PUBLIC SUMMARY DOCUMENT
Product: Ingenol, gel, 0.15 mg per g (0.015%), 70 mcg ingenol mebutate in 0.47 g single use tubes, 3, Picato®
Sponsor: LEO Pharma Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application
The submission sought an Authority Required listing for the field treatment of solar (actinic) keratoses of the face and scalp in patients where topical fluorouracil 5% (5-FU) is clinically inappropriate.

2. Background
This drug had not previously been considered by the PBAC.

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

4. Listing Requested and PBAC's View
Authority required
Field therapy for the treatment of solar keratoses of the face and scalp in patients where topical 5-FU is clinically inappropriate.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Solar (actinic) keratoses (SK) are a common premalignant condition of thick, scaly, or crusty patches of skin occurring on sun-exposed skin. The mechanism of action of ingenol mebutate in SK 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.

Alternative treatments include fluorouracil cream 50 mg per g (5%) (5-FU). The listing requested for ingenol mebutate was for use in a 5-FU intolerant or inappropriate sub-population (as 5-FU is photosensitive, it is not recommended for use by patients who are likely to be exposed to sunlight for extended periods).

There is no medication currently listed on the PBS for the treatment of SK.

6. Comparator
The submission nominated imiquimod cream 50mg per g (5%), 250mg single use sachets, as the main comparator. The submission also nominated diclofenac as a secondary comparator and used a comparison against no treatment in its economic evaluation.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials
The submission presented an indirect analysis of the pooled results of three randomised trials of ingenol mebutate (N=612) compared to the pooled results of two randomised trials of

imiquimod using placebo (vehicle gel) as the common comparator (N=808). All five trials were used for the vehicle arm (N=1248). For the safety analysis, two further imiquimod trials were added with results for a further 641 patients randomised to active therapy. The patient populations for all trials were comparable and representative of the proposed listing.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Ingenol mebutate 0.015% placebo controlled trials		
PEP005-015 Spencer	Multicenter, 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.	*J Am Acad Dermatol* (2010); 62(3): AB105.
PEP005-016 PEP005-025 Lebwohl et al.	Ingenol mebutate gel for Actinic Keratosis.	*New Engl J Med* (2012); 366 (11): 1010-9.
Imiquimod 5% placebo controlled trials		
Alomar*	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 keratoses on the head.	*British Journal of Dermatology* (2007); 157(1):133-41
Jorizzo	Vehicle-controlled, double-blind, randomized study of imiquimod 5% applied 3 days per week in one or two courses of treatment for actinic keratoses on the head.	*Journal of the American Academy of Dermatology* (2007); 57(2): 265-8
Korman	Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: Results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials.	*Archives of Dermatology* (2005); 141 (4):467-73
Szeimies*	Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology.	*Journal of the American Academy of Dermatology* (2004); 51(4):547-55

*Two of the imiquimod trials (Alomar 2007 and Szeimies 2004) used biopsy samples to histologically assess complete clearance and so were not eligible for the efficacy analysis, but were included in the safety analysis.

8. Results of Trials

The primary outcome measure was complete clearance of lesions at follow-up (time to follow-up varied between trials). Partial clearance, defined as ≥ 75% reduction in lesions, was used as secondary outcome measure.

The results of the indirect analyses are shown below. The first table contains the estimates of

the relative risk, and where the number needed to treat (NNT) was calculated during the evaluation. The second table contains the estimates of risk difference. The economic evaluation presented in the submission used only the estimates of risk difference.

Summary of results of the indirect comparison of ingenol mebutate and imiquimod for complete clearance of SK

Trial ID	Ingenol mebutate			Imiquimod			Indirect estimate RR (95% CI)
	RR (95% CI)	Ingenol n/N (%)	Placebo n/N (%)	Placebo n/N (%)	Imiq n/N (%)	RR (95% CI)	
Complete clearance							
PEP005-015	5.50 (1.77, 17.08) NNT=2.4[a]	16/32 (50%)	3/33 (9.1%)	-	-	-	
PEP005-016	16.54 (5.29, 51.74) NNT=2.9[a]	50/135 (37.0%)	3/134 (2.2%)	-	-	-	
PEP005-025	9.17 (4.36, 19.26) NNT=2.4[a]	67/142 (47.2%)	7/136 (5.1%)	-	-	-	
Jorizzo 2007	-	-	-	18/123 (14.6%)	66/123 (53.7%)	3.67 (2.32, 5.79) NNT=2.6[a]	
Korman 2005	-	-	-	18/250 (7.2%)	117/242 (48.3%)	6.71 (4.22, 10.68) NNT=2.4[a]	
Pooled[b]	**9.32 (5.40, 16.08)**	-	-	-	-	**4.96 (2.72, 9.03)**	
Q I^2 (95% CI)	Q=1.88 p=0.391 I^2=0%	-	-	-	-	Q=3.39 p=0.065 I^2=70.5% (0%, 93.4%)	**1.88 (0.84-4.23)**
Partial clearance							
PEP005-015	5.93 (2.31, 15.24)	23/32 (71.9%)	4/33 (12.1%)	-	-	-	
PEP005-016	8.93 (4.68, 17.04)	81/135 (60.0%)	9/134 (6.7%)	-	-	-	
PEP005-025	8.36 (4.69, 14.90)	96/142 (67.6%)	11/136 (8.1%)	-	-	-	
Jorizzo 2007	-	-	-	31/123 (25.2%)	75/123 (61.0%)	2.24 (1.73, 3.38)	
Korman 2005	-	-	-	34/250 (13.6%)	155/242 (64.0%)	4.71 (3.40, 6.53)	
Pooled[b]	**8.07 (5.46, 11.95)**	-	-	-	-	**3.38 (1.74, 6.55)**	
Q I^2 (95% CI)	Q=0.52 p=0.770 I^2=0%	-	-	-	-	Q=8.01 p=0.005 I^2=87.5% (51.4%, 96.8%)	**2.39 (1.11, 5.16)**

