PUBLIC SUMMARY DOCUMENT

Product: Methyl 5-aminolevulinate hydrochloride, cream, 160 mg/g, 2 g tube, Metvix®

Sponsor: Galderma Australia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The re-submission sought an authority required listing for the treatment of superficial Basal Cell Carcinoma (sBCC) in patients who cannot have surgery.

2. Background

At its November 2005 meeting, the PBAC rejected an application for an authority required listing for treatment of patients aged 18 years or older with primary sBCC or nodular basal cell carcinoma (nBCC) where surgery is inappropriate due to the risk of post-surgical morbidities or disfigurement. *(See Public Summary Document for November 2005).*

3. Registration Status

Methyl 5-aminolevulinate hydrochloride is registered by the TGA for:

(a) the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other registered therapies are unacceptable (April 2003).
(b) primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate (July 2003).
(c) the treatment of biopsy-proven squamous cell carcinoma in situ (Bowen's disease), where surgery is considered inappropriate (November 2006).

4. Listing Requested and PBAC's View

Authority Required

Treatment of superficial basal cell carcinoma (BCC) in patients who cannot have surgical excision, cryotherapy, or curettage with diathermy. The lesion must be previously untreated and the diagnosis confirmed by biopsy.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Some superficial BCC lesions may be difficult to treat with current available therapies. Metvix provides an alternative therapy for patients who are not suitable for current non-medicinal therapies.

6. Comparator

Appropriately, the submission nominated imiquimod as the main comparator.

7. Clinical Trials

New trial data presented as pivotal evidence in the re-submission was from one head-to-head non randomised study (Nikkels et al, 2005) of methyl 5-aminolevulinate used together with photodynamic therapy (MAL-PDT) compared with imiquimod.

As supportive evidence, the re-submission presented three trials for MAL-PDT: one randomised, multicentre, phase III trial of PDT with MAL cream 160mg/g in comparison with cryotherapy in patients with primary superficial basal cell carcinoma (T304) and two single arm non-comparative studies of MAL-PDT in sBCC (T310 and T205).

The re-submission also presented, as supportive evidence, three trials for imiquimod: one double blind, randomised vehicle-controlled trial (Geisse J et al, 2004) and two open-label single arm non comparative studies of imiquimod in sBCC (Gollnick H et al, 2005 and Shumack S et al, 2004).

These trials had been published at the time of submission, as follows:

Trial/First author	Protocol title	Publication citation
Primary comparative study		
Nikkels et al (2005)	Photodynamic therapy and imiquimod immunotherapy for basal cell carcinomas - Open, multicentre non-randomised study of photodynamic therapy with MAL cream 160mg/g in comparisons with imiquimod in patients with nBCC and sBCC.	Acta Clin Belg. 2005 Sep-Oct;60(5):227-34.
Supportive trials/studies: MAL-PDT		
T304		
Basset-Seguin N et al, 2005	MAL-PDT versus cryotherapy in primary superficial BCC: results of 48 month follow-up.	10th World Congress of Cancers of the Skin, Vienna [poster].
Basset-Seguin N et al, 2004	Photodynamic therapy using Metvix is as efficacious as cryotherapy in BCC, with better cosmetic results.	Journal of the European Academy of Dermatology and Venereology; 18(S2):413 [abstract].
Basset-Seguin N et al, 2004	MAL-PDT is as effective as cryotherapy in superficial BCC, with better cosmetic results:results of a European randomised multicentre study.	International Skin Cancer Conference, Zurich.
Basset-Seguin N et al, 2003	Photodynamic therapy using methyl aminolevulinate is as efficacious as cryotherapy in primary superficial basal cell carcinoma but with better cosmetic outcome.	61st Annual American Academy of Dermatology Meeting, San Francisco [poster abstract, P235].
Basset-Seguin N et al, 2003	Photodynamic therapy using methyl aminolevulinate is as efficacious as cryotherapy in primary superficial basal cell carcinoma but with better cosmetic outcome.	83rd Annual Meeting of British Association of Dermatologists, Brighton [poster abstract, P248].
Basset-Seguin N et al, 2001	Photodynamic therapy using Metvix is as efficacious as cryotherapy in BCC, with better cosmetic results.	European Academy of Dermatology and Venereology, Munich [poster abstract].
Basset-Seguin N et al, 2001	Photodynamic therapy using Metvix is as efficacious as cryotherapy in BCC, with better cosmetic results.	Journal European Academy of Dermatology and Venereology 15N(Suppl 2) [poster abstract, P226].
T310		
Viniciullo C et al, 2005	Photodynamic therapy with topical methyl aminolevulinate for “difficult-to-treat” basal cell carcinoma.	British Journal of Dermatology Vol 152 (pp 765-772).
Viniciullo C et al, 2004	MAL-PDT in patients with difficult to treat basal cell carcinoma: results of an Australian multicentre study.	Poster presented to the International Skin Cancer Conference, July 2004, Zurich.

