

**5.01 CALCIPOTRIOL with BETAMETHASONE,
Foam containing calcipotriol 50 micrograms with
betamethasone 500 micrograms (as dipropionate) per g, 60 g,
Enstilar[®],
LEO Pharma Pty Ltd.**

1 Purpose of Application

1.1 Restricted Benefit listing for calcipotriol plus betamethasone foam spray for treatment of chronic stable plaque type psoriasis.

2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
CALCIPOTRIOL + BETAMETHASONE DIPROPIONATE Foam spray, 50/500calcipotriol 0.05% + betamethasone (as dipropionate) 0.05% ,foam spray, 60g	1	1	\$ [REDACTED]	Enstilar [®] 50/500 foam LEO spray Pharma Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Chronic
Severity:	Stable
Condition:	Plaque type psoriasis vulgaris
PBS Indication:	<i>Chronic stable plaque type psoriasis vulgaris</i>
Restriction:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined Restricted benefit
Clinical criteria:	Chronic stable plaque type psoriasis vulgaris AND The condition must be inadequately controlled with either a vitamin D analogue or potent topical corticosteroid monotherapy AND <i>Patient must require more than 30 grams of the product per month</i>
Administrative Advice	Note Continuing Therapy Only For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

- 2.1 The Pre-Subcommittee Response (PSCR) (p3) claimed that the addition of the clinical criteria ‘Patient must require more than 30 grams of the product per month’ was not appropriate for the foam. The criterion was added specifically to the 60 g gel formulation due to its specific use in scalp psoriasis and the availability of the 30 g gel formulation. No 30 g foam formulation is intended to be developed. The PBAC agreed with the PSCR that this criterion was not required for the foam spray.
- 2.2 The ESC noted that the restriction for calcipotriol with betamethasone may need adjustment as no calcipotriol monotherapy products are currently listed on the PBS. Additionally the ESC suggested that the word stable included in the severity section of the restriction may not be the most appropriate wording for the indication as the calcipotriol with betamethasone products are indicated for flare-ups not stable disease.
- 2.3 The submission sought listing on the basis of a cost-utility analysis (CUA) compared with calcipotriol plus betamethasone gel.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

3 Background

- 3.1 Calcipotriol with betamethasone foam spray was approved for TGA registration on 5 October 2016 for the topical treatment of psoriasis vulgaris in adults. At the time of the PBAC consideration calcipotriol with betamethasone foam spray was not listed on the ARTG.
- 3.2 This is the first consideration of calcipotriol plus betamethasone foam spray by the PBAC. Calcipotriol plus betamethasone gel and calcipotriol plus betamethasone ointment are both listed on the PBS for the treatment of chronic stable plaque type psoriasis. The PBAC recommended a Restricted Benefit listing for calcipotriol plus betamethasone ointment at the July 2009 meeting. The PBAC recommended a Restricted Benefit listing for calcipotriol plus betamethasone gel at the November 2015 meeting.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

4 Clinical place for the proposed therapy

- 4.1 Psoriasis is an inflammatory skin disease with symptoms such as red scaly plaques, itchiness and flaking of the skin. Calcipotriol plus betamethasone foam spray is expected to be used in patients who are not adequately controlled with a vitamin D analogue or potent topical corticosteroid monotherapy.
- 4.2 The submission indicated that the requested listing is not likely to change the clinical place of calcipotriol plus betamethasone products in therapy. This is reasonable.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

