PUBLIC SUMMARY DOCUMENT

Product: Ingenol Mebutate 0.015% gel, 3 x 470 mg tubes, Picato®
Sponsor: LEO Pharma Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The resubmission requested listing as Restricted benefit for field therapy for the treatment of solar keratoses (SK) of the face and scalp in patients who have had a previously diagnosed squamous cell carcinoma (SCC).

2. Background

This was the second consideration by the PBAC of ingenol mebutate as field therapy for the treatment of solar keratoses of the face and scalp.

At the November 2012 meeting, the PBAC rejected the submission for ingenol mebutate on the basis that the clinical claim that treatment of solar keratosis with ingenol mebutate reduces the risk of SCC was not quantified, that the cost effectiveness in the PBS setting was unknown, and that the utilisation was uncertain, and was likely to be high and substantially underestimated in the submission. The Public Summary Document is available on the PBS website.

3. Registration Status

Ingenol mebutate was TGA registered on 9 November 2012 for the topical treatment of solar (actinic) keratoses in adults.

4. Listing Requested and PBAC's View

Restricted benefit

Field therapy for the treatment of solar keratoses of the face and scalp in patients who have had a previously diagnosed squamous cell carcinoma

Listing was requested on the basis of cost-effectiveness over no treatment, and dominant cost effectiveness compared to the non-PBS listed comparators imiquimod, 5-FU and diclofenac.

The PBAC agreed with the Economic Sub-Committee (ESC) that the restriction proposed in the resubmission was problematic, noting in particular that:

- an Authority Required listing (rather than listing as a Restricted Benefit) would be appropriate, as auditing is not feasible through Medicare data; and
- the restriction may prove difficult to adhere to in practice, given diagnosis of SCC is not described in the restriction and there will be some uncertainty about qualifying for PBS subsidised treatment in some circumstances (e.g. SCC in situ (Bowen's disease)).

Furthermore, the PBAC considered that it was unlikely that use of ingenol mebutate would be limited to field therapy for an area of treatment no greater than 25cm^2. The PBAC also considered that there may be a question of whether excluding treatment of areas slightly greater than 25cm^2 would be a matter of clinical judgement and not an appropriate element of the PBS restriction.

5. Clinical Place for the Proposed Therapy

Solar Keratosis is a common premalignant condition of thick, scaly, or crusty patches of skin occurring on sun-exposed skin. These lesions may remit spontaneously, particularly in people who are rigorous with sun protection.

The mechanism of action of ingenol mebutate in solar keratosis is not fully understood, but appears to be a combination of induction of local lesion cell death and promotion of an inflammatory response with neutrophils and other immunocompetent cells.

Solar keratoses may be treated for cosmetic or symptomatic reasons. The requested listing limits treatment with ingenol mebutate to patients that have had a prior SCC on the face or scalp.

6. Comparator

The resubmission nominated a 'mixed comparator' comprising three topical formulations (imiquimod, diclofenac 3% and 5-FU 5%) and 'no treatment', as the appropriate comparators.

The PBAC agreed with the ESC that imiquimod 5%, diclofenac 3% and 5-FU 5% were appropriate comparators for clinical purposes in this resubmission. The PBAC considered that "no treatment" was not an appropriate clinical comparator, noting that patients with solar keratosis were not likely to go untreated given that there are several treatment options available. However, the committee considered that this comparison was informative for estimating the cost-effectiveness of ingenol mebutate on the PBS, in the absence of any relevant PBS-listed comparators.

7. Clinical Trials

No head to head trials were available comparing ingenol mebutate 0.015% with the topical formulations of diclofenac 3%, 5-FU 5% or imiquimod 5%. The resubmission presented indirect comparisons against each comparator, using eleven trials, including three trials of ingenol mebutate used on the face and scalp. Compared to the November 2012 submission, two new ingenol mebutate trials (PEP005-014 and PEP005-028) and one new 5-FU trial (Krawchenko et al., 2007) were presented.

