NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisals and Guidance Information Services

Static List Review (SLR)

Title and TA publication number of static topic:	TA82; Tacrolimus and pimecrolimus for atopic eczema
Final decision:	The guidance will remain on the 'static guidance list'

1. Publication date:	August 2004
2. Date added to static list:	June 2009
3. Date the last searches were run:	Dec 2008/January 2009
4. Current 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.
5. Research recommendations from original guidance:	5.1 Given that 0.03% tacrolimus in children with moderate to severe atopic eczema has only been compared with 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 and pimecrolimus, 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. Current cost of technology/ technologies:	**Tacrolimus (Protopic 0.03% and 0.1% ointment, Astellas Pharma Ltd)** Ointment, tacrolimus (as monohydrate) 0.03%, net price 30 g = £19.44, 60 g = £35.46; 0.1%, 30 g = £21.60, 60 g = £39.40. Label: 4, 11, 28 **Pimecrolimus (Elidel, Meda, prescription only medicine)** Cream, pimecrolimus 1%, net price 30 g = £19.69, 60 g = £37.41, 100 g = £59.07. Label: 4, 11, 28
7. Cost information from the TA (if available):	**Tacrolimus**: 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).

	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).
8. Alternative manufacturers:	No alternative manufacturers found.
9. Changes to the original indication:	**Tacrolimus** **SPC during TA82**: 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. **Current SPC (Protopic, Astellas Pharma Ltd):** Protopic 0.03% ointment is indicated in adults, adolescents and children from the age of 2 years. Protopic 0.1 % ointment is indicated in adults and adolescents (16 years of age and above). Flare treatment *Adults and adolescents (16 years of age and above)* Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids. *Children (2 years of age and above)* Treatment of moderate to severe atopic dermatitis in children who failed to respond adequately to conventional therapies such as topical corticosteroid. Maintenance treatment Treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment

	(lesions cleared, almost cleared or mildly affected). **<u>Pimecrolimus</u>** **SPC during TA82:** 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. **Current SPC for pimecrolimus (Elidel, Meda):** 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
10. New relevant trials:	No new trials found.
11. Relevant NICE guidance (published or in progress):	NICE technology appraisal guidance [TA177] Alitretinoin for the treatment of severe chronic hand eczema Published date: August 2009. Reviewed: October 2012 - transferred to the static guidance list NICE interventional procedures guidance [IPG236] Grenz rays therapy for inflammatory skin conditions. Published date: November 2007. Review date to be confirmed NICE guidelines [CG57] Atopic eczema in children: Management of atopic eczema in children from birth up to the age of 12 years Published date: December 2007. Reviewed: July 2011 - the guideline should not be updated. Reviewed: February 2014 - the guideline should not be updated

	NICE technology appraisal guidance [TA81] Frequency of application of topical corticosteroids for atopic eczema Published date: August 2004. Reviewed: December 2007 - transferred to the static guidance list
12. Relevant safety issues:	Tacrolimus ointment (Protopic): possible risk of malignancies including lymphomas and skin cancers (2012) Medicines and Healthcare Products Regulatory Agency
13. Technical Lead comments and recommendation:	The license extension for tacrolimus and licence restriction for pimecrolimus (since TA82) were considered as part of the review decision in 2009, and were not regarded as reasons to review the guidance. • Considering the population reflected in the licence extension for tacrolimus (maintenance treatment for flare prevention) will already have this cream to treat their condition on an intermittent basis, implementation of any guidance on secondary prophylaxis for the same population will therefore be challenging. • The license restriction for pimecrolimus (to second line) remains consistent with existing guidance recommendations. There have been no changes to the indications for these technologies since the review decision in 2009. There have been no substantial pricing changes (only a minor reduction in price for 60g tacrolimus). Research recommendations from the original guidance included the conduct of head-to-head studies of tacrolimus and pimecrolimus. A number of studies have since completed, showing that tacrolimus is more effective than pimecrolimus. This evidence was available at the time of the review proposals in 2007 and 2009, at which point NICE concluded that the evidence would not change the recommendations in the existing guidance. The existing guidance already limits use of pimecrolimus (pimecrolimus is limited to the face and neck of children; tacrolimus can be used for all

	areas, in adults as well as children). The drug safety update from the MHRA (URL above, under 'Relevant safety issues') relates to a publication from the European Medicines Agency (EMA) in 2006, which recommended greater caution in the way tacrolimus and pimecrolimus are used in order to reduce potential risks of skin cancer and lymphoma as far as possible (the SPC was updated accordingly). During TA82, the Committee was aware of, and concerned by, the potential for the technologies to increase the risk of skin malignancy (although the guidance pre-dated the EMA publication). The potential risks were reflected in the guidance recommendations (section 1.5). The 2006 publication from the EMA has also been incorporated in TA82 (in the section 'Changes after publication'). The update from the MHRA does not contain any new recommendations, but does contain references to more recent epidemiological data (2009) which would not have been captured by the search in clinicaltrials.gov conducted as part of this review proposal. However it is unlikely that these would affect the Committee's recommendations (even though the research recommendations from TA82 emphasised the need for long-term surveillance for adverse effects of tacrolimus and pimecrolimus) and therefore a review of the guidance on this basis would not provide value for the NHS.

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Appendix 1 – explanation of options

Options	Consequence	Selected – 'Yes/No'
The guidance will remain on the 'static guidance list'	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The decision to review the guidance will be deferred to specify date or trial	NICE will consider whether a review is necessary at the specified date. NICE will actively monitor the evidence available to ascertain when a consideration of a review is more suitable.	No
A full consideration of a review will be carried out through the Review Proposal Process	There is evidence that could warrant a review of the guidance. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No
The guidance will be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No