5 Comparator

- 5.1 The submission nominated calcipotriol plus betamethasone gel as the main comparator. While calcipotriol plus betamethasone ointment was the most commonly used formulation in the 2015 calendar year, the submission argued that the distribution would shift over time with more use of the gel as a result of the revised PBS listing for the gel and the new 60 g pack size. The submission also argued that since both the foam spray and the gel are non-greasy aqueous formulations that at the point of prescribing, a physician who wished to prescribe a non-greasy formulation would choose between the foam spray and the gel. The PSCR (p4) argued that the nominated calcipotriol plus betamethasone gel was an appropriate comparator based on international data where the gel formulation was mostly replaced by the foam spray. The ESC agreed with this response however, it was noted that the 60 g gel formulation was initially targeted towards scalp psoriasis and this data was excluded from the comparison with the foam formulation.
- 5.2 The PBAC considered calcipotriol plus betamethasone gel to be the appropriate main comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission is based on one head-to-head trial comparing calcipotriol plus betamethasone foam spray to calcipotriol plus betamethasone gel and to foam spray vehicle and gel vehicle (LP0053-1003, n=463). The submission also included a trial comparing calcipotriol plus betamethasone foam spray to calcipotriol plus betamethasone ointment, and to gel vehicle and ointment vehicle based on one head-to-head trial (LEO90100-35, n=376). The PSCR (p3) stated that the foam spray is intended to be used on both body and scalp. However, the ESC noted the clinical trials used a modified PASI score that reflected the exclusion of administration to the scalp. In current clinical practice, the use of the product includes administration to the scalp, which would be the predominant use among some patients. The ESC questioned the rationale for excluding the administration to scalp psoriasis.
- 6.4 The ESC noted that the application to the TGA for registration was made on the basis of LEO90100-35 which compared the calcipotriol plus betamethasone foam spray to calcipotriol plus betamethasone ointment.
- 6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
LP0053-1003	A phase 3 trial comparing LEO 90100 aerosol foam with calcipotriol plus betamethasone dipropionate gel, aerosol foam vehicle, and gel vehicle in subjects with psoriasis vulgaris. An international, multi-centre, prospective, randomised, active- and vehicle-controlled, investigator blinded, 4-arm, parallel group 12-week trial.	11 September 2015 Internal study publication
LEO 90100-35	A phase 2 study comparing treatment with LEO 90100 with calcipotriol plus betamethasone ointment, LEO 90100 vehicle and ointment vehicle in subjects with psoriasis vulgaris. A multi-centre, prospective, randomised, investigator blinded, 4-arm, parallel group, 4-week study in subjects with psoriasis vulgaris. Koo J, Tying S, Werschler W et al. Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris – A randomized phase II study.	5 October 2015 <i>J Dermatolog Treat</i> 2016; 27(2):p120-127

Source: Table 8, p33 of the submission

6.6 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in economic analysis
Calcipotriol plus betamethasone foam spray versus gel						
LP0053-1003	463	R, MC, IB 12 weeks	High	Adults with psoriasis vulgaris	IGA, PASI75	PASI75
Calcipotriol plus betamethasone foam spray versus ointment						
LEO90100-35	376	R, MC, IB, 4 weeks	High	Adults with psoriasis vulgaris	Controlled disease, PASI75	Used for scenario analysis only based on PASI75

R=randomised; MC=multi-centre; IB=investigator blinded; IGA=Investigator's Global Assessment of disease severity; PASI75= Proportion of patients achieving at least a 75% reduction in the modified-Psoriasis Area and Severity Index from baseline.

Source: compiled during the evaluation

6.7 The comparison of calcipotriol plus betamethasone foam spray to calcipotriol plus betamethasone ointment was only presented as a secondary comparison.

Comparative effectiveness

- 6.8 Results for the primary outcome based on Investigator's Global Assessment of disease severity (IGA) for LP0053-1003 and Controlled disease for LEO90100-35 are outlined in Table 3 below.

Table 3: Results of the primary outcome of treatment success according to IGA/Controlled disease* across the direct randomised trials

	Calcipotriol + betamethasone n/N (%)	Calcipotriol + betamethasone n/N (%)	Relative risk (95%CI)	Number needed to treat (95% CI)	Risk difference (95% CI)	Odds ratio (95% CI) p-value	Breslow- Day test p- value
LP0053- 1003	Foam spray: Week 4*	Gel: Week 8*					
	70.8/185 (38.3)	42.2/188 (22.5)	<i>1.70 (1.24, 2.35)</i>	<i>6.32 (3.97, 14.83)</i>	<i>0.16 (0.07, 0.25)</i>	<i>2.55 (1.46, 4.46)</i> p<0.001	0.47
	Foam spray: Week 4**	Gel: Week 4**					
	68/180 (37.8)	36/183 (19.7)	<i>1.92 (1.26, 2.73)</i>	<i>5.86 (3.86, 12.42)</i>	<i>0.18 (0.09, 0.26)</i>	<i>2.45 (1.53, 3.93)</i> p=0.0002	
	Foam spray: Week 4***	Ointment: Week 4***					
LEO90100- 35	77/141 (54.6)	58/135 (43.0)	<i>1.27 (1.00, 1.63)</i>	<i>8.59 (4.32, 581)</i>	<i>0.12 (0.00, 0.23)</i>	<i>1.7 (1.1, 2.8)</i> p=0.025	0.023

Figures in italics were calculated during the evaluation

Treatment success according to IGA for LP0053-1003 and Controlled disease for LEO90100-35

*Note: Multiple imputation was used for missing data for the Week 4 to Week 8 comparison in LP0053-1003 with the proportion of patients achieving treatment success being the mean number of subjects across imputations.