These indirect comparisons were based on:

- Three ingenol mebutate 0.015% trials:
  - PEP005-015 - a multicenter, randomised, double-blind, vehicle-controlled, dose-ranging study to evaluate the safety and efficacy of 0.005%, 0.01% and 0.015% ingenol mebutate gel when used to treat actinic keratoses on the head (face or scalp);

- PEP005-016 and PEP005-025 – both multi-center, randomised, parallel group, double-blind, vehicle-controlled studies to evaluate the efficacy and safety of ingenol mebutate gel 0.015% in patients with actinic keratoses on the head (face or scalp).

- Two ingenol mebutate 0.05% trials:
  - PEP005-014 and PEP005-028 – both multi-center, randomised, parallel group, double-blind, vehicle-controlled studies to evaluate the efficacy and safety of ingenol mebutate gel 0.05% in patients with actinic keratoses on non-head locations.
- Two imiquimod 5% trials:
  - Jorrizo 2007 and Korman 2005:
- Three diclofenac 3% trials:
  - Rivers 2002, Stockfleth 2011 and Wolf 2001.
- One 5-FU 5% trial
  - Krawtchenko 2007

Trials PEP005-014 and PEP005-028 include data relating to ingenol mebutate 0.05% for use on the trunk and extremities, which was not consistent with the requested listing of ingenol mebutate 0.015% for the treatment of solar keratoses on the face and scalp. These trials were only used for the comparison with diclofenac.

The trials presented in the resubmission did not specifically recruit patients with a previous SCC which is the requested population for PBS listing. No data were presented to allow assessment of any differences in treatment effect in patients with a previous SCC.

The details of the trials presented in the submission are presented below.

Trial ID	Protocol title/ Publication title	Publication citation
Indirect comparison: Common reference – placebo/vehicle		
Ingenol mebutate 0.015%		
PEP005-015	A Phase 2, Multicentre, Randomized, Double Blind, Vehicle-Controlled, Dose-Ranging Trial to Evaluate the Safety and Efficacy of 0.005%, 0.01% and 0.015% ingenol mebutate Topical Gel when used to treat solar keratosis on the Head (Face or Scalp) Spencer J. Multicentre, randomized, double-blind, vehicle-controlled, dose-ranging study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel 0.005%, 0.01%, and 0.015% when used to Treat Actinic Keratoses on the Head.	*Journal of the American Academy of Dermatology.* 2010;62(3):AB105

Trial ID	Protocol title/ Publication title	Publication citation
PEP005-016	A Phase 3, Multicentre, Randomized, Parallel Group, Double-Blind, Vehicle-Controlled study Evaluating the Efficacy and Safety of ingenol Mebutate Gel 0.015% in Patients with Solar keratosis on the Head (Face or Scalp) Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol Mebutate Gel for Actinic Keratosis.	*The New England Journal of Medicine.* 2012;366(11):1010-1019
PEP005-025	A Phase 3, Multicentre, Randomized, Parallel Group, Double-Blind, Vehicle-Controlled Trial Evaluating the efficacy and Safety of ingenol mebutate Gel 0.015% in the treatment of Solar Keratosis on the Head (Face or Scalp) Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol Mebutate Gel for Actinic Keratosis.	*The New England Journal of Medicine.* 2012;366(11):1010-1019
Ingenol mebutate 0.05%		
PEP005-014	A Phase 3, Multicentre, Randomized, Parallel-group, Double-blind, Vehicle-Controlled study Evaluating the Effiacy and Safety of ingenol mebutate Gel 0.05% in Patients with Actinic keratosis on the Trunk and Extremities Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol Mebutate Gel for Actinic Keratosis.	*The New England Journal of Medicine.* 2012;366(11):1010-1019
PEP005-028	A Phase 3, Multicentre, Randomized, Parallel-group, Double-Blind, Vehicle-Controlled study Evaluating the Efficacy and Safety of ingenol mebutate Gel 0.05% in Patients with Actinic keratosis on the Trunk and Extremeties Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol Mebutate Gel for Actinic Keratosis.	*The New England Journal of Medicine.* 2012;366(11):1010-1019
Imiquimod 5%		
Alomar 2007	Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratosis on the head. Alomar A, Bichel J, McRae S.	*British Journal of Dermatology*. 2007;157(1):133-141
Jorizzo 2007	Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratosis on the head. Jorizzo J, Dinehart S, Matheson R, Moore JK, Ling M, Fox TL, McRae S, Fielder S, Lee JH.	*Journal of the American Academy of Dermatology*. 2007;57(2):265-268