Trial/First author	Protocol title	Publication citation
Viniciullo C et al, 2003	Photodynamic therapy using methyl aminolevulinate in patients with basal cell carcinoma.	European Academy of Dermatology and Venereleogy Congress, Barcelona, [poster].
Viniciullo C et al, 2005	Photodynamic therapy with topical methyl aminolaevulinate for "difficult-to-treat" basal cell carcinoma.	British Journal of Dermatology 2005; 152:765-772
T205		
Horn M et al, 2003	Topical methyl aminolevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional therapy.	British Journal of Dermatology 2003; 149:1242–9.
Supportive trial/studies: imiquimod		
Geisse J et al, 2004	Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: Results from two phase III, randomised, vehicle-controlled studies.	J Am Acad Dermatol 2004;50:722-733
Gollnick H et al, 2005	Recurrence rate of superficial basal cell carcinoma following successful treatment with imiquimod 5% cream: interim 2-year results from an ongoing 5-year follow-up study in Europe.	Eur J Dermatol 2005;15(5):374-381
Shumack S et al, 2004	5% Imiquimod Cream for the Treatment of Large Superficial Basal Cell Carcinoma	Arch Dermatol 2004;140(10):1286-1287

8. Results of Trials

The results of the primary outcome for the trials/studies presented in the re-submission are summarised in the tables below.

Results of the primary comparative study:

MAL-PDT versus imiquimod, percentage of patients with complete response at 12 weeks post treatment

Trial	MAL-PDT n/N (%)	Imiquimod n/N (%)	Difference 95% CI
Nikkels et al (2005)	12/13 (92%)	6/8 (75%)	17.3%(-16.0%, 50.6%)

The primary comparative study (Nikkels et al 2005) was not randomised. There were very few numbers of cases in each arm of the study (13 patients treated with MAL-PDT and eight patients treated with imiquimod) and the subjects enrolled into the study appeared to be a selection of cases previously treated by the investigators. The study report did not report any predefined statistical analyses of efficacy outcomes or any predefined α values.

Results of the supportive trial/studies: MAL-PDT

Proportion of patients with complete response at 3 months post treatment (reported for all treated patients), and verified by biopsy when performed

Trial	MAL-PDT n/N (%)	Cryotherapy n/N (%)	ARD (95% CI)^	RR (95% CI)^
T304[+]	54/60 (90%)	52/58 (90%)	0.00 (-0.11, 0.11)	1.00 (0.88, 1.12)
T310 (single arm)[*=]	82/102 (80%)	NA	NA	NA
T205 (single arm)*[=]	61/85 (72%)	NA	NA	NA

* the re-submission presented results for studies T205 and T310 in terms of number of sBCC lesions treated as a single patients can have a mixture of BCC lesions types in these studies.
^ calculated in Revman (random effects) during the evaluation.
= reported for histologically confirmed complete response rate

For trial T304, the re-submission reported the number and proportion of complete responders, expressed in terms of the numbers of lesions and the numbers of patients; results were presented for the per protocol lesions/patients (primary analyses).

For studies T310 and T205, because patients with sBCC and nBCC were enrolled in the studies, the re-submission presented efficacy outcomes in terms of the number of sBCC lesions treated. These were not the primary outcomes evaluated in the studies; the primary outcome was the percentage of patients with complete response at 3 months post treatment.

Results of the supportive trial/studies: Imiquimod

Composite clearance rates (patient response) at 12 weeks post treatment

Trial	Imiquimod 5 times /week n/N (%)	Placebo n/N (%)	ARD (95% CI)^	RR (95% CI)^
Geisse et al (2004)	139/185 (75%)	6/360[a] (2%) *NR*	0.73 (0.67, 0.80)	45.08 (20.3, 100.11)
Gollinick et al (2005)	163/182 (89.6%)	NA	NA	NA
Shumack et al (2004)	83%	NA	NA	NA

[a] number of patients in combined placebo groups for the two dosages in the Geisse et al (2004) trial.
^ calculated in Revman (random effects) during the evaluation

The results of the composite clearance rates (patient response) at 12 weeks post treatment were reported for the supportive trial/studies of imiquimod on a per patient basis.