**Note: The Week 4 to Week 4 comparison was based on observed cases, and assumed missing data was non-response. However, the percentages did not include all patients randomised to treatment.

***Note: Last observation carried forward used to account for missing data

Source: Table 20, 21, p53-54 and Table 32, p64 of the submission

- 6.9 While patients in trial LP0053-1003 could be treated for up to 12 weeks (with the option for treatment to be stopped if IGA was clear), the primary outcome was assessed at 4 weeks for calcipotriol plus betamethasone foam spray and at 8 weeks for calcipotriol plus betamethasone gel, consistent with the proposed duration for the foam spray and the recommended duration of therapy of up to 8 weeks for the gel.
- 6.10 For the IGA outcome there was a statistically significant difference in favour of calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone gel in LP0053-1003. There was also a statistically significant difference in favour of calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone ointment in LEO90100-35, based on the primary outcome.
- 6.11 The result for the secondary outcome of PASI75 (the proportion of patients achieving at least a 75% reduction in the modified-Psoriasis Area and Severity Index from baseline) are reported below. The response based on PASI75 formed the basis of the outcomes used for the economic evaluation.

Table 4: Results for proportion of patients achieving PASI 75* for the direct randomised trials

Trial	Calcipotriol + betamethasone n/N (%)	Calcipotriol + betamethasone n/N (%)	Absolute difference	Odds ratio (95% CI) p-value	Breslow-Day test p-value
LP0053- 1003	Foam spray: Week 4*	Gel: Week 8*			
	96.5/185 (52.1)	65.1/188 (34.6)	17.5%	2.18 (1.37 to 3.47) p=0.001	0.35
	Foam spray: Week 4**	Gel: Week 4**			
	93/180 (51.7)	45/183 (24.6)	27.1%	3.21 (2.07 to 4.99) p<0.00001	
	Foam spray: Week 4***	Ointment: Week 4***			
LEO901 00-35	71/141 (50.4)	55/135 (40.7)	9.7%	1.7 (1.0 to 2.7) p=0.052	0.85

Figures in italics were calculated during the evaluation

PASI75 = Proportion of patients achieving at least a 75% reduction in the modified-Psoriasis Area and Severity Index from baseline.

*Note: Multiple imputation was used for missing data for the Week 4 to Week 8 comparison in LP0053-1003 with the proportion of patients achieving treatment success being the mean number of subjects across imputations.

**Note: The Week 4 to Week 4 analysis was based on observed cases, and assumed missing data was non-response. While the submission stated that the results for the Week 4 to Week 4 comparison for trial LP0053-1003 were based on an intention-to-treat analysis (Table 24, p57), they were not. The submission excluded the results of patients with missing data.

***Note: Full analysis set, no missing data

Source: Table 23 and 24, p56-57 and Table 33, p65 of the submission

- 6.12 Based on the PASI75 outcome in trial LP0053-1003, there was a statistically significant difference in favour of calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone gel at both Week 4 and at Week 8 (with Week 8 being the pre-specified time point for analysis of the primary and secondary trial outcomes). In trial LEO90100-35, compared to calcipotriol plus betamethasone ointment, the difference in response based on PASI75 was not significant ($p=0.052$).
- 6.13 Results for the change in utility index score for the EQ-5D-5L, from baseline to Week 4 for calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone gel at Week 8, are shown in Table 5.

