PUBLIC SUMMARY DOCUMENT
Product: Imiquimod, cream, 12.5 mg per 250 mg single use sachets (5%), Aldara®
Sponsor: 3M Pharmaceuticals Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

The submission sought an authority required listing for imiquimod cream sachets for primary (previously untreated) superficial basal cell carcinoma (sBCC) where surgery is considered inappropriate.

2. Background

This drug has not previously been considered by the PBAC for the treatment of superficial basal cell carcinoma.

3. Registration Status

Imiquimod was registered by the TGA on 18 August 1998 for the treatment of external genital and perianal warts /condyloma acuminata in adults. Imiquimod was registered on 22 July 2004 for the primary treatment of confirmed superficial basal cell carcinoma where surgery is considered inappropriate.

4. Listing Requested and PBAC's View

Authority Required

Primary treatment of biopsy confirmed superficial basal cell carcinoma where surgery is considered inappropriate based on one or more of the following clinical presentations:

(i) poorly defined tumour margin;
(ii) minimum tumour size of 2 cm or more in at least one dimension;
(iii) tumour location or tumour number risks damage to underlying structures or cosmetic deformity;
(iv) patient specific contraindications limited to pre-existing illness or concomitant therapies.

The following information must be provided at the time of application:

(i) a biopsy report. Alternative confirmation by dermatoscopy may be provided by a dermatologist.
(ii) a description of the clinical presentation where surgery is considered inappropriate.

NOTE: The maximum quantity authorised provides sufficient supply for a treatment course with allowance for rest periods. Where treatment rest periods are fewer or not required applications for authorisation of up to 30 sachets can be made. No applications for repeats will be authorised

See Recommendations and Reasons for PBAC's view on restriction.

5. Clinical Place for the Proposed Therapy

Imiquimod cream would provide an alternative treatment for patients for whom surgical excision of primary superficial basal cell carcinoma is not appropriate.

6. Comparator

The submission nominated current usual care, including cryotherapy, curettage and cautery, surgical excision (performed even when considered inappropriate) and photodynamic therapy with methyl-5aminolevulinate (MAL-PDT) as the comparator.

7. Clinical Trials

In the absence of head-to-head randomised trials directly comparing imiquimod with the main comparators, the submission presented single-arm comparisons of randomised trials and non-comparative studies. The key imiquimod trials were two randomised, double-blind, placebo-controlled, parallel-design, phase III multi-centre trials (1393-IMIQ and 1408-IMIQ) that evaluated the efficacy and safety of imiquimod. There were three supporting studies of imiquimod: a randomised, double-blind, placebo-controlled, parallel-design, phase II multi-centre trial of imiquimod in treatment of multiple tumours and two non-comparative, open-label studies. For comparator studies, the submission presented Thissen et al (2000) and Basset-Seguin et al (2003), randomised, parallel-design trials comparing surgical excision with cryotherapy and cryotherapy with MAL-PDT, respectively, as key trials and 5 supporting studies

The list of key trials and supportive studies that formed the basis of the submission is tabulated below.

Trial/First author	Protocol title	Publication citation
Geisse J et al 1393-IMIQ	Vehicle-Controlled, Double-Blind Study to Assess the Safety and Efficacy of Imiquimod 5% Cream for the Treatment of Superficial Basal Cell Carcinoma.	J Am Acad Dermatol 2004; 50(5):722-33.
Geisse J 1408-IMIQ	Vehicle-Controlled, Double-Blind Study to Assess the Safety and Efficacy of Imiquimod 5% Cream for the Treatment of Superficial Basal Cell Carcinoma.	J Am Acad Dermatol 2004; 50(3):P127 (Meeting Abstract).
Thissen MRTM	Cosmetic results of cryotherapy versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck.	Dermatological Surgery 2000; 26:759-64.
Basset-Seguin N	Photodynamic therapy using methyl aminolevulinate is as efficacious as cryotherapy in basal cell carcinoma, with better cosmetic results [abstract].	Br J Dermatol 2003; 149(suppl 64):46.

8. Results of Trials

In the key trials, imiquimod was significantly more effective than placebo in achieving immediate clearance of sBCCs with pooled absolute rate difference of 73% (95% CI: 63%, 85%) and 79% (95% CI: 65%, 93%) for complete and histological clearance, respectively. There was a positive correlation between response and the severity of local skin reactions. The complete response rates (complete or histological) in sub-groups (age, sex and skin type) were not different from the overall treatment group.

In supporting studies, the immediate histological clearance of large tumours and multiple tumours (calculated per tumour) appeared similar to histological clearance in key trials (when comparing rates of tumour clearance in the imiquimod arm). In the long-term study, 86.4% of patients that achieved an immediate clinical cure were free of clinical signs of sBCC recurrence at 2 years.

An analysis of acute tumour clearance or recurrence at 2 years indicated that imiquimod has lower clearance rates than the comparators MAL-PDT, cryotherapy and surgical excision, but has lower 2-year recurrence than MAL-PDT and cryotherapy.

In the key trials, there were significantly more adverse events in imiquimod-treated patients than in the vehicle group. The majority of events were local skin reactions at the application site with itching and burning being the most common.

Adverse events with MAL-PDT were generally restricted to local skin reactions, occurring in ~30% of patients. Oedema, leakage, erythema and crusting at the treatment site appeared frequent with cryotherapy; however the relative severity of the symptoms compared with imiquimod remained uncertain. Difficulties with wound healing and complications appeared to be more frequent with cryotherapy than with surgery, and these events were not observed with imiquimod therapy.

