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: March 2008

1. Purpose of Application

The submission sought a Section 85 Authority Required listing for the treatment of superficial Basal Cell Carcinoma (sBCC) in patients who cannot have surgery.

2. Background

At the 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. The PBAC rejected the submission because of the inappropriate restriction, 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.

At the July 2007 meeting, the PBAC rejected a submission for an Authority Required listing for treatment of sBCC in patients who cannot have surgery because of uncertain comparative effectiveness and uncertain cost effectiveness.

3. Registration Status

Methyl 5-aminolevulinate hydrochloride is TGA registered for:

- Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other registered therapies are unacceptable. (April 2003)
- Primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate. (July 2003)
- 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. The date of the pathology report and name of the Approved Pathology authority must be provided at the time of application.

The wording as proposed by the Restrictions Working Group was:

Authority required

Treatment of biopsy confirmed primary (previously untreated with the sole exception of lesions treated with methyl aminolevulinate photodynamic therapy in the preceding 3 months) superficial basal cell carcinoma (sBCC) in a patient~~s~~ for whom surgical excision, cryotherapy, or curettage with diathermy are inappropriate and topical drug therapy is required. The date of the pathology report and name of the Approved Pathology Authority must be provided at the time of application.

NOTE:

No applications for increased maximum quantities and/or repeats will be authorised. Treatment of recurrent (previously treated) lesions will not be authorised.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Metvix would provide an alternative therapy for the treatment of superficial basal cell carcinomas in patients where current non-medicinal therapies are inappropriate.

6. Comparator

The submission nominates imiquimod as the main comparator. The PBAC accepted that this was appropriate.

7. Clinical Trials

The re-submission presented new trial data, in addition to the data presented in the previous re-submission. The re-submission presented a comparison of methyl aminolevulinate photodynamic therapy (MAL-PDT) versus standard care, imiquimod versus standard care and an indirect comparison of MAL-PDT versus imiquimod.

The re-submission presented a randomised controlled trial of MAL-PDT versus cryotherapy in patients with "high risk" basal cell carcinoma and five non-randomised single arm studies of MAL-PDT in patients with basal cell carcinomas. Only the randomised trial specifically enrolled patients with superficial BCC (sBCC). However, where studies enrolled patients with BCC, the re-submission only presented results for the sub-group of patients with sBCC.

The re-submission presented the results of three randomised trials comparing imiquimod versus vehicle and five non-randomised studies of imiquimod. Two randomised trials and three non-randomised studies specifically enrolled patients with sBCC and one randomised trial and two studies enrolled patients with basal cell carcinoma. In trials/studies that enrolled patients with BCC, the re-submission only presented results for the sub-group of patients with sBCC.

The Nikkels et al. (2005) study was presented as the pivotal evidence in the previous re-submission, and is presented as supportive evidence in the current re-submission.

Studies published at the time of the submission are summarised in the table below.

Trial/First author	Protocol title	Publication citation
MAL-PDT trials/studies		
T307	A multicentre, phase III, double blind study of photodynamic therapy (PDT) with Metvix® 160 mg/g cream in comparison to PDT with placebo cream in patients with primary nodular basal cell carcinoma.	19/07/02
Tope W et al, 2003	Randomized prospective comparison of topical methyl aminolevulinate photodynamic therapy versus placebo photodynamic therapy in nodular basal cell carcinoma.	9th World Congress on Cancers of the Skin, May 2003, Sevilla [oral presentation]
Tope WD et al, 2004	Comparison of topical methyl aminolevulinate photodynamic therapy versus placebo photodynamic therapy in nodular BCC.	Journal of the European Academy of Dermatology and Venereology;18(S2):413 [abstract].