Table 5: Change in EQ-5D-5L index score from baseline (observed cases) in LP0053-1003

	Calcipotriol plus betamethasone foam spray (n=185)	Calcipotriol plus betamethasone gel (n=188)	Difference (calcipotriol plus betamethasone foam spray – gel)
Mean at Week 4 (SD)	0.092 (0.130)	0.033 (0.147)	0.059
Mean at Week 8 (SD)	0.072 (0.146)	0.056 (0.141)	0.016

Note: The submission indicates that the index score excludes data from the two psoriasis bolt-on dimensions

SD=standard deviation

Source: Table 28, p61 of the submission

- 6.14 For the pre-specified Week 4 to Week 8 comparison, the difference in the mean change in utility index score at Week 4 for calcipotriol plus betamethasone foam spray compared to Week 8 for calcipotriol plus betamethasone gel was 0.029. This was statistically significant ($p=0.023$). The submission stated that the utility scores derived from this instrument were used in the economic evaluation. However, the economic model presented by the submission only used utility index values for patients treated with calcipotriol plus betamethasone foam spray who responded based on PASI75, and for patients treated with the vehicle foam spray who did not respond.

Comparative harms

- 6.15 The submission presented detailed safety outcomes for the trials but did not provide statistical comparisons of the observed adverse events. Relative risk was calculated during the evaluation. Table 6 provides a summary of the key adverse events in trial LP0053-1003 and trial LEO90100-35.

Table 6: Summary of key adverse events in the direct randomised trials

	Calcipotriol plus betamethasone foam spray n=185	Calcipotriol plus betamethasone gel n =188	RR (95% CI)
LP0053-1003, n (%) [*]			
All TEAEs	77 (41.6)	85 (45.2)	0.92 (0.73, 1.16)
Severe TEAEs	6 (3.2)	5 (2.7)	1.22 (0.40, 3.71)
ADRs	14 (7.6)	7 (3.7)	2.03 (0.85, 4.81)
AEs leading to withdrawal	4 (2.2)	4 (2.1)	1.02 (0.28, 3.66)
	Calcipotriol plus betamethasone foam spray n=135	Calcipotriol plus betamethasone ointment n =141	RR (95% CI)
LEO90100-35			
All TEAEs	16 (11.3)	14 (10.4)	1.19 (0.61, 2.32)
Severe TEAEs	0 (0.0)	1 (0.7)	0 (0, 3.99)
ADRs	1 (0.7)	4 (3.0)	0.26 (0.04, 1.71)
AEs leading to withdrawal	0 (0.0)	1 (0.7)	0 (0, 3.99)

^{*}Number of patients experiencing each event

Figures in italics were calculated during the evaluation

TEAE = treatment emergent adverse event; ADR = adverse drug reaction; AE = adverse event; SAE = serious adverse event; RR = relative risk

Source: Table 29, p62 and Table 36, p68 of the submission

- 6.16 Itch was experienced more often in patients using calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone gel (2.7% versus 0.5%) in trial LP0053-1003.
- 6.17 Overall, there were no significant differences in adverse events and adverse drug reactions between patients treated with calcipotriol plus betamethasone foam spray compared to either the gel or the ointment formulations.
- 6.18 As the longest trial duration (trial LP0053-1003) included only 12 weeks of treatment with 2 weeks of follow-up for safety, there is a lack of long-term safety data. This lack of long-term safety data limits any conclusions that can be drawn regarding the comparative safety of calcipotriol plus betamethasone foam spray to the gel and ointment formulations.

Benefits/harms

- 6.19 A summary of the comparative benefits and harms for calcipotriol plus betamethasone foam spray versus calcipotriol plus betamethasone gel, and for calcipotriol plus betamethasone foam spray versus calcipotriol plus betamethasone ointment is presented in the table below.

Table 7: Summary of comparative benefits and harms for calcipotriol plus betamethasone foam spray and calcipotriol plus betamethasone gel

Trial	Treatment		RR (95% CI)	Event rate/100 patients*		RD (95% CI)
Benefits :Treatment success according to IGA/Controlled disease						
	Calc + Bet foam spray	Calc + Bet gel		Calc + Bet foam spray	Calc + Bet gel	
LP0053-1003	70.8/185 (Week 4)	42.2/188 (Week 8)	1.70 (1.24, 2.35)	38.3	22.5 (Week 8)	0.16 (0.07,0.25)
	68/180 (Week 4)	36/183 (Week 4)	1.92 (1.26, 2.73)	37.8	19.7 (Week 4)	0.18 (0.09, 0.26)
	Calc + Bet foam spray	Calc + Bet ointment				
LEO90100-35	77/141	58/135	1.27 (1.00, 1.63)	54.6	43.0	0.12 (0.00, 0.23)
Harms						
	Calc + Bet foam spray	Calc + Bet gel	RR (95% CI)	Calc + Bet foam spray	Calc + Bet gel	RD (95% CI)
Pruritis						
LP0053-1003	5/185	1/188	5.08 (0.80, 32.65)	2.7	0.5	0.02 (-0.01, 0.06)

* Maximum duration of exposure: LP0053-1003 = 12 weeks; LEO90100-35 = 4 weeks.