Trial ID	Protocol title/ Publication title	Publication citation
Korman 2005	Dosing with 5% Imiquimod Cream 3 Times per Week for the Treatment of Actinic Keratoses Korman N, Moy R, Ling M, Matheson R, Smith S, McKane S, Lee JH	*Archives of Dermatology*. 2005;141(4):467-473
Szeimies 2004	Imiquimod 5% cream for the treatment of acitinic keratosis: Results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. Szeimies R-M, Gerritsen M-J, Gupta G, Ortonne JP, Serresi S, Bichel J, Lee JH, Fox TL	,*Journal of the American Academy of Dermatology.* 2004;51(4):547-555
Diclofenac 3%		
Rivers 2002	Topical treatment of actinic keratosis with 3.0% diclofenac in 2.5% hyaluronan gel. Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin Y	.*British Journal of Dermatology.* 2002;146:94-100
Stockfleth 2011	Low dose 5-fluorouracil in combination with salicylic acid as a new lesion-directed option to treat topically actinic keratosis: histological and clinical study results. Stockfleth E, Kerl H, Zwingers T, Willers C.	*British Journal of Dermatology.* 2011;165(5):1101-1108.
Wolf 2001	Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. Wolf JE Jr, Taylor JR, Tschen E, Kang S	*International Journal of Dermatology.* 2001;40(11):709-713.
Multi-step indirect comparison: Common reference – placebo/vehicle and imiquimod 5%		
5-FU 5%		
Krawtchenko 2007	A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratosis: a comparison of clinical and histological outcomes including 1-year follow-up. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E.	*British Journal of Dermatology*. 2007, 157(Supp 2):34-40

8. Results of Trials

Clearance of Solar Keratosis

With regards to comparative effectiveness, the table below presents the results of the indirect comparisons of ingenol mebutate 0.015%, ingenol mebutate 0.05%, imiquimod 5%, diclofenac 3% and 5-FU 5% for complete clearance of solar keratosis.

Summary of results of the indirect comparisons of ingenol mebutate 0.015%, ingenol mebutate 0.05%, imiquimod 5%, diclofenac 3% and 5-FU 5% for the complete clearance of solar keratosis

		Treatment Effect	
Comparison	**Trials included**	**Trials included**	**RD (%) (95% CI)**
Mixed comparators			
Ingenol mebutate 0.015% vs. imiquimod 5%	Ingenol mebutate 0.015%: • PEP005-015 • PEP005-016 • PEP005-025 Ingenol mebutate 0.05% • PEP005-014 • PEP005-028 Imiquimod 5% • Jorizzo 2007 • Korman 2005	1.88 (0.84, 4.23)	-2.0 (-10.4, 6.4)
Ingenol mebutate (0.015%, 0.05%) vs diclofenac 3%	Diclofenac 3%	**3.41 (1.98, 5.88)**	**14.2 (3.8, 24.6)**
Ingenol mebutate 0.015% vs. diclofenac 3% (November 2012)	• Rivers 2002 • Stockfleth 2011 • Wolf 2011	**3.89 (2.02, 7.48)**	**17.9 (8.5, 27.3)**
Ingenol mebutate 0.015% vs. 5-FU 5%	5-FU 5% • Krawtchenko 2007	1.66 (0.72, 3.80)	-13.2 (-33.8, 7.4)

[a] Same as the results presented in the November 2012 submission

The following table presents the results of the comparison of ingenol mebutate 0.015% with no treatment.