Tope WD et al, 2004	Comparison of topical methyl aminolevulinate photodynamic therapy versus placebo photodynamic therapy in nodular basal cell carcinoma: results of a North American study.	International Skin Cancer Conference, Zurich [poster].
T308	A multi-centre, phase III, double-blind study of photodynamic therapy (PDT) with Metvix® 160mg/g cream in comparison to PDT with placebo cream in patients with primary nodular basal cell carcinoma.	27/11/02
Foley P et al, 2004	MALPDT or placebo cream in nodular basal cell carcinoma: results of an Australian double blind randomized multi-centre study.	4th Euro PDT Meeting, Stirling Scotland [poster].
Foley P et al, 2004	MALPDT or placebo cream in nodular basal cell carcinoma: results of an Australian double-blind randomized multi-centre study.	International Skin Cancer Conference, Zurich [poster].
Foley P et al, 2003	A phase III randomized study comparing photodynamic therapy (PDT) using methyl aminolevulinate or placebo cream in nodular basal cell carcinoma (NBCC)	European Academy of Dermatology and Venereology Congress, Barcelona [poster].
Soler AM et al, 2001	A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevuinate-based photodynamic therapy alone and with prior curettage.	*Journal of Dermatology* 145: 146-471.
Surrenti T et al, 2007	An open-label trial to evaluate efficacy, safety, tolerability and cosmetic outcome of MAL-PDT in patients with superficial and nodular BCCs.	*European Journal of Dermatology* 17 (5): 412-5.
Caekelbergh K & Annemans L, 2006	Treatment of actinic keratosis and basal cell carcinoma with METVIX® (MAL-PDT) in real life practice: a cost of illness and model validation study.	Value in Health; 9(6); A283 [poster].
Caekelbergh K & Annemans L, 2006	Study report "Observational study regarding the use of Metvix® (MALPDT) in real life practice in Actinic Keratosis and Basal Cell Carcinoma"	September 05 2006 Version No. 5.0
Imiquimod trials/studies		
Sterry W et al, 2002	Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomised studies comparing low frequency dosing with and without occlusion.	*British Journal of Dermatology*, 147:1227-1236
Marks R et al, 2001	Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: Results of a multi-center 6-week dose-response trial.	*J Am Acad Dermatol*, 44: 807-813.
Peris K et al, 2005	Imiquimod Treatment of Superficial and Nodular Basal Cell Carcinoma: 12- Week Open-Label Trial.	*Dermatol Surg*, 31: 318-323.
Vidal D et al, 2004	Open study of the efficacy and mechanism of action of topical imiquimod in basal cell carcinoma.	*Clin Exp Dermatol*, 29: 518-525
Geisse J et al, 2002	Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: A double-blind, randomised, vehicle-controlled study.	*Journal American Academy of Dermatol*, 47: 390-398.

8. Results of Trials

The key results of the additional MAL-PDT and imiquimod studies presented in the re-submission are summarised in the table below.

Results of patient response rates in the additional MAL-PDT/imiquimod trials/studies presented in the re-submission

Trial/study	MAL-PDT/ imiquimod n/N (%)	Placebo n/N (%)
MAL-PDT		
Soler et al, 2001	NR	NA
Surrenti et al, 2007	NR	NA
Caekelbergh et al, 2006	88.6%[a]	NA
Imiquimod		
Geisse et al, 2002[b]	5x/week: 21/26 (80.8) 3x/week: 15/29 (51.7)	6/32 (18.8)
Marks et al, 2001[b]	3x/week: 23/33 (70)	NA
Peris et al, 2005[c]	70/75 (93.3)	NA
Sterry et al, 2002[b]	3x/week with occlusion: 20/23 (87) 3x/week w/o occlusion: 19/25 (76) 2x/week with occlusion: 9/21 (43) 2x/week w/o occlusion: 12/24 (50)	NA
Vidal et al, 2004[b]	3x and 5x/week: 4/4 (100)	NA

Notes:

[a] value for primary sBCC lesions *(could not be verified).* For sBCC (primary and non-primary) complete response was observed in 75/88 (85.2%). Complete response was assessed 6 months post-treatment.

[b] six weeks post-treatment.

[c] time point of assessing complete response was not reported.

Patient response rates at 12 weeks post treatment for MAL-PDT ranged from 72% (T205) to 90% (T304), and patient response rates at 12 weeks post treatment for imiquimod dosed at five times per week ranged from 75% (Geisse et al, 2004) to 90% (Gollnick et al, 2005). The patient response rates in the MAL-PDT trials/studies were results at 3 months after the last treatment, where a proportion of patients underwent re-treatment. Thus they do not solely represent recurrence rates following a single course of MAL-PDT treatment (i.e. two treatments, 1 week apart).