RD = risk difference; RR = risk ratio; Calc + Bet = calcipotriol plus betamethasone; IGA = Investigator's Global Assessment of disease severity

Figures in italics were calculated during the evaluation

Treatment success for LP0053-1003 and Controlled disease for LEO90100-35

Note: Multiple imputation was used for missing data for the Week 4 to Week 8 comparison in LP0053-1003 with the proportion of patients achieving treatment success being the mean number of subjects across imputations. *The Week 4 to Week 4 analysis was based on observed cases, and assumed missing data was non-response. However, the Week 4 to Week 4 analysis was not ITT as not all patients randomised to treatment were included in the analysis.*

Source: Compiled during the evaluation from Tables 20-21, p53-54 and Table 32, p64 of the submission

- 6.20 On the basis of direct evidence presented by the submission, for every 100 patients treated with calcipotriol plus betamethasone foam spray in comparison to calcipotriol plus betamethasone gel:
- Approximately 18 additional patients would experience treatment success according to Investigator's Global Assessment of disease severity (IGA) over a mean duration of exposure of 4 weeks for both the foam spray and the gel.

Clinical claim

- 6.21 The submission claimed that calcipotriol plus betamethasone foam spray has superior efficacy and a non-inferior safety profile compared to calcipotriol plus betamethasone gel. This claim was based on the evidence provided by trial LP0053-1003. The claim for superior efficacy was adequately supported by the evidence. While safety was similar for calcipotriol plus betamethasone foam spray and the gel, the short duration of the trial (12 weeks) was insufficient to determine long-term safety outcomes.
- 6.22 The submission did not put forward a claim for calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone ointment.

- 6.23 The PBAC considered that the claim of superior comparative effectiveness of the calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone gel was reasonable.
- 6.24 The PBAC considered that the claim of non-inferior safety profile of the calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone gel was reasonable.

Economic analysis

- 6.25 The submission presented a four state Markov model (Flare, Response, Non-response and Post-topical) comparing calcipotriol plus betamethasone foam spray to calcipotriol plus betamethasone gel. Treatment was modelled through the application of utility index scores from trial LP0053-1003. A cost-utility analysis was appropriate, given the available evidence.

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	48 weeks* in the model base case versus 4 weeks in the trial
Outcomes	Costs and QALYs
Methods used to generate results	Expected value analysis, with results reported for a single hypothetical 'average' patient
Cycle length	4 weeks. A half-cycle correction was not used.
Transition probabilities	Derived from rates of response in the trial LP0053-1003 and converted to 'per cycle' probabilities of transition using the function "Prob=1-EXP(-rate × time)"
Discount rate	5% for costs and outcomes

*The submission reported results at 48 weeks assuming 12 cycles, rather than at 52 weeks as stated in the submission

QALY = quality adjusted life year

Source: constructed during the evaluation

- 6.26 Key drivers of the model are provided in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Time point for analysis of response	The model used Week 4 response rates for the foam spray and the gel rather than Week 4 for the foam spray and Week 8* for the gel, which was the primary endpoint in the trial	High, favours Cal + Bet gel
Utilities	The model applied the baseline utility index score of 0.80 to responders and non-responders, resulting in a mean change in utilities of 0.10 for responders and 0.03 for non-responders. Based on the higher baseline utility index score of 0.81 for non-responders in the trial, the mean change in utility index score for non-responders was 0.02	Moderate, favours Calc + Bet gel
Response rate	The higher response rate with the foam spray compared to the gel results in delayed movement into the post-topical state. While the model used results based on the modified PASI75 score, results based on IGA result in a higher incremental cost/QALY	Low, favours Calc + Bet foam spray

*The recommended treatment duration for calcipotriol plus betamethasone gel is 4 weeks for scalp psoriasis and up to 8 weeks for body psoriasis

Calc + Bet = calcipotriol plus betamethasone; PASI75 = Proportion of patients achieving at least a 75% reduction in the modified-Psoriasis Area and Severity Index from baseline; IGA = Investigator's Global Assessment of disease severity

Source: compiled during the evaluation

- 6.27 The results of the cost-utility analysis are presented in Table 10 below.