Summary of results of the comparisons of ingenol mebutate 0.015% with no treatment for the complete clearance of solar keratosis

No treatment[a]			
PEP005-015		**5.50 (1.77, 17.08)**	**40.9 (21, 60.8)**
PEP005-016		**16.54 (5.29, 51.74)**	**34.8 (26.3,43.3)**
PEP005-025		**9.17 (4.36, 19.26**	**42.0 (33.0, 51.0**
Meta analyses (ingenol mebutate 0.015%):		**9.32 (5.40, 16.08)**	**38.5 (32.5, 44.4)**
Chi-square (Q) for heterogeneity; p=I^2 statistic with 95% CI		Q=0.52, p=0.770, I^2=0%	Q=1.00, p=0.608, I^2=0%

The analyses showed no statistically significant difference between ingenol mebutate 0.015% and imiquimod 5% for the primary outcome of complete clearance. The analyses also demonstrated that ingenol mebutate 0.05% and ingenol mebutate 0.015% were statistically significantly superior to diclofenac 3% for the same outcome. The PBAC agreed with the ESC that it was inappropriate to use trial data based on treatment with 0.05% ingenol mebutate, as this presentation of ingenol mebutate is a different strength to the strength proposed for listing.

The multi-step indirect comparison between ingenol mebutate 0.05% and 5-FU 5% indicated that there was no statistically significant difference for the primary outcome of complete

clearance. The PBAC noted that Krawtchenko 2007 trial involved a small number of patients and was open-label, and there were differences in the treatment areas used: 25cm^2 in the trials for the indirect comparison of ingenol mebutate 0.015% vs. imiquimod 5% and 50cm^{2}in Krawtchenko 2007. The PBAC considered that, given these differences between the trials and the inherent uncertainties of a multi-step indirect comparison, the results of the analysis were not sufficiently reliable to inform the comparative effectiveness of ingenol mebutate 0.015% vs 5-FU 5%.

The PBAC considered that the data comparing ingenol mebutate with no treatment indicated that ingenol mebutate is superior to no treatment.

The resubmission also presented results for partial clearance of solar keratosis. The results of this comparison are presented below:

Summary of results of the indirect comparison of ingenol mebutate 0.015% and imiquimod 5% for partial clearance of solar keratosis

		Partial clearance rate			Treatment effect	
Trial	**Time of CC**	**ING 0.015%**	**VG**	**IMI 5%**	**RR (95% CI)**	**RD (%) (95% CI)**
Ingenol mebutate 0.015% trials						
PEP005-015	Day 57	23/32 (71.9%)	4/33 (12.1%)	-	**5.93 (2.31, 15.24)**	**59.8 (40.6, 78.9)**
PEP005-016	Day 57	81/135 (60.0%)	9/134 (6.7%)	-	**8.93 (4.68, 17.04)**	**53.3 (44.0, 62.6)**
PEP005-025	Day 57	96/142 (67.6%)	11/136 (8.1%)	-	**8.36 (4.69, 14.90)**	**59.5 (50.6, 68.5)**
			Meta analyses:	Random effects model	**8.07 (5.46, 11.95)**	**56.8 (50.7, 63.0)**
				Chi-square (Q) for heterogeneity; p=I^2 statistic with 95% CI	Q=0.52, p=0.770, I^2=0%	Q=1.00, p=0.608, I^2=0%
Imiquimod 5% trials						
Jorizzo 2007	Day 84	-	31/123 (25.2%)	75/123 (61.0%)	**2.42 (1.73, 3.38)**	**35.8 (24.2, 47.3)**
Korman 2005	Day 168	-	34/250 (13.6%)	155/242 (64.0%)	**4.71 (3.40, 6.53)**	**50.4 (43.1, 57.8)**
			Meta analyses:	Random effects model	**3.38 (1.74, 6.55)**	**43.8 (29.4, 58.2)**
				Chi-square (Q) for heterogeneity; p=I^2 statistic with 95% CI	Q=8.01, p=0.005 I^2=87.5% (51.4%, 96.8%)	Q=4.45, p=0.035 I^2=77.5% (1.7%, 94.9%)
				Indirect comparison: ingenol mebutate 0.015% vs imiquimod 5%	**2.39 (1.10, 5.16)**	13.0 (-2.6, 28.7)

Abbreviations: IMI = imiquimod; ING = ingenol mebutate; VG vehicle gel

The resubmission claimed that the indirect comparison of partial clearance rates demonstrated that ingenol mebutate 0.015% was statistically significantly superior to imiquimod 5%. The PBAC noted that statistical significance was only achieved for the measure of relative risk (RR = 2.39, 95% CI: 1.10, 5.16), with no statistically significant difference being reported for risk difference (RD = 13.0%, 95% CI: -2.6%, 28.7%). The PBAC considered that the claim of superior comparative effectiveness of ingenol mebutate 0.015% over imiquimod 5% in terms of partial clearance was not adequately supported and the relevance of partial clearance as a clinical outcome was not established.