RR=relative risk; NNT=number needed to treat; Imiq=imiquimod

[a] calculated during the evaluation with NNT=1/risk difference

Summary of results of the indirect comparison of ingenol mebutate and imiquimod for complete and partial clearance of SK; Risk difference estimates

Trial ID	Ingenol mebutate			Imiquimod			Indirect estimate RD (95% CI)
	RD (95% CI)	Ingenol n/N (%)	Placebo n/N (%)	Placebo n/N (%)	Imiq n/N (%)	RD (95% CI)	
Complete clearance							
PEP005-015	40.9 (21, 60.8)	16/32 (50%)	3/33 (9.1%)	-	-	-	
PEP005-016	34.8 (26.3, 43.3)	50/135 (37.0%)	3/134 (2.2%)	-	-	-	
PEP005-025	42.0 (33.0, 51.0)	67/142 (47.2%)	7/136 (5.1%)	-	-	-	
Jorizzo 2007	-	-	-	18/123 (14.6%)	66/123 (53.7%)	39.0 (28.2, 49.8)	
Korman 2005	-	-	-	18/250 (7.2%)	117/242 (48.3%)	41.1 (34.1, 48.2)	
Pooled	**38.5 (32.5, 44.4)**	-	-	-	-	**40.5 (34.6, 46.4)**	**-2.0 (-10.4, 6.4)**
Partial clearance							
PEP005-015	59.8 (40.6,78.9)	23/32 (71.9%)	4/33 (12.1%)	-	-	-	
PEP005-016	53.3 (44.0, 62.6)	81/135 (60.0%)	9/134 (6.7%)	-	-	-	
PEP005-025	59.5 (50.6, 68.5)	96/142 (67.6%)	11/136 (8.1%)	-	-	-	
Jorizzo 2007	-	-	-	31/123 (25.2%)	75/123 (61.0%)	35.8 (24.2, 47.3)	
Korman 2005	-	-	-	34/250 (13.6%)	155/242 (64.0%)	50.4 (43.1, 57.8)	
Pooled	**56.8 (50.7, 63.0)**	-	-			**43.8 (29.4, 58.2)**	**13.0 (-2.7, 28.7)**

RD=risk difference; Imiq=imiquimod

The PBAC noted that the results of the indirect comparison showed that the relative risk of the primary outcome measure of complete clearance with ingenol was not significantly different to that of imiquimod. The relative risk of partial clearance (defined as less than or equal to 75 % clearance of lesions), which was a secondary outcome measure, did show a statistically significant advantage for ingenol over imiquimod, however the risk differences for each of complete clearance and partial clearance failed to achieve statistical significance. The PBAC further considered that the indirect comparison was limited by comparability of the two data sets including the potential risk of bias in the trials (noting that although all trials were blinded skin reactions could lead to unblinding), and the differences in the duration of treatments (which has implications for follow-up, outcome assessment and discontinuations).

The majority of adverse reactions were self-limiting. Adverse reactions that required treatment were treated with concomitant medications, and resulted in no serious medical outcomes or permanent side-effects. The incidence and profile of adverse events was similar across agents and adverse event-related discontinuation was low for both ingenol mebutate and imiquimod. Given the limited time ingenol mebutate has been available, consideration of the extended assessment of comparative harms was not possible. The trial-based evidence indicated a low risk of harm associated with ingenol mebutate based on available data.

9. Clinical Claim

The submission claimed that ingenol mebutate is safer and more effective than imiquimod.

The PBAC considered that the clinical claim of superior efficacy and safety over imiquimod was inadequately supported.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission also presented a cost utility analysis comparing ingenol to no treatment. The submission presented a secondary analysis of ingenol mebutate compared to no treatment which estimated a cost per QALY of less than $15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost per year to Government in the range of $10 - $30 million in Year 5.

The PBAC considered that the submission's utilisation estimates were highly uncertain and likely to be a substantial underestimation of the overall cost to the PBS. The PBAC considered that there was a large potential for use in place of non-subsidised topical 5-FU given the shorter duration of treatment and lower cost to the consumer.