Table 10: Results of the economic evaluation

Component	Calcipotriol plus betamethasone foam spray	Calcipotriol plus betamethasone gel	Increment
Costs	\$ [REDACTED]	\$302.66	\$ [REDACTED]
QALY	0.8403	0.8337	0.0067
Incremental cost/QALY gained at 48-week time point			\$ [REDACTED]
Incremental cost/QALY gained at 52-week time point			\$ [REDACTED]

QALY = quality adjusted life year

Source: Table 61, p108 of the submission

- 6.28 The submission calculated the incremental cost/QALY gained to be less than \$15,000/QALY based on only 48 weeks in the model rather than a full year. This difference in the outcome was minor, with a 52-week model reducing the incremental cost/QALY gained to less than \$15,000/QALY. The ESC noted that the modelled costs for all presentations of calcipotriol plus betamethasone included wastage, as mean drug use from the trials was rounded up to the nearest pack size.
- 6.29 In clinical practice, patients are likely to be treated with calcipotriol plus betamethasone gel for longer than the 4-week period of time that was modelled. Should patients be treated with the gel for 8 weeks, the submission calculated that use of the foam spray would be cost saving. The ESC noted that if patients responded earlier to treatment, that continuation of use may cease prior to the standard 4 week treatment period. Outside of a clinical trial environment, patients may adjust their use according to response to treatment and frequency of flare ups. This could potentially reduce total volume used. The ESC also noted that over a 4-12 week time frame, early termination of treatment due to a response followed by a second episode or flare up may represent a cost saving.
- 6.30 The submission attributed the cost of a specialist consultation to patients who moved into the post-topical state following non-response to treatment. While it is not clear that a specialist consultation would be required for all patients who do not respond to treatment, this does not substantially affect the ICER.
- 6.31 While EQ-5D-5L scores were reported in the clinical study report for trial LP0053-1003, which compared the foam spray to the gel, the scores for each treatment group were not directly used to inform the economic evaluation. Rather, the model applied the mean utility index score for calcipotriol plus betamethasone foam spray PASI75 responders to all PASI75 responders in the model, and the mean utility index score for foam spray vehicle PASI75 non-responders to all PASI75 non-responders in the model. This approach was not justified in the submission.
- 6.32 The submission also presented a scenario analysis of calcipotriol plus betamethasone foam spray compared to calcipotriol plus betamethasone ointment using the recommended treatment durations of 4 weeks for calcipotriol plus betamethasone foam spray and 4 weeks for calcipotriol plus betamethasone ointment. Compared to the ointment, the submission calculated that use of calcipotriol plus betamethasone foam spray would result in an incremental cost/QALY gained of \$15,000/QALY - \$45,000/QALY (based on a 48-week end point for the model). The submission used the average weighted number of packs of calcipotriol plus betamethasone foam spray used across both the LP0053-1003 and the LEO90100-35 trials, rather than the number of packs required based on the quantities of the therapies used in LEO90100-35. In an analysis conducted during the evaluation, using the number of packs required to provide the quantities used in

LEO90100-35 (3 x 60 g packs of the foam spray and 5 x 30 g packs of the ointment) resulted in an incremental cost/QALY gained of \$45,000/QALY - \$75,000/QALY (based on a 48-week end point for the model). The ESC noted that cost effectiveness over a longer timeframe was dependent on the distribution of use, particularly in regards to any leftover product when flare ups are controlled. Should the patient experience another relapse, the patient will most likely use the left over product from the previous flare up.

Drug cost/patient/4-week course: \$ [REDACTED]

- 6.33 The submission estimated a cost of \$ [REDACTED] per patient per 4-week course based on the requested price and assuming 2 x 60 g packs per patient per course. This compared to \$144.98 for calcipotriol plus betamethasone 60 g gel for 4 weeks of treatment, and to \$217.47 assuming an 8-week course of therapy with the gel. The primary endpoint in trial LP0053-1003 was at Week 4 for the foam spray and at Week 8 for the gel. As the recommended course of treatment for the gel is 4 weeks for scalp psoriasis and up to 8 weeks for body psoriasis, the cost per course for a patient treated with the gel is likely to be in between \$144.98 and \$217.47.