Overall, the PBAC considered that ingenol mebutate 0.015% has non-inferior comparative effectiveness to imiquimod, and is superior to diclofenac for the outcome of complete clearance of solar keratoses. The PBAC did not consider that the data were adequate to support the claim of non-inferior comparative effectiveness to 5-FU.

Link between clearance of solar keratosis and reduction in progression to SCC

The PBAC noted that the resubmission presented two studies to support a claim of a relationship between solar keratosis clearance and reduction in risk of SCC. Anwar, Wrone et al (2004) concluded that 90% of SCCs occur at or adjacent to a solar keratosis lesion, while Mostow (1992) concluded that patients with an increased number of solar keratoses are at increased risk of developing an SCC. The resubmission also noted several studies demonstrating that solar keratosis and SCC are contiguous and have molecular/genetic similarities involving the p53 gene. The PBAC noted advice from dermatologists regarding the accepted relationship between solar keratosis and SCC.

The PBAC noted that no data were presented to quantify the risk of SCC in patients with a prior SCC. The PBAC agreed with the ESC that these patients with prior SCC may be at a higher risk of recurrent SCC, but did not consider that the extent of benefit modelled in the resubmission had been adequately justified. The PBAC therefore considered that it was not possible to quantify the clinical benefit in terms of reduced SCCs that would accrue from clearance of solar keratoses.

The PBAC noted the study in the resubmission by Dodson et al (1991). This study used data from Marks et al 1988 and Marks et al 1996 to model the risk of malignant transformation to SCC on a per-lesion basis, and describe risk on a per-patient basis. The resubmission then applied the calculations from Dodson et al. to Criscione et al. (2009). Criscione et al reported a risk of progression from solar keratosis to SCC (invasive or in situ) of 0.89% at year 1, and 4.03% at year 5. On this basis the resubmission then estimated a rate of malignant transformation in patients with a prior history of SCC of 40.78% over ten years and 4.078% over one year.

The PBAC noted that Dodson et al (a modelling study rather than an observational cohort) used a number of assumptions, including that transformation of a lesion was independent of other lesions, and that the rate of transformation over the life span of the lesion is constant. The PBAC also noted the additional complex modelling presented in the resubmission to estimate the risk of malignant transformation of solar keratosis to SCC.

The PBAC considered that the assumptions used by Dodson et al were not accurately reflective of the natural history of solar keratoses, which can and do regress. The PBAC

considered that the estimates of risk of malignant transformation using of Dodson et al were likely to be highly uncertain. The PBAC therefore considered that these estimates were inadequately supported and were likely to be overestimated.

The PBAC also recalled that the Independent Review report for imiquimod for the treatment of solar keratosis (2009) concluded that the risk of progression from solar keratosis to SCC is low (0.1 to 0.24% per year). The report also noted that the 10 year risk of an individual developing metastatic SCC arising from solar keratosis is in the range of 0.03 to 0.33%, and that approximately 40% of SCCs arise de novo, with no pre-existing solar keratosis.

With regards to comparative harms, application site reactions were one of the more frequently reported adverse reactions in the randomised trials. The rates of these reactions ranged from 30% to 63% in the treatment arms, with the exception of PEP005-025, PEP005-014 and Rivers 2002, which reported lower instances of application site reactions (5 to 17%). In November 2012, the PBAC noted that the incidence and profile of adverse events was similar for ingenol mebutate and imiquimod in the trials presented.

9. Clinical Claim

The resubmission described ingenol mebutate as non-inferior to imiquimod 5% and 5-FU 5% and superior to diclofenac 3% for complete clearance of solar keratoses. The PBAC considered these claims were reasonable, with the exception of the comparison versus 5-FU 5%.

