: history of flexural involvement (that is, affecting the bends of the elbow or behind the knees); history of a generally dry skin; personal history of other atopic disease (in children under 4 years, history of atopic disease in a first-degree relative may be included); visible flexural dermatitis as defined by a photographic protocol; and onset below the age of 2 years (not used in children under 4 years). Clinicians will need to agree locally on how to identify people with mild atopic eczema for audit purposes.</p>
<p>2. Topical tacrolimus is considered, within its licensed indications, as an option for the second-line treatment of moderate or severe atopic eczema in adults and children aged 2 years and over in the following circumstances:</p> <p>a. the individual's atopic eczema has not been controlled by topical corticosteroids <b>and</b></p> <p>b. there is a serious risk of important adverse effects from further</p>	<p>100% of adults and children aged 2 years and older with moderate or severe atopic eczema that has not been controlled by topical corticosteroids and where there is a serious risk of important adverse effects from further topical corticosteroid use</p>	<p>None</p>	<p>Clinicians will need to agree locally on how to identify people with moderate or severe atopic eczema and how to document that topical tacrolimus has been considered, within its licensed indications, as an option, for audit purposes.</p> <p>'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. Clinicians will need to agree locally on what constitutes adequate use of appropriate potency topical corticosteroids, for audit purposes, but anxiety around topical corticosteroid use alone should not be considered an indication for treatment with tacrolimus.</p> <p>Irreversible skin atrophy includes telangiectasia, increased transparency and shininess of the skin and the appearance of striae.</p>

<p>topical corticosteroid use, particularly irreversible skin atrophy</p>			
<p>3. Pimecrolimus is considered, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face or neck in children aged 2 to 16 years in the following circumstances:</p> <p>a. the child's facial atopic eczema has not been controlled by topical corticosteroids <b>and</b></p> <p>b. there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.</p>	<p>100% of children aged 2 to 16 years with moderate atopic eczema on the face or neck that has not been controlled by topical corticosteroids and where there is a serious risk of important adverse effects from further topical corticosteroid use</p>	<p>None</p>	<p>See above for definitions.</p>

<p>4. Treatment with tacrolimus or pimecrolimus is initiated only by a physician with a special interest and experience in dermatology</p>	<p>100% of people who are prescribed tacrolimus or pimecrolimus</p>	<p>None</p>	<p>'A physician with a special interest and experience in dermatology' can be a physician or a general practitioner.</p>
<p>5. Treatment with tacrolimus or pimecrolimus is initiated only after careful discussion between the prescribing physician and the patient of the potential risks and benefits of all appropriate second-line treatment options</p>	<p>100% of people who are prescribed tacrolimus or pimecrolimus</p>	<p>None</p>	<p>Clinicians will need to agree locally on how the discussion with the patient is documented, for audit purposes. Risks of topical tacrolimus include side effects such as a burning or tingling sensation, pruritus, erythema, folliculitis, herpes simplex, acne, increased sensitivity to hot and cold, alcohol intolerance and lymphadenopathy. Risks of pimecrolimus include side effects such as a burning sensation, pruritus, erythema, skin infections (including folliculitis, herpes simplex and zoster, impetigo and molluscum contagiosum), papilloma (rarely) and local reactions such as pain, paraesthesia, peeling, dryness, oedema and worsening of eczema. The discussion should make clear to the patient that the potential long-term adverse effects of topical tacrolimus or pimecrolimus are not yet known and that it is possible that topical immunomodulators might increase the risk of skin malignancy in the long-term. Second-line treatment options, in addition to tacrolimus and pimecrolimus, include systemic corticosteroids, phototherapy and systemic use of immunosuppressants such as ciclosporin. Clinicians will need to agree locally on the risks and benefits of second-line treatment options that are discussed with the patient, for audit purposes.</p>

**Calculation of compliance**

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.