PUBLIC SUMMARY DOCUMENT
Product: Pimecrolimus, cream, 1%, 15 g, Elidel®

Sponsor: Novartis Pharmaceuticals Australia

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought to extend the current authority required PBS listing for pimecrolimus 1% cream to include the treatment of patients with atopic dermatitis who are over 18 years of age.

2. Background

An application to list pimecrolimus 1% cream on the PBS as an authority required benefit for use in patients requiring a temporary break from topical corticosteroids was rejected by the Committee at the December 2003 meeting because of uncertain clinical benefit in the proposed population and uncertain and unacceptable cost-effectiveness.

At the November 2004 meeting, the PBAC recommended an authority required listing for pimecrolimus for the treatment of facial or eyelid atopic dermatitis in patients aged between 3 months and 18 years in whom topical corticosteroids were contraindicated who meet certain criteria; and the short-term (up to 3 weeks) intermittent treatment of atopic dermatitis of the face or eyelids in patients aged between three months and eighteen years who fail to achieve satisfactory disease control with intermittent topical corticosteroid therapy, and where more than 3 months has passed since the initial diagnosis of atopic dermatitis.

The March 2006 meeting was advised of the action taken by the sponsor to amend the approved Product Information and advise medical practitioners following safety concerns with pimecrolimus following reports of skin cancers and lymphoma.

The European Medicines Agency's Committee for Medicinal Products for Human Use also conducted a safety review of pimecrolimus. The report concluded that the use of this product outweighed the risk, but it should be used with greater caution in order to reduce potential risks of skin cancer and lymphoma as far as possible. The report also made recommendations for prescribers, which agrees with the current PBS restriction.

3. Registration Status

Pimecrolimus 1% cream was approved for registration on 29 May 2003. The approved indications are "for patients 3 months of age and older with atopic dermatitis (eczema) for short term treatment of signs and symptoms; and intermittent long-term treatment of emerging and resolving lesions in atopic dermatitis where the use of a topical corticosteroid is not yet warranted, no longer needed, or is inadvisable (according to the usage restrictions in the respective topical corticosteroid Product Information)."

4. Listing Requested and PBAC's View

The requested extension to listing sought replacement of the words "between 3 months and 18 years" in the listings with the words "at least 3 months".

For the PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Pimecrolimus would provide therapy for patients in whom topical corticosteroid use is contraindicated or where continuous use is inadvisable, in patients who are over the age of 18 (extending the previous listing which was limited to those aged 3 months to 18 years).

6. Comparator

The submissions nominated topical corticosteroids (TCS) or vehicle as the comparator. This was as previously agreed by the PBAC.

7. Clinical Trials

New trial data were presented in the re-submission. In addition to Trials DE-01 and B308 described in the previous submission, one new randomised double blind controlled trial (C2442) compared pimecrolimus against vehicle in patients with facial atopic dermatitis (AD) for 6 weeks. Unlike the other trials, this trial directly measured effectiveness and usage and determined utility weights in patients who most closely resembled the requested indication. The trials published at the time of the submission were as follows:

Trial/First author	Publication title	Publication citation
C2442/ Weise-Riccardi et al	Randomized vehicle-controlled trial of pimecrolimus cream 1% in adult patients with mild to moderate head and neck atopic dermatitis intolerant of, or dependent on TCS.	Journal of Investigative Dermatology, 2006; 126: Abstract 275 (67th Annual Meeting of the Society for Investigative Dermatology)
B308/ Luger TA et al.	Long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis.	Journal of Dermatological Treatment 2004;15: 169-178.
DE-01/ Meurer M et al	Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study.	Dermatology 2002; 205:271-277.
Meurer M et al.	Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis.	Dermatology 2004; 208: 365-372.

The PBAC noted in Trial C2442, 15% of patients were between 12 and 18 years and this might have improved the results in favour of pimecrolimus. Trial results without these patients were not available.