The resubmission claimed that clearance rates of solar keratosis will reduce the risk of malignant transformation to a SCC. The PBAC considered that this claim was not adequately supported because although it was reasonable to accept that solar keratosis clearance will reduce the risk of transformation to SCC, the resubmission did not adequately quantify the reduction in risk of SCC that would accrue from clearance of solar keratosis.

The resubmission described ingenol mebutate as non-inferior in terms of comparative safety over imiquimod 5%, diclofenac 3% and 5-FU 5%. The PBAC considered this claim to be reasonable.

10. Economic Analysis

The resubmission claimed that ingenol mebutate is cost-effective against the comparator of no treatment and dominates the mixed comparator of imiquimod, 5-FU and diclofenac.

The economic claim was supported by a modelled cost-utility analysis (CUA) based on the claim of superior efficacy and non-inferior safety. The resubmission presented an ICER less than $15,000/QALY compared to no treatment, based on modelling the outcome of complete clearance from the clinical trials, applied to solar keratosis patients with a prior SCC and extrapolated to 40 years (from one treatment in the trials) and applying utility weights from 2 studies.

The resubmission presented an economic model with a Markov structure. It used 1-year cycles, extrapolated for 40 years from a baseline age of 60 years in patients who have had a prior SCC. The health states in the model were:

- Solar keratosis;
- Squamous cell carcinoma;
- Post-SCC with metastatic risk;
- Metastasis with elevated risk of death, and;
- Death.

The resubmission assumed that the probability of progression of a solar keratosis lesion to SCC is constant over time and is unaffected by progression of another lesion. The PBAC considered that this assumption was not reasonable given that solar keratoses can and do regress, and that it is therefore difficult to predict the evolution of a single lesion. The PBAC noted the ESC's concern that the calculated annual rate of progression in the resubmission was high, based on the approach of Dodson et al of probability per patient, rather than per lesion (average 7.7 per patient). The PBAC agreed with the ESC that a rate of 40.78% in year 10 of the model was inappropriately applied, as this would suggest that there were no clinical interventions to treat emerging lesions in a patient over a decade. Given that current clinical practice involves screening patients with solar keratosis regularly and intervening early, the PBAC considered that the estimated rate of transition of solar keratosis to malignant lesions that was used in the model would not be observed in practice.

The PBAC agreed with the ESC that the resubmission's estimate (based on Rowe et al (1992)) that 25.1% of patients with recurrent SCCs develop metastatic disease over a period of 5 years was not clinically plausible. The PBAC considered that this implied no clinical intervention once a lesion was detected. The PBAC noted that this estimate differs from the rates reported in the Independent Review for Imiquimod, which stated that "…*the risk of development of metastatic cancer is between 0.5 and 3.3%. Based on these figures the 10 year risk of an individual developing metastatic SCC arising from* solar keratosis *is in the range of 0.03 to 0.33%"*. Further, Rowe et al estimated the metastatic potential of recurrent SCC (i.e. treatment failures) rather than incident SCCs. Rowe et al states that SCCs that have recurred locally at the treatment site are more likely to develop a local recurrence again after repeat treatment. The PBAC considered that the resubmission overestimated the potential for incident SCC to metastasise.

The PBAC noted that under the following conditions, the ICER for ingenol mebutate increases to between $45,000 and $75,000/QALY:

- age 70 years at baseline
- time horizon of 2 years only (Fuchs 2007 found progression to SCC takes approx. 2 years)
- 1% rate of progression from solar keratosis to SCC, based on Marks, 1988 (a per lesion, rather than per patient value)
- a 3.3% rate of metastases (Imiquimod Independent Review Report – 2009, p4)
- 8% p.a. die from metastatic and survivors live for a further 16 years
- only one treatment per year (not two treatments as in the resubmission)
- no cost-offsets
- no discounting of benefits.

The PBAC considered that the ICER could plausibly be higher, as the resubmission did not present convincing evidence to quantify the risk reduction of developing SCCs that would

arise from treatment with ingenol mebutate (bringing into question the projected health benefits associated with avoiding SCCs).

The utility estimates used in the model were taken from two studies identified in a literature search. Chen et al (2004) was based on a time-trade off method administered in clinic patients in two US hospitals, and Littenberg et al was based on a paper based standard gamble questionnaire administered in a cohort of patients recruited through outpatient clinics in US hospitals. Both studies were designed to explore methods for obtaining utilities for dermatology populations. The estimated utilities from these studies are presented below:

Utility results from literature search for resubmission.

