PUBLIC SUMMARY DOCUMENT
Product: Methyl aminolevulinate, cream, 160 mg per g, 2g tube, Metvix®
Sponsor: Galderma Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

The submission sought an Authority required listing for treatment of patients aged 18 years or older with primary superficial basal cell carcinoma (sBCC) or nodular basal cell carcinoma (nBCC) where surgery is inappropriate due to the risk of post-surgical morbidities or disfigurement.

2. Background

Methyl aminolevulinate has not been previously considered by the PBAC.

3. Registration Status

Metvix is registered by the TGA for the treatment of (a) thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other registered therapies are unacceptable, and (b) primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate.

4. Listing Requested and PBAC's View

Authority required

Treatment, by a dermatologist or general practitioner with expertise in the management of basal cell carcinoma (BCC), of patients aged 18 years or older with primary superficial or nodular BCC where surgery is inappropriate due to the risk of post-surgical morbidities or disfigurement. The lesions must be confirmed as superficial BCC or nodular BCC either histologically by biopsy or by specialist opinion.

A patient may be considered inappropriate for surgery if they:
(a) have large lesions (measuring >10 mm on the face or >20 mm on the body), or
(b) cannot clinically tolerate invasive therapy, or
(c) have a poor ability for wound care due to poor social and care networks, or
(d) are at a high risk of disfigurement including keloid scarring, or
(e) have poor vasculature, or
(f) have one or more of the following comorbidities:
    (i) treatment with anticoagulant medication
    (ii) high risk of surgical complications
    (iii) immunosuppression
    (iv) diabetes, or
(g) have had an inadequate response to standard therapies for prior BCC lesions.

Details of the unsuitability for surgical excision must be provided at the time of application.
Note: Metvix cream must be activated using a specialised red light source (Aktilite®).

See Recommendations and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Metvix would provide an alternative treatment for superficial and/or nodular BCC where lesions are considered inappropriate for surgery. Current treatment for basal cell carcinomas

(BCCs) in Australia includes surgical excision, curettage and cautery, cryotherapy, topical imiquimod, Mohs' microscopically controlled surgery, and radiotherapy.

6. Comparator

The submission nominated surgical excision as the appropriate comparator.

See Recommendations and Reasons for PBAC's view.

7. Clinical Trials

The submission presented a single randomised open-label trial (Trial T303) comparing treatment of patients with nodular basal cell carcinoma with MAL against surgical excision over a follow-up period of 36 months as the basis of the comparison. The primary outcome measure was an unblinded assessment of patient complete response with a secondary outcome of unblinded assessment of cosmetic response. A further 3 randomised trials comparing MAL with cryotherapy, or placebo cream, and 2 non-comparative studies were provided as supportive evidence.

The PBAC was concerned that the subjects in the key trial were not representative of those for whom PBS listing was sought because the trial excluded patients with characteristics where surgery would be inappropriate.

8. Results of Trials

The results of the key trial are summarised in the table below.

Patient complete response in Trial T303 (ITT population)

Follow-up duration	Patient complete response		ARD (95% CI)	RR (95% CI)	NNT (95% CI)
	MAL	Surgical excision			
3 months	45/53 (85%)[a] 43/53 (81%)[b]	46/50 (92%)	-0.07 (-0.19, 0.05)[a] -0.11 (-0.24, 0.02)[b]	0.92 (0.80, 1.06) 0.88 (0.77, 1.03)	
12 months	41/53 (77%)	45/50 (90%)	-0.13 (-0.27, 0.01)	0.86 (0.72, 1.0)	
24 months	32/53 (60%)	41/50 (82%)	-0.22 (-0.39, -0.05)	0.74 (0.57, 0.95)	-5 (-3, -20)
36 months	30/53 (57%)	38/50 (76%)	-0.19(-0.37, -0.02)	0.75 (0.56, 0.99)	-5 (-3, -50)

MAL = methyl aminolevulinate, ITT = intention to treat,

At all follow up time points for trial T303 surgical excision outperformed MAL for the outcome of complete patient response, with statistically significant more patients displaying complete response at 24 and 36 months.