Estimated PBS usage & financial implications

- 6.34 This submission was not considered by DUSC. The submission used a market share approach to estimate usage and financial implications to the PBS. The market share approach relied on estimation of the market size from PBS services data and IMS sales data, as well as in-house sales forecasts.
- 6.35 The submission estimated that the requested listing will:
- Result in patients being initiated or switched to the foam spray from the currently PBS listed 30 g ointment and 60 g gel formulations.
 - Result in market growth, with additional patients being prescribed calcipotriol plus betamethasone foam spray due to superior efficacy and patient experience.
- 6.36 Table 11 provides a summary of the estimated net costs to the PBS/RPBS for the requested listing.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Market share	%	%	%	%	%
Packs*					
Submission's estimate of net cost/year for calcipotriol plus betamethasone foam spray	\$	\$	\$	\$	\$
Reduction in cost to PBS/RPBS from other drugs	-\$	-\$	-\$	-\$	-\$
Submission's estimate of net cost to the PBS/RPBS	\$	\$	\$	\$	\$
<i>Revised total cost to PBS/RPBS of calcipotriol plus betamethasone foam spray</i>	\$	\$	\$	\$	\$
Reduction in cost to PBS/RPBS from other drugs	(as per submission's estimates above)				
Revised net cost to PBS/RPBS	\$	\$	\$	\$	\$
<i>Revised net cost to PBS/RPBS over 5 years</i>	\$				

*Assuming 1.7 packs per service as estimated by the submission

These figures do not include patient co-payments

Figures in italics were revised during the evaluation since the submission's cost did not include the cost of calcipotriol plus betamethasone foam spray packs due to additional market growth

Source: Table 71-81, p117-123 of the submission, and Section E workbook

The redacted table above shows that at year 5, the estimated number of packs was 100,000 – 200,000 per year and the net cost to PBS would be less than \$10 million.

- 6.37 The net cost is due to the higher DPMQ requested and the cost of treating additional patients that the submission expected would otherwise not have been treated with a combination calcipotriol plus betamethasone product.
- 6.38 The submission predicted growth of 4% in 60 g equivalent packs for the calcipotriol plus betamethasone market in the absence of a PBS listing for the foam spray, and additional market growth due to a listing for the foam spray of 12.8% in Year 1 to 5.0% in Year 5. No justification was provided for these estimates of additional market growth and the submission's calculations incorrectly did not include these growth rates in the financial estimates. The additional growth in the market, as estimated by the submission, was included in the estimates calculated during the evaluation. The ESC noted that the proposed market growth could be conservative, mainly due to the improvements in the application of the product. The ESC noted in the PSCR (p1) that the sponsor is the sole supplier of the combination calcipotriol plus betamethasone products and that the market growth was based on historical growth in the psoriasis market with an increase due to the novel presentation of the foam formulation. The ESC also noted that calcipotriol with betamethasone foam may become a first line product for patients with psoriasis.
- 6.39 The submission's estimated financial implications are sensitive to the number of packs dispensed per service beyond the maximum quantity, of 1 pack. It is likely that the submission's estimate of 1.7 packs per service for the foam spray is an overestimate. With a recommended course of therapy of 4 weeks, rather than up to 8 weeks for the gel for body psoriasis, it is considered that the need for additional

packs per service is unlikely to be as high as anticipated by the submission. The ESC noted in the PSCR (p2) that the sponsor updated the estimate of packs per service to 1.4 for the calcipotriol plus betamethasone gel (and 1.9 for the calcipotriol plus betamethasone ointment) based on March to June 2016 sales figures. If there are no increased maximum quantities per prescription (packs per service of 1.0) of calcipotriol plus betamethasone foam spray, the total net cost of listing the foam spray over 5 years to the PBS will be reduced from the submission's estimate of \$20 - \$30 million to \$10 - \$20 million.