Trial ID	N	Mean utility score
Solar keratosis		
Chen 2004	9	0.981
Littenberg 2003	16	0.989
Weighted average		**0.986**
Non-melanoma skin cancer		
Chen 2004		0.976
Littenberg 2003		0.995
Weighted average		**0.9855**

In Chen et al (2004) only 9 patients contributed results for a utility of living with solar keratosis. The severity of the solar keratosis for the 9 patients is not reported in terms of age, prior history or number and location of lesions. In Littenberg et al (2003) only 16 patients contributed to the estimate for the utility of living withsolar keratosis, and patient characteristics were not reported.

The PBAC considered it implausible that, according to Littenberg, patients with non-melanoma skin cancer would have a higher utility (0.995) than patients with solar keratosis (0.989), noting that non-melanoma skin cancer is the more serious of the two conditions. Given the differences in methods between the two studies, the PBAC was of the view that the difference in utilities was more likely to be driven by the utility methods and the individual heterogeneity in the very small samples from which the estimates were derived. The PBAC also did not consider that the difference in the weighted average utility between the two conditions (0.0005) was meaningful or could be considered to represent the effect of these conditions on a patient's quality of life. Overall, the PBAC did not consider that the utility estimates provided by Chen et al and Littenberg et al were reliable or informative for decision making.

The PBAC noted that the sponsor's pre-PBAC response proposed that if it were assumed that solar keratoses do not transform to SCC, by setting that variable to zero in the model, the ICER produced remained below $15,000 per QALY. The sponsor claimed that this indicated that treating solar keratoses alone, without assuming a reduction in SCCs related health impacts and costs, represents a cost-effective intervention. The PBAC noted this sensitivity analysis, and also considered that this quantified the extent to which the results of the model

are driven by the assumed utility benefit from treatment of solar keratosis, which the PBAC did not consider reliable.

The PBAC considered that, without evidence to quantify the health benefit associated with SCC reduction, the benefit of clearance of solar keratoses was limited to what could be considered cosmetic benefits only. The PBAC considered that the data presented did not demonstrate that cosmetic treatment of solar keratoses would deliver a tangible health benefit in terms of quality of life. The PBAC did not consider that the utilities derived from the two utility studies provided evidence of a utility gain from cosmetic treatment of solar keratosis. In particular the PBAC noted that the utility of being event free is assumed to be 1, but there is no evidence from either of the utility studies to support this assumption.

The PBAC concluded that the ICER estimated in the sponsor's pre-PBAC response (assuming zero progression of solar keratosis to SCC, but a utility benefit from treatment of solar keratosis), although within a range that PBAC would normally consider to be acceptable, was not reliable because the resubmission did not present any evidence that clearance of solar keratosis would provide an appreciable health gain in terms of improved quality of life.

11. Estimated PBS Usage and Financial Implications

The resubmission estimated that between 50,000 and 100,000 patients would be treated with ingenol mebutate, at a cost to the PBS of between $10 and $30 million in Year 5 of listing.

The resubmission provided a primary (most likely) estimate of ingenol mebutate use, based on current use of private prescription topical therapies, expert opinion to ascertain the proportion of private prescription use that would meet the proposed eligibility criteria for ingenol mebutate, and assumed future market growth with listing of ingenol mebutate. The resubmission also provided an upper limit of use, based on epidemiological derivation of the number of patients with squamous cell carcinoma (SCC), and expert opinion to estimate the proportion of these who would meet the proposed eligibility criteria for ingenol mebutate.

The PBAC noted the Drug Utilisation Sub-Committee (DUSC) advice that the primary estimates were more than doubled by plausible alterations to the assumptions such as a higher number of prescriptions per patient to account for treatment of multiple fields, higher uptake of field therapy, and 100% of SCC patients having subsequent solar keratosis.

