PUBLIC SUMMARY DOCUMENT
Product: Imiquimod, cream 50 mg per g (5%), 250 mg single use sachets, 12, Aldara™,
Sponsor: iNova Pharmaceuticals (Aust) Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application:

The submission sought an extension to listing to include solar keratosis on the face or scalp as field therapy in patients with multiple lesions.

2. Background

Imiquimod cream was considered by the PBAC at its November 2005 for the treatment of superficial basal cell carcinoma (sBCC). The Committee rejected imiquimod for listing because the restriction was considered inappropriate, the trials were not representative of those for whom PBS listing was sought, and the cost-effectiveness was both uncertain and inadequately demonstrated.

In July 2006, the PBAC considered a re-submission for imiquimod for the treatment of sBCC. The PBAC recommended an authority required listing for imiquimod on the basis of acceptable cost-effectiveness compared to placebo for patients who cannot have surgical excision, cryotherapy or curettage. As previously, the PBAC acknowledged that imiquimod has a clinical place in the treatment of sBCC, but considered it should not be available as first line treatment, as surgery is more effective than imiquimod.

Imiquimod was listed for sBCC on 1 December 2006.

3. Registration Status

Imiquimod is listed on the Australian Register of Therapeutic Goods with three approved indications including:

- treatment of solar (actinic) keratosis on the face and scalp;

Imiquimod was registered 4 November 2005 for treatment of solar (actinic) keratosis in the face and the scalp. It is also registered for the following indications:

- primary treatment of confirmed sBCC where surgery is considered inappropriate;
- treatment of external genital and perianal warts/condyloma acuminata in adults.

4. Listing Requested and PBAC's View

Authority Required

Solar keratosis on the face or scalp in a patient with normal immune function who has multiple clinically evident solar keratosis lesions and requires topical drug treatment as field therapy

NOTE:

The patient or carer must be able to understand and administer the imiquimod dosing regimen.

No applications for increased maximum quantities and/or repeats will be authorised.

For PBAC' view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Solar keratoses (SK) are thickened, scaly patches of skin caused by too much sun exposure. Solar keratosis is also known as actinic keratosis (AK). Imiquimod is a topical cream that is applied to the area of skin on the face and scalp to be cleared of solar keratosis. As a field therapy, imiquimod is intended to clear both clinically evident (visible) and sub-clinical (below the skin) SK lesions.

6. Comparator

The submission nominated both topical 5-fluorouracil (Efudix®), as the most widely prescribed topical treatment for solar keratosis, and cryotherapy as the appropriate comparators. The PBAC considered this was appropriate.

For PBAC's view, see Recommendations and Reasons.

7. Clinical Trials

The submission presented one randomised trial (H2H trial), the key pivotal trial, comparing imiquimod (5% cream three times per week, four weeks treatment, four weeks rest; if lesions remained another four weeks treatment) with 5-FU (5% ointment twice daily for four weeks) and cryotherapy (one session, if lesions not cleared within 2 weeks another session) in patients with SK on the face or scalp (Stockfleth 2007).

The submission also presented one supportive prospective randomised (unpublished) trial (Foley 2006) comparing the effectiveness of imiquimod with cryotherapy. Furthermore, the submission presented three randomised trials comparing imiquimod (5% cream three times per week, four weeks treatment, four weeks rest; if lesions remained another four weeks treatment) with placebo.

The pivotal randomised H2H study was published at the time of the submission, and is listed as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Stockfleth 2007 further referred to as H2H Trial	A randomized study of topical 5 % Imiquimod (Aldara®) versus topical 5-Fluorouracil versus topical cryotherapy in immunosufficient patients with actinic keratoses – single center study. Protocol No: IQ vs 5-FU vs Cryo H2H	Krawtchenko N, Roewer-Huber J, Ulrich M et al. A randomised study of topical 5% imiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up, British Journal of Dermatology 2007; 157 (Suppl 2): 34-40.

8. Results of Trials

There was no difference in acute clearance rates (i.e the percentage of patients in each treatment group with 100% of SK lesions cleared) between imiquimod and 5-FU and cryotherapy treatments in the H2H trial. However, the sustained clearance rate of the total treatment fields (i.e percentage of patients with cleared SK lesions remaining clear and with no new lesions) in all patients at twelve months after the end of treatment were 73%, 33% and 4% of patients after imiquimod, 5-FU and cryotherapy treatment, respectively. The higher field clearance rate of imiquimod in the Intention to Treat (ITT) analyses was statistically significantly different from that of 5-FU ($p=0.01$) and cryotherapy ($p<0.0005$). The majority of the patients who were completely cleared by imiquimod (in the short term) remained cleared 12 months later, whereas in the 5-FU and cryotherapy groups the proportion of completely cleared patients decreased with time.

There was a statistically significant difference in acute complete (100%) clearance rates, favouring imiquimod in the placebo-controlled trials, both individually and in the meta-analysis. The PBAC noted that the 100% clearance rates of imiquimod in these studies are similar to that reported by Foley but lower than that reported in H2H trial.

