7.13 INGENOL MEBUTATE, gel 0.15 mg/g (0.015%), 3 x 0.47 g Picato®, LEO Pharma Pty Ltd

1 Purpose of Application

1.1 This minor re-submission is to request a Restricted Benefit listing for treatment, as field therapy, of solar keratosis (SK) of the face and scalp.

1.2 The proposed broader restriction, removing the requirement of a previously confirmed diagnosis of squamous cell carcinoma (SCC), is managed by a [redacted] and RSA. Altered model variables, including the assumption of no progression from SK to SCC, produce a new base case ICER of $15,000/QALY - $45,000/QALY (a sensitivity analysis incorporating new utility values for treatment of SK reduces the ICER to to less than $15,000/QALY).

2 Requested listing

2.1 The re-submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
INGENOL Gel, 0.15mg/g (0.015%), 70mcg ingenol in 0.47g single use tubes, 3	1	0	Picato® LO

Condition:	Solar *(actinic)* keratoses
Restriction:	Restricted benefit
Clinical criteria:	The treatment must be field therapy AND The treatment must be for three days only AND The condition must be on the patient's face; OR The condition must be on the patient's scalp
Administrative Advice	Note No increase in the maximum quantity of number of units may be authorised No increase in the maximum number of repeats may be authorised

2.2 Listing is requested on a cost-effectiveness basis with ingenol compared to no treatment (placebo).

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 Ingenol mebutate 0.15 mg/g (0.015%) gel was approved by the TGA for the topical treatment of solar (actinic) keratoses in adults in April 2013.

3.2 This is the third PBAC submission for ingenol. Major submissions were rejected by PBAC in November 2012 and November 2013.

3.3 The PBAC rejected the November 2013 resubmission for PBS listing of ingenol 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 SK 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 SK (paragraph 7.1, Nov 2013 PBAC minutes).

4 Clinical place for the proposed therapy

4.1 Ingenol is intended for treatment, as field therapy, of solar keratosis (SK) of the face and scalp.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 The resubmission nominates no treatment (or placebo) as the comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 As a minor submission, there was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ingenol including shorter treatment course than other available treatment options, which may lead to improved patient compliance. The field therapy was considered in the consumer comments to be effective and easier for patients and/or carers to use. Availability on the PBS would also mean it could save costs on future surgery.

6.3 The PBAC noted that this advice was supportive of the evidence provided in this and previous submissions.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical trials

6.4 No new clinical data were presented. Previously presented clinical data were not presented or reviewed.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

6.5 The premise of the cost effectiveness evaluation changed in this submission from valuing prevention of SCC and metastatic disease to treating solar keratosis only.

6.6 The model structure has not changed from the November 2013 submission. For that submission, the ESC considered that the model structure was valid but was concerned that the model was driven by values and assumptions that favour ingenol. This minor re-submission focusses solely on the cost-effectiveness of treating solar keratoses. There is no assumed risk of progression to SCC or in turn metastatic disease. Table 1 below summarises the assumptions in the model base case, compared to the November 2013 submission model, and the cost-effectiveness results. Most of these assumptions were explored by ESC in a scenario analysis which resulted in a similar ICER of $49,599/QALY (see ESC Advice November 2013 and paragraph 6.29 of the PBAC Minutes).

Assumptions adopted in economic model base case, compared to original 2013 submission model – parameters and cost-effectiveness results

Parameter	Value in current model	Value in 2013 model	Comment/Source
Population	General	Prior SCC	As per scope of current submission
Age at baseline (years)	70	60	ESC scenario analysis (page 7.6.ESC ADV.5)
Time horizon (years)	2	40	ESC scenario analysis (page 7.6.ESC ADV.5)
Discounting of costs and benefits (annual)	0%	5%	ESC scenario analysis (page 7.6.ESC ADV.5)
SK to SCC progression (annual)	0%	1.55%	Evaluate risk by assuming no SCC prevention
Adjustments algorithms linking efficacy with compliance	Off	On	ESC scenario analysis (page 7.6.ESC ADV.5)
Model results			
Incremental costs	$[redacted]	$[redacted]	
Incremental QALYs	[redacted]	[redacted]	
ICER ($/QALY gained)	$[redacted]	$[redacted]	

Source: Table 1 of July 2014 minor re-submission, p11.

6.7 The revised base case ICER in this re-submission uses the same utilities as the November 2013 submission. These utilities were based on a weighted average of the utility values from published studies, Chen 2004 (only 9 patients contributed to the results for utility of living with SKs) and Littenberg 2003 (only 16 patients contributed to the results for utility of living with SKs), and result in an incremental utility gain of 0.014. PBAC did not have confidence in the use of these utilities given the size of the studies and it was considered implausible that, according to Littenberg, patients with non-melanoma skin cancer would have a higher utility (0.995) than patients with SK (0.989), noting that non-melanoma skin cancer is the more serious of the two conditions. (see PBAC minutes November 2013, paragraphs 6.31 to 6.33).