For the PBAC's comments on trial results see Recommendations and Reasons.

9. Clinical Claim

The submission made a number of claims, as there were multiple comparators:

1. Imiquimod is significantly more effective than non-interventional monitoring (placebo).
2. Imiquimod is no worse than MAL-PDT cryotherapy or curettage and cautery.
3. Imiquimod is less effective than surgical excision.

See Recommendations and Reasons for the PBAC's comments.

10. Economic Analysis

The submission presented a preliminary (trial-based) economic evaluation using a cost-effectiveness approach. The resources included were drug costs only.

The trial-based incremental cost/extra initial cure gained over placebo at 4.5 months from the start of treatment was < $15,000.

The submission also presented a modelled economic evaluation. The approach used decision analysis. The resources included were drug costs, cost of comparator therapies, cost of the management of non-cures and relapses and rates of substitution of comparator therapies by imiquimod.

The base case modelled incremental cost/extra "cure" achieved at 2 years (over the current situation in which imiquimod is not listed) was <$15,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients/year would be up to 10,000 to 50,000 in Year 3 of listing. This was considered a likely underestimate by the PBAC, mostly due to risk of usage beyond the requested restriction.

The financial cost/year to the PBS was estimated to be up to $5 to $10 million in Year 3, again a likely underestimate, mostly due to likely usage beyond the requested restriction.

12. Recommendation and Reasons

The PBAC considered that the patient eligibility criteria in the requested restriction were wide, imprecise and allowed for a substantial possibility of usage beyond the intent of the requested restriction. Of particular concern was the likelihood that patients and prescribers might trade off an accepted improvement in cosmesis in place of optimal tumour control, irrespective of whether surgery is clinically inappropriate or not, because the criteria for inappropriate use are much broader than absolute contraindications which would exclude surgery as a clinical option. A concern was that a general practitioner who is not inclined to perform surgery might be tempted to use imiquimod instead of referring the patient to another doctor experienced in the more effective treatment modality of surgical removal of sBCC. Furthermore, the PBAC was of the view that the request that a dermatologist be granted an authorisation without a biopsy raises the possibility of treatment of other BCC types against which imiquimod has no evidence of effectiveness. The PBAC thus considered that any restriction should mandate each and every diagnosis of sBCC by biopsy.

The PBAC considered it was critical that usage of imiquimod is appropriately targeted to ensure best practice and quality use of medicines as well as optimising cost-effectiveness. In particular, the restriction as requested did not provide sufficient clarity of the clinical place of imiquimod by presenting a rigorous basis for unequivocally determining when surgical excision and possibly other interventions are not viable clinical options. One possibility suggested was sBCC below the knee in elderly patients where healing following other interventions is expected to be slow and complicated, but sBCC in this area of the skin are comparatively uncommon and this might raise new concerns about defining a lower age limit and about difficulties with blistering as an expected toxicity following imiquimod. The PBAC agreed that another possible approach could be a restriction that includes the words "when more efficacious treatments are considered inappropriate".

The PBAC agreed that imiquimod was demonstrated to be an effective treatment for sBCC, but the primary sources of clinical evidence require comparisons across single arms of different studies, with inherent difficulties in minimising bias across these comparisons. Although the key imiquimod trials were well-conducted vehicle-controlled randomised trials, those for the comparators were mostly non-comparative and of a lesser quality. The PBAC was aware that a randomised trial comparing imiquimod with surgical excision was underway. The subjects in the imiquimod trials were not directly representative of those for whom PBS listing was sought and often not comparable to those in the comparator studies. The PBAC noted ESC advice that the statistical analysis of comparisons across these single arms is not methodologically strong.

The PBAC considered that that the nature of the evidence hinders the interpretation of the clinical results so that the therapeutic relativity claims are not conclusively supported. However, although the therapeutic claim that imiquimod is less effective than surgical excision was not supported by direct comparative evidence, the PBAC agreed that this claim is probably reasonable. It was more difficult to determine the therapeutic relativity of imiquimod against the three other interventions assessed (MAL-PDT, cryotherapy and curettage and cautery), but a conclusion that imiquimod is no worse than these was supported by the findings that, although the point estimates of initial cure rates for the comparative interventions are all numerically more favourable than for imiquimod, some of the point estimates of long-term recurrence rates are more favourable for imiquimod than for the other interventions.

Although the PBAC accepted that imiquimod is probably no worse than the non-surgical comparators, the PBAC did not accept the approach used in the modelled cost-effectiveness analysis, which is based on the claim of additional health benefits for imiquimod over the comparators. The PBAC noted that surgical excision, cryotherapy and curettage and cautery are all cheaper per case than imiquimod for GPs and, of these three, only surgical excision is more expensive per case than imiquimod for specialists. Thus, for the majority of the inferred substitutions, imiquimod is dominated based on these numerical estimates. The modelled economic evaluation obscured the conclusions from these more direct comparisons. Thus, even accepting that there might be numerical differences in initial cure and recurrence rates, the key comparative elements of the model did provide a strong economic basis to recommend listing.

Other problems with the economic model were also noted.

The PBAC agreed that there is a clinical place for imiquimod, as identified by correspondence in support of listing,. However, the patient population had not been adequately defined in the submission. The PBAC noted that the Pre-PBAC Response had offered a risk-sharing arrangement in the form of a rebate, although no details were presented as to how this might operate.

The PBAC therefore rejected the submission because of the inappropriate restriction, because the trials were not representative of those for whom PBS listing was sought and because of uncertain and inadequately demonstrated cost-effectiveness.

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