The submission claimed that in the H2H trial, all treatments were generally well tolerated and that no safety findings beyond the established knowledge of any of the study treatments were found. The number of adverse events and serious adverse events was low in all study groups. In the Foley trial local administration site reactions were common and experienced in both treatment arms and in the placebo-controlled trials, the most frequently reported AEs were application site reactions (itching): significantly more often for imiquimod than placebo patients.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described imiquimod as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over 5-FU.

The submission described imiquimod as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over cryotherapy.

The PBAC expressed concerns about the safety of imiquimod when used as field therapy.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation. The model was a single cohort, discrete time, SK-free survival model with a three-year time horizon and a quarter-year time step. The outcome was the number of SK-free years lived in the three year period. Because the acute clearance rate is the same for imiquimod and the comparators (5-FU and cryotherapy) based on the H2H study results, the health outcome was determined by the proportion of people in each treatment group with recurrent lesions plus new lesions at 12 months.

Based on the H2H study, the economic evaluation results for imiquimod as a SK field clearance therapy one year and three years post treatment, expressed as the incremental cost per recurrence-free year, were:

Therapy	ICER ($/recurrence- free year)
STEP 1: ONE YEAR	
IMQ vs. 5-FU	$783
IMQ vs. Cryotherapy	$467
IMQ vs. Placebo	$717
STEP 2: THREE YEARS	
IMQ vs. 5-FU	$195
IMQ vs. Cryotherapy	$157
IMQ vs. Placebo	$331

The results of one-way sensitivity analyses indicated that the model was most sensitive to the clinical outcomes used, quarterly recurrence rates and inclusion of a biopsy. The results of two-way sensitivity analyses indicated that the model (vs. 5-FU) was most sensitive to using individual acute clearance rates from the H2H trial combined with the lower 95% CI of the sustained clearance failure rate with an ICER of $1,846 per recurrence-free year.

11. Estimated PBS Usage and Financial Implications:

The submission estimated that the likely financial cost per year to the PBS to be up to $9.7 million in Year 5 (recalculated during the evaluation to be up to $17.5 million in Year 5). However, the PBAC considered that the submission underestimated the eligible patient population while overestimating the use (i.e. number of prescriptions) of imiquimod within this sub-population. The net effect was an underestimate in the total use and PBS cost of imiquimod within the eligible population. However the uncertainty due to the potential for use outside the restriction and the treatment preference of both clinicians and patients would also impact significantly on these estimates.

12. Recommendation and Reasons:

The PBAC agreed that the primary analysis of interest is the comparison with 5-fluoruracil gel (5-FU, Efudix®) as the two treatments are alternative options for field therapy, whereas cryotherapy can only be used to treat extant lesions and even then it cannot be used in all circumstances where field therapy might be appropriate. The PBAC further agreed with the restriction wording proposed by the RWG, but requested the sponsor provide further input on the need to restrict treatment to patients with normal immune function.

The PBAC had major concerns around the adequacy of the provided data for making a listing recommendation. With respect to the comparison of the effectiveness of imiquimod and 5-FU, the pivotal H2H trial involved only a very small number of patients, was unblinded, and appeared to have had as its primary outcome an assessment of oncogenes (p53 and $p16^{INK4A}$) pre- and post-treatment, although it was acknowledged that different sources provide conflicting information on what should constitute the primary outcome.

However, the safety of imiquimod when used as a field therapy was of concern to PBAC.

The TGA-approved product information (PI) for imiquimod states that imiquimod cream should not be used in an area greater than 25 cm^2 due to the potential to cause local skin reactions. No safety data were presented on the use of imiquimod over areas greater than 50 cm^2, but the maximum skin area that can be covered by the contents of one sachet (intended for a single use application) is 389 cm^2. This area is in contrast to the recommendation for 5FU where up to 500 cm^2 can be treated at one application. In trial H2H the imiquimod treatment area was 50 cm^2. No safety data were presented for sequential use on different 25 cm^2 patches of skin in the same patient. On the other hand, the evidence from Phase 2 trials suggested a higher risk of systemic side effects when larger skin areas are treated, and safety issues reported with the use of imiquimod in Europe were considered likely to be amplified in the Australian setting.

The economic model presented utilises the same structure as the model previously presented for basal cell carcinoma (BCC) and the PBAC considered this inappropriate in the context of SK, a disease which has a much longer course. Additionally, although the incremental cost-

effectiveness ratio is reported as the cost per SK recurrence free year, the value of treating SK has not been conclusively established by the submission.

The PBAC further noted that the ESC had raised a number of other clinical and economic concerns with the data presented and agreed that they would need to be addressed in any future submission.

Therefore, the PBAC rejected the request to extend the PBS listing of imiquimod to include field therapy of multiple clinically evident SK because of uncertain evidence of effectiveness and safety over the comparator and the resulting uncertain cost-effectiveness.

Recommendation
Rejected

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

The sponsor chose not to comment.