8. Results of Trials

There was a statistically significant difference in the number of responders (defined as a

≥ 60% improvement in head/neck Eczema Area and Severity Index (EASI) score from baseline), at all weeks favouring pimecrolimus in the new key trial C2442. Post-hoc analysis of responders (defined as above) in Trial DE-01 also found a significant advantage of pimecrolimus compared with vehicle. However, the proportion of responders was higher in both treatment groups due to the availability of TCS to aid in management of the disease. Compared with TCS (Trial B308), pimecrolimus was found to be less effective compared with 1% hydrocortisone treatment in a post-hoc analysis of response (defined as above). Trial C2442 also recruited patients between 12 and 18 years of age (15% of cohort). This may have improved the overall response to pimecrolimus treatment over what might be expected in adult only patients.

Quality of life measures were also obtained for all three trials. For the new Trial (C2442), quality of life as measured by the Dermatology Life Quality Index (DLQI) was shown to improve from baseline by a mean of 31.2 ± 78.8 percent (n = 86) in the pimecrolimus arm while quality of life actually worsened by a mean of 19.4 ± 96.45 percent (n = 75) after 6 weeks of treatment in the vehicle arm. Comparison of data from the other two trials shows a similar effectiveness compared with vehicle at six weeks (Trial DE-01), but not at 24 weeks. Improvements in DLQI scores favoured TCS treatment at 3 weeks and 6 months compared with pimecrolimus in Trial B308, but not at 12 months.

In trial C2442 skin atrophy and telangiectasia from previous topical corticosteroid use was assessed at baseline and 6 weeks after treatment with pimecrolimus or vehicle cream. At the end of 6 week treatment phase the changes from baseline indicated statistically significant improvement only for the pimecrolimus-treated patients for both skin atrophy ($p < 0.01$) and telangiectasia ($p < 0.05$).

The re-submission presented new toxicity data from Trial C2442. From this trial the incidence of adverse events at 6 weeks was found to be no different between the pimecrolimus and vehicle groups. The submission stated that there were more infections, infestations and nervous system disorders in the pimecrolimus group but that this may be due to the high drop-out rate in the vehicle group due to lack of treatment efficacy (data was not presented in the submission). There were no reported deaths or serious adverse events reported in the 6 weeks of the trial.

From Trial DE-01, application site burning, dysmenorrhea and cough were statistically significantly more frequent in the pimecrolimus group compared with the control group. Trial B308 was a safety and tolerability study with a primary endpoint of skin infections. There was a trend towards fewer skin infections in patients treated with pimecrolimus compared with TCS (69/328 (21%) vs 80/330 (24.2%)).

9. Clinical Claim

The submission claimed pimecrolimus is significantly more effective than vehicle cream and has similar toxicity, and is less effective than TCS but has less toxicity.

The Committee noted the submission provided the results of an additional study, C2442 in adults, but that the results of this study may have been somewhat confounded by the 15% of the trial population in the 12 - 18 age bracket. Notwithstanding the PBAC considered that the submission's claim that pimecrolimus was significantly more effective

than vehicle cream and had similar toxicity, and was less effective than topical corticosteroids but had less toxicity, was reasonable.

10. Economic Analysis

An updated preliminary economic evaluation is presented. The trial-based incremental cost per extra responder (defined as a 60% or more improvement from baseline of the head and neck EASI score) was < $150 comparing pimecrolimus with vehicle (Trial C2442). Pimecrolimus was dominated when compared with TCS, and this was unchanged from the previous submission.

An updated modelled economic evaluation using 4 models was presented.

The base case modelled incremental discounted cost per extra discounted QALY (using EQ-5D data from Trial C2442) was < $15,000 for listing 1 (adult patients contraindicated for TCS) and for listing 2 vehicle comparison (adult patients unresponsive to or needing respite from TCS). Pimecrolimus was dominated by TCS under listing 2.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of 15 g tubes dispensed per year would be in the range of 10,000 – 50,000 for listing 1 and > 200,000 in listing 2 in Year 4 of listing, while the financial cost per year to the PBS was estimated to be < $ 10 million for adults under listing 1 and listing 2 in Year 4.