The re-submission presented new toxicity data from the non-randomised comparative study of MAL-PDT versus imiquimod. The key results are presented below.

Local and non-local adverse events for primary comparative study: MAL-PDT versus imiquimod reported at 6 months

Adverse events Reported by Nikkels et al (2005)	MAL-PDT n/N (%)			IMIQUIMOD n/N (%)		
Severity	**+**	**++**	**+++**	**+**	**++**	**+++**
Erythema, oozing, ulceration and crusts	NR	NR	NR	0	2/8 (25)	6/8 (75)
Crusts	2/13 (15)	1/13 (8)	NR	NR	NR	NR
Pain	7/13 (54)	NR	NR	NR	NR	NR
No crust and no pain	6/13 (46)	NR	NR	NR	NR	NR

Severity is graded as + minimal, ++ moderate, or +++ intense

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The re-submission described MAL-PDT as being no worse than imiquimod in terms of effectiveness and toxicity and exhibits at least equivalent or better safety profile and compliance rate.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The re-submission provided a preliminary economic evaluation. On the assumption of equal effectiveness of MAL-PDT and imiquimod for the requested PBS restrictions, the re-submission compared the costs per treatment course of MAL-PDT versus imiquimod.

The re-submission assumed that a full course of methyl-5-aminolevulinate (2 g tube: cream used for 2 treatments one week apart) was equivalent to a full course of imiquimod (cream used 5 days per week for 6 weeks, the re-submission assumed 70% of patients will use 24 sachets and 30% will use 30 sachets (as per the full course recommended in the TGA-approved product information)).

The evaluation advised that the re-submission had sourced costs for GP, dermatologist visits and biopsy from the 2004 Medicare Benefits Schedule, thus the costs used in the estimation of the cost of MAL-PDT treatments and imiquimod treatments were likely to be underestimated.

For PBAC's comments, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 5 of listing the likely number of patients /year would be in the range 10,000 – 50,000 and the financial cost/year to the PBS (not excluding co-payments or subtract any savings in use of other drugs) to be < $10 million.

12. Recommendation and Reasons

The PBAC considered that, for consistency with the current imiquimod restriction, any restriction for MAL-PDT should be amended to include the wording "The date of the pathology report and name of the Approved Pathology Authority must be provided at the time of application." Further a NOTE stipulating "No applications for increased maximum quantities and/or repeats will be authorised" should be included. The Committee accepted that it was unnecessary to require that patients be immunocompetent, unlike with imiquimod.

The PBAC questioned whether the patients enrolled in the trials/studies forming the evidentiary basis of the re-submission were representative of those for whom PBS listing of MAL-PDT was sought. Some trials/studies included patients with nBCC lesions, whereas the requested PBS listing is only for sBCC; some trials/studies restricted patient or lesions from participating in the study/trial because the lesions were of a size outside those specified in the trial protocol, whereas the requested restriction does not specify size of lesions able to be treated on PBS with MAL-PDT; some studies enrolled patients with difficult to treat BCC, and who had lesions that had been previously treated, whereas the requested PBS listing is for primary (previously untreated) sBCC lesions.

In addition, in view of the low numbers in the only study carrying out a direct comparison with imiquimod and the resulting wide confidence intervals, the PBAC considered that this

trial lacked scientific rigour and it was difficult to be confident about a conclusion that MAL-PDT is no worse than imiquimod in terms of safety and efficacy.

Given the uncertainty over the clinical comparison, the cost-minimisation approach was not considered to be justified. The costs of imiquimod were overestimated, as the PBAC considered the assumption that 30% of patients would require a full course of 30 applications with imiquimod to be unjustified. Further, the assumption that only dermatologists prescribe imiquimod was unjustified.

The costs of MAL-PDT were considered to have been underestimated. There was uncertainty about the re-submission's assumptions that the costs of photoactivation, which occurs three hours after the cream application, would be included in the cost of the GP or dermatologist visit. There are currently no MBS item numbers for PDT associated with MAL activation. The re-submission's assumption that 25% of patients would receive treatment with MAL-PDT via the GP and 75% via the dermatologist is not supported with any evidence. Given the time between application and photoactivation of the MAL cream is three hours, the re-submission's assumption that patients will be charged only once for two visits to the GP or dermatologist in one day was not substantiated.

The PBAC therefore rejected the submission because of uncertain comparative effectiveness and uncertain cost effectiveness. The Committee acknowledged that MAL-PDT would provide an alternative therapeutic option.

Recommendation
Reject

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 intends to work collaboratively with the PBAC to secure reimbursement of Metvix.