The PBAC agreed with the DUSC that the market growth assumptions were not justified, considering the perceived advantages of a 3-day course over the currently-available therapies which all require longer treatment times. The PBAC also noted that multiple ingenol mebutate treatments may be prescribed for a patient over a given year. This would include both prescribing for different fields of solar keratoses, and repeat treatments for the same field (including new lesions and recurrences). The PBAC therefore considered that the estimate of an average of two treatments per year was a potential underestimate.

The PBAC agreed with the DUSC that there is very high potential for treatment of solar keratoses in all patients, not just those with previously diagnosed SCC on the face or scalp, because of a lack of other PBS subsidised therapies. The PBAC noted the survey of dermatologists presented in the resubmission in which, asked how many times they would

retreat a field, half of the responses (11/22) indicated that they would retreat indefinitely. The PBAC concluded that the total utilisation and cost could be significantly higher than estimated in the resubmission.

12. Recommendation and Reasons

The PBAC rejected the resubmission for PBS listing of ingenol mebutate for solar keratosis, on the basis that convincing data were not presented to quantify the reduction in risk of SCC that would be attributed to solar keratosis clearance. The PBAC also considered it could not rely on the data were presented to inform an assessment of the quality of life benefit of treating solar keratosis.

The PBAC agreed that imiquimod 5%, diclofenac 3% and 5-FU 5% were appropriate comparators for clinical purposes in this resubmission.

The PBAC agreed that ingenol mebutate is non-inferior to imiquimod and superior to diclofenac for complete clearance of solar keratoses. The PBAC considered that the claim of non-inferior comparative effectiveness to 5-FU 5% was not adequately supported. The PBAC considered that ingenol mebutate is non-inferior in terms of comparative safety compared with imiquimod 5%, diclofenac 3% and 5-FU 5%. The PBAC considered that ingenol mebutate is superior in terms of comparative effectiveness compared with no treatment, and inferior in terms of comparative safety.

The PBAC considered that convincing data were not presented to quantify the reduction in risk of SCC that would be attributed to solar keratosis clearance. The PBAC considered that such data would be essential to establish solar keratosis clearance as a surrogate outcome for reduction in progression to SCC. The PBAC therefore considered that it was not possible to quantify the clinical benefit in terms of reduced SCCs that would accrue from clearance of solar keratoses.

PBAC considered that the model presented in the resubmission was not able to be used to reliably estimate the cost effectiveness of ingenol mebutate. The PBAC considered that key issues with the model included an overestimate of the rate of annual progression from solar keratosis to SCC, and an overestimate of the proportion of patients with recurrent SCCs that develop metastatic disease. The PBAC noted that plausible adjustments in the model parameters (patient age at baseline, time horizon, rate of progression from solar keratosis to SCC, rate of metastasis and number of treatments, among other factors) generated an ICER between $45,000 and $75,000/QALY. The PBAC considered that the ICER could plausibly be higher in the absence of convincing evidence to quantify the risk reduction of developing SCCs that would arise from treatment with ingenol mebutate.

The PBAC did not consider that the resubmission's utility estimates for solar keratosis clearance were reliable or informative for decision making. Given the differences in methods between the two studies that provided the utility estimates, the PBAC was of the view that the difference in utilities was more likely to be driven by the utility methods and the individual heterogeneity in the very small samples from which the estimates were derived. The PBAC also did not consider that the difference in the weighted average utility between the two conditions (0.0005) was meaningful or could be considered to represent the effect of these conditions on a patient's quality of life. The PBAC considered that the data presented did not

demonstrate that cosmetic treatment of solar keratoses would deliver a tangible health benefit in terms of quality of life.

The PBAC noted the ICER estimated in the sponsor's pre-PBAC response of less than $15,000 (assuming zero progression of solar keratosis to SCC). The PBAC noted this sensitivity analysis, and also considered that this quantified the extent to which the results of the model are driven by the assumed utility benefit from treatment of solar keratosis, which the PBAC did not consider reliable.

The PBAC considered that the estimates of market growth, utilisation were not adequately supported. The PBAC therefore considered that the total cost of PBS listing of ingenol mebutate could be significantly higher than estimated.

The PBAC noted that this resubmission meets the criteria for an Independent Review

Outcome:
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

Leo Pharma are disappointed with this outcome and will continue to work on PBS listing to ensure the best possible outcome for its patients.