The submission stated that the listing of pimecrolimus for adults would not have an additional impact on the PBS budget because the sponsor was willing to maintain the risk-sharing threshold at its current level and subsume the adult indication for pimecrolimus in the net cost to the PBS based on the estimated utilisation in children and adolescents.

12. Recommendation and Reasons

The PBAC recommended listing on the basis of acceptable comparative efficacy and cost- effectiveness over topical corticosteroids (TCS) and vehicle cream in the requested populations. The Committee noted the submission provided the results of an additional study, C2442 in adults, but that the results of this study may have been somewhat confounded by the 15% of the trial population in the 12 - 18 age bracket. Notwithstanding the PBAC considered that the submission's claim that pimecrolimus was significantly more effective than vehicle cream and had similar toxicity, and was less effective than topical corticosteroids but had less toxicity, was reasonable.

The Committee noted that the submission presented updated modeled economic evaluations. Of the four models presented, the Committee considered Model 4, which uses EQ-5D data from trial C2442 to determine utility gain to be the most relevant. The base case modelled incremental discounted cost per extra discounted QALY estimated by this model is < $15,000 for listing 1 (adult patients contraindicated for TCS) and < $15,000 for listing 2 vehicle comparison (adult patients unresponsive to or needing respite from TCS). Pimecrolimus is dominated by TCS under listing 2. The Committee considered these estimates to be acceptable.

It was further noted that the sponsor had committed to maintaining the risk sharing threshold for pimecrolimus at its current level (that is based on the listing in children and adolescents only).

The Committee considered that a maximum quantity of 4 x 15 g tubes per patient per year will be adequate for most patients, and that larger amounts would expose patients to the risk of additional toxicity.

The PBAC noted the safety issues with the use of pimecrolimus and considered that a pharmacovigilance program is required.

Recommendation

Pimecrolimus, cream, 1%, 15 g

Amend the current listing as follows:
Restriction: Authority required_[listing 1]
Treatment of facial or eyelid atopic dermatitis in patients aged at least 3 months with 1 or more of the following contraindications to topical corticosteroids:
(i) perioral dermatitis
(ii) periorbital dermatitis
(iii) rosacea
(iv) epidermal atrophy
(v) dermal atrophy
(vi) allergy to topical corticosteroids
(vii) cataracts
(viii) glaucoma
(ix) raised intraocular pressure.

Authority required [listing 2]
Short-term (up to 3 weeks) intermittent treatment of atopic dermatitis of the face or eyelids in patients aged at least 3 months who fail to achieve satisfactory disease control with intermittent topical corticosteroid therapy, and where more than 3 months have passed since the initial diagnosis of atopic dermatitis.

Failure to achieve satisfactory disease control with intermittent topical corticosteroid therapy is manifest by:
(i) failure of the facial skin to clear despite at least 2 weeks of topical hydrocortisone 1% applied every day; or
(ii) failure of the facial skin to clear despite at least 1 week of a moderate or potent topical corticosteroid applied every day; or
(iii) clearing of the facial skin with at least 2 weeks of topical hydrocortisone 1% applied every day, but almost immediate and significant flare in facial disease (within 48 hours) upon stopping topical corticosteroids, occurring on at least 2 consecutive occasions; or
(iv) clearing of the facial skin with at least 1 week of a moderate or potent topical corticosteroid applied every day, but almost immediate and significant flare in facial disease (within 48 hours) upon stopping topical corticosteroids, occurring on at least 2 consecutive occasions.

NOTE:
No applications for increased maximum quantities and/or repeats will be authorised. Only 1 authority application per 6 months, per patient, will be authorised.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis is pleased that the PBS listing for pimecrolimus will be extended to adults with facial atopic dermatitis, and thanks the PBAC for this decision.