6.8 A sensitivity analysis is presented using a new cross sectional [redacted] study [redacted]

6.9 The mean utility value for the [redacted] The fact that the median is [redacted]

6.10 Patients in [redacted] study who had [redacted] These differences were not statistically significant. [redacted]

6.11 This is likely to significantly overestimate the utility gain as a result of treatment as the assumption that [redacted] Of the many subgroup values reported by the authors perhaps a more relevant comparison might be the one that compares 'current AK' [redacted] with 'not current AK' [redacted] This incremental utility gain would be [redacted] and is also non-significant.

6.12 Regardless of which numbers are used, there are significant issues with the study design that mean that it is not possible to determine how much of the difference in QoL can be attributed to either the presence of, or treatment of SK/AK, or instead to underlying differences in the groups in other factors that are more likely to affect QoL as measured by the EQ5D. This is because there is not 1) a randomised comparison of treated/untreated patients, or 2) pre and post treatment utilities in the same patients, meaning that any differences reported could well be driven by differences between the respondent groups in comorbidities, age, etc. that are likely to have a greater impact on the domains of the EQ5D. By presenting them the way the authors have, it implies that other factors that might influence QoL are evenly distributed across the groups (as might reasonably be expected in a RCT), but there is no information on the relative distribution of these other factors in the subgroups that are presented to make any assessment of this.

6.13 The PBAC considered it difficult to quantify the value of treatment with ingenol given the current re-submission focussed on the cosmetic clearance of SK. As a frame of reference, the PBAC recalled it had recommended poly-L-lactic acid in March 2009 for the treatment of severe facial lipoatrophy caused by therapy for HIV infection on the basis of clinical need and high and uncertain but acceptable cost effectiveness compared with placebo. Taking into account that cosmetic clearance was the claimed major benefit for ingenol in this resubmission, the accepted value of poly-L-lactic acid was considered a reasonable starting point, although the clinical context was different. The PBAC recalled in the case of poly-L-lactic acid that despite some economic uncertainty in that submission, the trial results had demonstrated significant improvements in social function and mental health. The PBAC considered that a comparable improvement in QoL had not been demonstrated for ingenol, for which the submission was predicated on cosmetic clearance and patient preference. Thus, PBAC considered an ICER up to $20,000/QALY might be reasonable for ingenol treatment of SK. The PBAC recalled that this was comparable with the ICER accepted for poly-L-lactic acid in March 2009.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Estimated PBS usage & financial implications

6.14 Based on new UK GP prescribing data, the base case for the financial implications assumes only 1.4 treatments per patient per year (the November 2013 submission assumed 2 treatments per patient per year and was considered a likely underestimate by DUSC). The model assumes 2 treatments per patient per year.

6.15 The estimated net cost to the PBS is less than $10 million in year 1 rising to $10 - $20 million in year 5.

Expected usage and cost of ingenol mebutate and other topical therapies

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients on RPBS					
Units on RPBS*					
Patients on PBS					
Units on PBS*					
Net cost to PBS					

**the figures in Table 9 of the resubmission for units on RPBS and units on PBS did not match the figures from the Picato BIM 2014 Riskshare.xlsx spreadsheet. These figures have been updated to reflect the values in the spreadsheet.*

6.16 The Pre-PBAC response (p3) highlighted that the proportion of patients considered 'eligible for field treatment' was derived from a 2013 Clinician survey. This Clinician's survey of [redacted] prescribers was presented in the November 2013 submission (Appendix 15) and is the source of the 'expert opinion' input to the current minor submission. Previous DUSC advice (November 2013, p4) was that given the lack of available data to estimate the eligible population DUSC considered that a clinician survey was a sensible approach and noted the comparatively large survey sample in the resubmission (n=[redacted]). However the DUSC were concerned about the administration of the survey:

- Representativeness is unknown
- Response rate was low for dermatologists and is not known for GPs
- The original instrument was not provided with the submission
- No information was provided on missing results
- Average values were reported without information on variation.

6.17 The Pre-PBAC response further clarified that there is no double counting of the 'decision to treat' variable as was suggested in the PEB overview of the minor re-submission (paragraph 4 page PEB OVR 7.13.6). Rather, this reflects the decision by the clinician (potentially in consultation with the patient) as to whether field therapy is more appropriate than treatment of individual lesions by cryotherapy, based upon the density of SK lesions on the affected area of skin.