The following table summarises the results for the outcomes of lesion response and recurrence rates in all of the MAL-PDT and imiquimod trials/studies presented in the re-submission. The results for these outcomes were not presented in the previous re-submission.

Results of lesion response and recurrence rates in all MAL-PDT and imiquimod trials/studies presented in the re-submission

Trial/study	Lesion response		Recurrence rate	
	MAL-PDT/ imiquimod n/N (%)	Cryotherapy/ Placebo[a] n/N (%)	MAL-PDT/ imiquimod n/N (%)	Cryotherapy/ Placebo[a] n/N (%)
MAL-PDT				
T304	109/114 (96)*	94/105 (90)*	Patient 24[c]: 18/55 (33) 60[d]: *23*/55 (*42*) sBCC 24[c]: 18/109 (17) 60[d]: 23/109 (21)	Patient 24[c]: *10/52* (*19)* 60[d]: *11/52* (*21)* sBCC 24[c]: *18/94 (19)* 60[d]: *19/94 (20)*
T310	84/92 (91)*[,b]	NA	Patient 24[c]: 16/82 (16) 60[d]: 23/82 (28) sBCC 24[c]: 11/84 (13) 60[d]: 18/84 (21)	NA
T205	42/49 (86)*[,b]	NA	Patient 24[c]: 10/64 (16) 60[d]: 18/64 (28) sBCC 24[c]: 10/42 (24) 60[d]: 16/42 (38)	NA
Soler et al, 2001	119/131 (91)[b,i]	NA	sBCC: 12/119 (9)[i]	NA
Surrenti et al, 2007	84/94 (89)[b,j]	NA	sBCC: 2/84 (2.4)[k]	NA
Caekelbergh et al, 2006	NR	NA	NR	NA
Imiquimod				
Geisse et al, 2004	NR	NA	NR	NA
Gollnick et al,	NR	NA	*Patient: 10.4%*[l]	NA
Shumack et al,	NR	NA	NA	NA
Geisse et al, 2002	NR	NR	NR	NR
Marks et al, 2001	NR	NA	NR	NA
Peris et al, 2005	NR	NA	Patient: 2/70 (2.9)[m]	NA
Sterry et al, 2002	NR	NA	NR	NA
Vidal et al, 2004	NR	NA	Patient: 0/4 (0)[n]	NA

Notes:

Patient=patient recurrence rate, sBCC=sBCC recurrence rate, NR=not reported, NA-not applicable

* at 3 months

[a] cryotherapy for MAL-PDT and placebo for imiquimod trials

[b] sBCC lesions

[c] at 24 months after the last treatment of patients in complete response 3 months after the last treatment (21 month recurrence rate)

[d] at 60 months after the last treatment of patients in complete response 3 months after the last treatment (57 month recurrence rate)

[i] after a follow-up of at 24-48, mean 35 months

[j] one month following two MAL-PDT sessions

[k] after a follow-up period of 6-18 months, mean 12 months

[l] The calculation is based on the ratio of the estimated proportion of subject who remained clear by the initial complete response rate. The final recurrence rate is 1 – the results of the ratio (*89.6% at 12 weeks*)

[m] after a follow-up period of 12-34 months, mean 23 months

[n] after a 2 year follow-up

The results showed the lesion response rate in the MAL-PDT trials/studies ranged from 86% (T205) to 96% (T304). The patient recurrence rates reported in the MAL-PDT trials/studies ranged from 16% (T310) to 33% (T304) at 12 months and between 28% (T310) and 42% (T304) at 60 months (where reported), the patient recurrence rates reported for these MAL-PDT trials/studies were results at 12 and 60 months after the last treatment, where a proportion of patients underwent re-treatment thus, they do not solely represent recurrence rates following a single course of MAL-PDT treatment (two treatments 1 week apart). The patient recurrence rates reported for the imiquimod trials/studies ranged from 0% (Vidal et al, 2004) to 10.4% (Gollnick et al, 2005) (where reported). The PBAC noted the comparison of the patient recurrence rates in the MAL-PDT and imiquimod trials/studies was limited as the trials/studies differed when the lesion response and recurrence rates were determined. Lesion recurrence rates in the MAL-PDT trials/studies ranged from ranged from 2.4% (Surrenti et al, 2007) to 38% (T205), where reported.