12. Recommendation and Reasons

The PBAC considered that the requested restriction was unworkable as the patient population for whom 5-FU is clinically inappropriate was not defined and hence that it was difficult to determine the patient population for whom use was proposed. The PBAC further noted that ingenol mebutate (ingenol) was proposed to be used where a non-PBS listed medicine was not clinically appropriate, as topical 5-FU is not currently listed on the PBS for the treatment of solar keratosis. Therefore, comparison against a non-PBS-listed product was not considered informative in establishing the cost-effectiveness of ingenol.

The PBAC considered that the comparison to imiquimod was not informative about the cost effectiveness of ingenol in the PBS setting as the PBAC had considered imiquimod for field therapy of multiple clinically evident solar keratosis lesions at its July 2008 meeting and rejected the submission on the basis of uncertain evidence of efficacy and safety and resulting uncertain cost effectiveness. The PBAC further noted that the secondary comparator, diclofenac, is also not listed on the PBS for the treatment of solar keratosis and again therefore the resulting comparison was not informative for assessment of the cost effectiveness of ingenol.

The PBAC considered that the clinical claim of superior efficacy and safety over imiquimod was inadequately supported. The submission presented an indirect comparison of the pooled results of three randomised trials of ingenol mebutate with the pooled results of two randomised trials of imiquimod using placebo (vehicle gel) as the common comparator. The PBAC noted that the results of the indirect comparison showed that the relative risk of the primary outcome measure of complete clearance with ingenol was not significantly different to that of imiquimod. The relative risk of partial clearance (defined as less than or equal to

75 % clearance of lesions), which was a secondary outcome measure, did show a statistically significant advantage for ingenol over imiquimod, however the risk differences for each of complete clearance and partial clearance failed to achieve statistical significance. The PBAC further considered that the indirect comparison was limited by comparability of the two data sets including the potential risk of bias in the trials (noting that although all trials were blinded skin reactions could lead to unblinding), and the differences in the duration of treatments (which has implications for follow-up, outcome assessment and discontinuations).

The PBAC noted that the claim of superior safety over imiquimod was based on the clinical expectation that ingenol will have a shorter duration of side effects resulting from shorter treatment durations compared with imiquimod. The PBAC considered that the claim of superior safety was unsubstantiated, noting that the incidence and profile of adverse events was similar for ingenol and imiquimod in the trials presented.

The PBAC considered that the claims of superior efficacy and safety over diclofenac were inadequately supported.

The PBAC considered that the evidence presented in the submission did not sufficiently support the link between clearance of solar keratosis as a surrogate outcome for reduction in progression to squamous cell carcinoma (SCC). No data were presented to support quantification of the reduction in risk of progression to SCC from reduction in solar keratosis.

The PBAC noted that the economic model assumed non-inferiority of ingenol to imiquimod (despite the submission claiming superior efficacy) and that a cost-minimisation analysis was presented in terms of the cost per additional responder defined by complete clearance over a twelve month period. The submission concluded from the analysis that ingenol is cost saving. The PBAC considered that the comparisons in the economic model were highly sensitive to assumptions about the treatment regimen for imiquimod, the treatment algorithm, and the likelihood that imiquimod costs were significantly overstated.

The submission also presented a cost utility analysis comparing ingenol to no treatment. The PBAC considered the time-trade-off (TTO) study used by the submission to estimate the utility weights associated with the different treatments (no treatment, ingenol, imiquimod, and diclofenac) was not reliable. The PBAC considered there were numerous concerns about the conduct of the TTO study including:

- the potential for framing bias introduced by the ranking of task and the order of presentation of the health states;
- the wording of the health state scenarios which was difficult to interpret and made explicit comparisons between the health states - for example, the attributes of chance of spontaneous and partial clearance had a probability specified for one of the health states and described the probability for the other two health states relative to this: "less than half the relative rate of health state 1 and health state 3";
- the unconventional presentation of the TTO questions which was based on a series of responses to multiple choice questions;
- the mismatch between the duration of the risk of progression to SCC (over 10 years) and the survival time to be traded (20 years).

The PBAC considered that the submission's utilisation estimates were highly uncertain and likely to be a substantial underestimation of the overall cost to the PBS. The PBAC

considered that there was a large potential for use in place of non-subsidised topical 5-FU given the shorter duration of treatment and lower cost to the consumer. The PBAC noted that the key parameters in the submission's estimates were based on a survey of clinicians with responses from two general practitioners and six dermatologists. The PBAC considered that the survey was small, was not reported well in the submission, and that the results did not provide a reliable basis for utilisation estimates. The PBAC also considered that longer studies in this area have shown that solar keratoses recur and patients may require periodic treatments.

The PBAC therefore rejected the submission on the basis that the clinical claim that treatment of solar keratosis with ingenol reduces the risk of SCC was not quantified, that the cost effectiveness in the PBS setting is unknown, and that the utilisation is uncertain, and is likely to be high and substantially underestimated in the submission.

The PBAC acknowledged and noted the consumer comments on this item.

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 declined comment.