6.18 The resubmission proposed an RSA, in the form of a price-volume agreement, to address the uncertainty of the number of treatments per patient per year. The [redacted]

Price level	ex-man price	DPMQ	Volume threshold
Entry			
Middle			
Final			

6.19 PBAC considered the proposed RSA [redacted] at the nominated thresholds was not sufficient, as the risk would mostly be borne by the Commonwealth. The PBAC considered that a more appropriate proposal [redacted]

[redacted]

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC rejected the submission for PBS listing of ingenol for solar keratosis on the basis that the value of treating SKs was unknown. The utilities presented in both the base case and the sensitivity analysis were not considered reliable and therefore the variability of the ICER from the ICER from $15,000/QALY- $45,000/QALY (base case) to less than $15,000/QALY (sensitivity analysis) was not accepted as realistic.

7.2 This minor resubmission proposed a new broader restriction for ingenol to include all patients with SKs, presented a new economic model examining the cost effectiveness of the clearance of SKs, recalculated the likely utilisation for the new restriction and proposed a risk share agreement.

7.3 No new clinical data were presented but the PBAC recalled previous trial data (3 ingenol 0.015% (PEP005-015, PEP005-016, PEP005-025), plus 2 ingenol 0.05% trials (PEP005-014, PEP005-028) that demonstrated complete clearance of SK in 43% of ingenol treated patients compared to 4.3% in the placebo treated group.

7.4 The PBAC acknowledged that there was likely to be a quality of life impact of clearing SKs from the face however the value of this effect was not quantified. It was also recognised that patients may prefer treatment with three days of ingenol compared to comparators such as 5-FU cream or cryotherapy, and that this preference could drive utilisation.

7.5 The PBAC recalled that the sponsor is currently running an active-controlled phase 4 study that will report in 2018 and will provide additional information about the effects of ingenol treatment on the risk of developing SCCs.

7.6 The economic model presented in this resubmission is the same model presented in the November 2013 submission without the offsets for the development and treatment of SCCs. The PBAC recalls that they were satisfied with the structure of this model but remain concerned about the lack of demonstrable improvement in quality of life outcomes in the long term related to SK clearance.

7.7 The PBAC recalled previous concern with Chen & Littenberg utility values. In November 2013, the PBAC did not consider that the utility estimates for SK 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 SKs would deliver a tangible health benefit in terms of quality of life. (November 2013 PABC minutes, paragraph 7.6).

7.8 In this minor resubmission a new [redacted] utility study [redacted], unpublished) was presented in a sensitivity analysis and improved the incremental

utility threefold, reducing the ICER from $15.000/QALY to $45,000/QALY. The PBAC did not consider the new utility values reliable for the following reasons:

- The population in the [redacted] study likely differs significantly from an Australian population.
- There were significant issues with the study design. It is not possible to determine how much of the difference in QoL can be attributed to either the presence of, or treatment of SK/AK, or instead to underlying differences in the groups in other factors that are more likely to affect QoL [redacted]
- The utilities are calculated on the basis of [redacted]
- The utility gain of [redacted] is likely to significantly overestimate the QoL gain as a result of treatment with ingenol as the assumption that severe AK is equivalent to all SK is implausible, as is the assumption that 'less severe' is equivalent to 'clear'. The difference is based on [redacted], and this may not translate to the gain from treatment that results in clearance of SK.
- The PBAC noted that the utility gain of [redacted] from [redacted] implies that a [redacted] (for the outcome of clearance of SK). The PBAC considered this to be implausible.

7.9 As a result of these concerns about both sets of utilities the PBAC had no confidence in the outcome of the modelled value of treating SK using ingenol over no treatment.

7.10 The PBAC considered the utilisation estimate to be highly uncertain, given:

- The new estimate of patients who would be eligible for, and treated with, ingenol relies on a prevalence estimate of SK that has not been previously presented or evaluated;
- inappropriate application of two 'decision to treat' variables (one of which is not justified).
- UK GP prescribing data to justify the number of treatments per patient per year being [redacted] is not reliable, particularly in light of DUSC's previous advice of ingenol (Nov 2013) that the assumed use of 2 treatments per patient per year were considered a likely underestimate. Also, utilisation in a UK general practice population is unlikely to be applicable to an Australian population.

7.11 The PBAC therefore rejected the minor re-submission on the basis of unknown value of treating SK. The PBAC considered a utility study using Australian (or similar) population conducted over a relevant timeframe (eg 12 months) and with an appropriate instrument may be a solution. The PBAC was also concerned that the value of treatment with ingenol had not been considered in the context of other available therapies, which may likely have lower value in regards to treatment burden for patients and associated MBS costs. A major resubmission would be required to address these concerns.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.