Patient lesion recurrence in Trial T303

Follow-up duration	Patient lesion recurrence		ARD % (95% CI)	RR (95% CI)
	MAL	Surgical excision		
12 months	2/43 (5%)	0/45 (0%)	5 (–2, 11)	N/C
24 months	3/35 (9%)	0/41 (0%)	9 (–1, 18)	N/C
36 months	5/35 (14%)	1/39 (3%)	12 (–1, 24)	5.6 (0.7, 45.4)

MAL = methyl aminolevulinate, ARD = absolute risk difference, RR = relative risk, CI = confidence interval, N/C = not calculable

As 36 months follow up 14 % of patients treated with MAL experienced recurrent lesions compared to 3% of patients who had undergone surgical excision.

Cosmetic outcome in Trial T303

	Cosmetic outcome		Risk difference (95% CI)	Relative risk (95% CI)	NNT (95% CI)
	MAL	Surgery			
3-month assessment (Investigator assessed)					
Excellent/good	35/45 (78%)	15/46 (33%)	0.45 (0.27, 0.63)	2.4 (1.5, 3.7)	2 (2, 4)
Fair/poor	7/45 (16%)	30/46 (65%)	–0.50 (–0.67, –0.32)	0.2 (0.1, 0.5)	

MAL = methyl aminolevulinate,

The data show that treatment with MAL results in significantly better cosmetic outcomes than surgical excision. The evaluation of these patients was by an unblinded investigator.

With respect to adverse effects, the data showed that MAL is no more toxic than surgery when compared over a period of 36 months.

See Recommendations and Reasons for the PBAC's view of the trial results.

9. Clinical Claim

The submission stated that for the outcomes of complete patient response and lesion recurrence, MAL is less effective than surgical excision, but has similar levels of toxicity and better cosmesis.

See Recommendations and Reasons for the PBAC's view on the Clinical Claim.

10. Economic Analysis

The submission presented a preliminary (trial-based) economic evaluation. The choice of the cost effectiveness approach was considered valid by the PBAC. Resources included were cost of MAL, cost of surgical excision, clinical visits, cost of biopsy, and associated equipment (eg Aktilite, dressings).

The trial-based incremental discounted cost/extra discounted patient with complete response and good to excellent cosmetic outcome at 36 months was <$15,000. Excluding the cosmetic outcome, MAL was dominated by surgery, being more expensive per treatment cycle compared with surgical excision and being less effective (only 55% of treated patients in complete response at 36 months compared with 76% for surgery).

The submission presented a modelled economic evaluation. The choice of the cost-effectiveness approach was valid. Cost-utility analysis was not possible due to the absence of quality of life data for BCC patients. The type of model used was a simple decision analysis. The model was not based on the number of lesions/patient, but rather on surface area of lesions. A total lesion area of $\leq 1000mm^2$ would only require one tube of cream/treatment cycle, $\leq 2000mm^2$ would require 2 tubes/cycle, etc. The resources included were drug costs, clinical visits, surgical procedures, biopsies, dressings and equipment.

The base case modelled incremental discounted cost/extra discounted extra month with complete lesion response and excellent/good cosmetic outcome was <$15,000. Again, however, without the inclusion of cosmetic response, MAL was dominated by surgery with an incrementally higher cost at 36 months and 6 fewer months with complete response.

See Recommendations and Reasons for the PBAC's views.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the financial cost/year to the PBS would be less than $10 million in Year 5, which the PBAC considered a likely underestimate in the submission due to an underestimation of patient numbers.

12. Recommendation and Reasons

The PBAC considered that the patient eligibility criteria in the requested restriction were ambiguous and subjective and thus could allow for the majority of people with nBCC and sBCC to be eligible for treatment with methyl aminolevinulate as a first-line therapy. For example, the words "may be" when defining whether surgery is inappropriate would not enable the individual adjudicating authorisation to exclude a patient who does not meet any of the six suggested definitions.