The re-submission presented new toxicity data from the additional MAL-PDT and imiquimod studies presented in the re-submission, where safety data were reported. The toxicity data presented in the additional MAL-PDT and imiquimod trials/studies were consistent with those reported in the studies presented in the previous re-submission.

9. Clinical Claim

The submission described MAL-PDT as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over imiquimod.

The PBAC noted that as with the previous re-submission, the evidence base from which the MAL-PDT and imiquimod comparison is made was subject to significant bias.

The PBAC considered that the re-submission contained no new data which would cause the Committee to alter its previous view that it lacked confidence that MAL-PDT is no worse than imiquimod in terms of efficacy and safety.

10. Economic Analysis

The re-submission presented a cost minimisation analysis. The equi-effective dose of MAL-PDT versus imiquimod was two sessions of MAL-PDT one week apart equalling 24 sachets of imiquimod. This was changed from the previous re-submission where one course of MAL-PDT was claimed to be equivalent to 24 sachets of imiquimod in 70% of patients and 30 sachets of imiquimod in 30% of patients.

The PBAC noted the appropriate number of imiquimod sachets to use in the cost-minimisation analysis was a continuing area of economic uncertainty for the Committee. Although the PBS allows up to 12 sachets of imiquimod with one repeat to be provided to a patient for the treatment of each lesion, the clinicians present felt that most lesions would be treated with less than the maximum number of sachets and that a repeat dispensing would not always be required. The PBAC considered this uncertainty could be resolved through an analysis of the Medicare Australia dispensing data for imiquimod.

11. Estimated PBS Usage and Financial Implications

The submission estimated likely number of patients was between 10,000 and 50,000 in Year 5 at a financial cost/year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC agreed that the restriction wording proposed by the Restrictions Working Group was appropriate, noting that the sponsor has accepted this wording in the pre-PBAC response.

The PBAC considered that the re-submission contained no new data which would cause the Committee to alter its previous view that it lacked confidence that MAL-PDT is no worse than imiquimod in terms of efficacy and safety. Acceptance of the claim in the pre-PBAC response that "MAL-PDT is non-inferior to imiquimod" continues to be hampered by a lack of scientific rigour in the studies which form its evidentiary base.

The Committee further considered that the data on recurrence rates show that MAL-PDT has recurrence rates at 2 and 5 years which suggested recurrences was greater with MAL-PDT than that associated with imiquimod.

A continuing area of economic uncertainty for the Committee was the appropriate number of imiquimod sachets to use in the cost-minimisation analysis. Although the PBS allows up to 12 sachets of imiquimod with 1 repeat to be provided to a patient for the treatment of each lesion, the clinicians present felt that most lesions would be treated with less than the maximum number of sachets and that a repeat dispensing would not always be required. The PBAC considered this uncertainty could be resolved through an analysis of the Medicare Australia dispensing data for imiquimod.

The PBAC also noted that there continues to be some dispute about which costs should be included in the cost-minimisation analysis, with the sponsor alternately including or excluding the same costs. The Committee confirmed that a cost-minimisation analysis should consider costs to society and therefore that the exclusion of non-government costs from the analysis in the pre-PBAC response was inappropriate.

The Committee therefore again rejected the application because of uncertain comparative effectiveness and additionally because of problems with the cost-minimisation analysis.

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

With reference to the comparative effectiveness of Metvix-PDT therapy in the context of difficult to treat superficial basal cell carcinoma, the sponsor considers Metvix as a more appropriate topical treatment for superficial basal cell carcinomas in immunocompromised patients and in those patients who are unable to self medicate. The sponsor will consider the options available and refers readers to its website (www.treatskincancer.com or www.metvix.com) for further information.