The presentation of surgical excision as the single main appropriate comparator was considered problematic given the intention of the requested restriction for patients in whom surgery is considered inappropriate. The PBAC considered that surgery is arguably less appropriate, but is not excluded in patients with BCC in sensitive sites. Therefore, other treatments such as cryotherapy, curettage, diathermy, radiotherapy or imiquimod would likely be tried as alternatives and so direct and indirect comparisons with these therapies would have been informative. The PBAC was also concerned that patients may be treated with an inferior modality on the basis of improved cosmesis in situations where surgery could have been used. In that context, the PBAC agreed that a restriction that includes the words "when more efficacious treatments are considered inappropriate" may be appropriate, despite the argument in the Pre-Sub-Committee Response that this suggested restriction is not appropriate in the absence of evidence that methyl aminolevinulate is inferior to treatments other than surgical excision.

The PBAC was concerned that the subjects in the key trial were not representative of those for whom PBS listing was sought because the trial excluded patients with characteristics where surgery would be inappropriate.

The PBAC noted that treatment with methyl aminolevinulate was less effective than surgical excision for the outcomes of patient complete response and patients experiencing recurrent lesions up to 36 months' follow-up. However, unblinded assessment determined that a significantly higher proportion of patients with complete response had good to excellent cosmetic outcomes compared to surgical excision. Due to the open-label nature of the subjective assessment performed by the investigator, the validity of the cosmetic outcomes was less convincing than if a more rigorous trial design involving adequate blinding of the observer of the outcome had been used.

The PBAC also noted that the submission hinged upon the use of the outcome "patient complete response AND excellent to good cosmesis" in the economic evaluations. However, it was unclear as to the validity of the use of this composite outcome in this manner because both components are subjective and they were assessed by investigators who were not blinded to the treatment allocated. Further, this composite outcome was generated post hoc and was not considered in the original trial. This composite outcome reverses the direction of effect compared with the a priori specified primary outcome of patient complete response and implicitly infers that each of the component outcomes should be given equal weight and value. The PBAC did not accept that good cosmesis should be given equal weight and value to response.

The PBAC also noted that the model relied on expert opinion to estimate the average lesion treatment area seen in the BCC patient population satisfying the requested restriction. The presentation of the cost-effectiveness in terms of cost/extra month spent in the health state represented by the composite outcome made it difficult to compare its cost-effectiveness against other treatments within the health system. The PBAC noted that a cost-utility analysis was not possible in the absence of any studies evaluating quality of life in patients with BCC. However, given that the basis of the modelled economic evaluation included improved cosmesis, the PBAC considered that a cost-utility analysis would have been informative, particularly to weight more appropriately, the relative value of BCC response and cosmetic outcome.

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 the primary outcome of the trial showed methyl aminolevulinate to be inferior to surgery; 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

In accordance with clinical expert opinion and the data available it is the position of the sponsor that:-

<u>1/ Metvix (MAL-PDT) should be indicated in patients where surgery is inappropriate.</u>
The sponsor agrees that surgical excision is the treatment of choice for nBCC and sBCC and therefore should remain the comparative treatment. However in cases where surgery may be considered inappropriate due to the location (e.g. mid-face), size and number of lesions, alternative treatment should be considered. MAL-PDT has shown long term efficacy (5 years) comparative to standards of care in BCC, surgery & cryotherapy in 2 pivotal studies, and in 2 open studies in patients where surgery was considered in appropriate. Today, no other alternative therapies provide more evidence than is available for MAL-PDT.

<u>2/ MAL-PDT brings value to patients and to health authorities.</u>
The sponsor has shown a strong patient's preference toward MAL-PDT compared to alternative treatments in clinical trials. Furthermore, the outcome of interest in the submission is based on the combination of two outcomes that were defined a priori. Based on this outcome, the economic evaluation showed the use of MAL-PDT to be economically justified.

Before a new submission, the sponsor would like to have the opportunity to work with the committee on:
-The definition of the listing to ensure that patients are selected fairly and only those who will receive the most benefit are identified; and
-How best to evaluate medicines that improve skin cancer management