- 6.40 Overall, as the submission used a limited market share approach to estimate the likely financial impact of listing calcipotriol plus betamethasone foam spray on the PBS and relied solely on in-house sales forecasts for market growth, there is uncertainty regarding the overall impact of listing calcipotriol plus betamethasone foam spray on the PBS.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Restricted Benefit listing of calcipotriol with betamethasone foam spray, on a cost-utility basis against the ointment, for the treatment of chronic stable plaque psoriasis vulgaris subject to a cap on PBS expenditure over the first five years of listing to limit the net cost to no more than \$20 million. The PBAC noted the PBS cost was sensitive to the assumed number of packs per service and further recommended that the usage of calcipotriol with betamethasone foam spray be reviewed following listing.
- 7.2 The PBAC was satisfied that calcipotriol with betamethasone foam spray provided, for some patients, a significant improvement in efficacy over calcipotriol with betamethasone gel for treatment of chronic stable plaque psoriasis vulgaris.
- 7.3 The PBAC considered the proposed main comparator of calcipotriol with betamethasone gel appropriate. The PBAC accepted the arguments in the submission that (without the foam spray formulation) the use of the gel formulation was likely to increase over time and that the foam spray and gel are alternative non-greasy aqueous formulations. The PBAC noted that the ointment was less acceptable for patients with extensive psoriasis.
- 7.4 The PBAC noted the head-to-head randomised trial comparing the foam spray and gel demonstrated the superior effectiveness of the foam spray using the IGA and PASI75 outcomes. The PBAC noted the key trials included in the submission did not allow use for scalp psoriasis, and the PASI score was modified accordingly. The PBAC considered that the foam spray would be used in scalp psoriasis, and noted the clinical data presented in the Pre-PBAC suggesting that the foam spray was at least as effective for treating the scalp as for treating the trunk and limbs.
- 7.5 The PBAC noted itch was more commonly experienced by patients using the foam spray than the gel. The PBAC noted that overall there were no significant differences in adverse events for patients treated with the foam spray compared to either the gel or the ointment formulations, although noted this was based on short-term studies of

8 to 12 weeks duration. However, the PBAC considered that the safety profile of the foam spray was unlikely to be significantly different to that of the gel formulation.

- 7.6 The PBAC noted the number of cans of foam spray used by patients and the amount administered during the treatment of each flare up was uncertain, and specifically the proportion of patients who required less than 120 g (2 cans) versus more than 120 g (3 cans) was uncertain.
- 7.7 The PBAC noted that the foam spray had the potential to become the preferred formulation for patients as it demonstrated improved skin penetration and bioavailability, and has a faster effect. Further, the foam spray was easier to use and was likely to be more acceptable to patients than either the gel or the ointment formulation.
- 7.8 The PBAC noted the financial forecasts were sensitive to the assumed market growth and the number of packs per service. The PBAC considered that the growth assumed in the submission may have been underestimated. The PBAC noted that the estimated PBS cost over 5 years was \$20 - \$30 million based on 1.7 packs per service, and that this reduced to \$10 - \$20 million if there is 1 pack per service. Updated data were provided in the PSCR suggesting 1.4 packs per service. Overall, the PBAC considered the financial estimates to be uncertain and recommended that a Risk Sharing Arrangement should be put in place to manage the uncertainty of packs per service. The Committee therefore recommended that a financial cap be implemented set at the level of the financial estimates updated with the number of packs per service as per the PSCR, along with the estimated number of services as outlined in the submission. A rebate should apply beyond these caps to reimburse the Commonwealth the majority of expenditure above these updated estimates.
- 7.9 The PBAC requested that the 24 month DUSC utilisation review includes a comparison of the predicted and actual number of packs per service.
- 7.10 The PBAC recommended that calcipotriol with betamethasone foam spray be restricted to use where the condition is inadequately controlled by potent topical corticosteroid monotherapy, rather than either potent topical corticosteroid or vitamin D analogue monotherapy, noting that there are no calcipotriol single agent topical preparations listed on the PBS. The PBAC recommended that the restrictions for other topical calcipotriol with betamethasone combination products listed on the PBS be aligned by removing inadequate control of the condition with a vitamin D analogue or calcipotriol.
- 7.11 The PBAC recommended that the Early Supply Rule should not apply.
- 7.12 The PBAC advised that calcipotriol with betamethasone foam spray is suitable for prescribing by nurse practitioners as continuing therapy only.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
CALCIPOTRIOL + BETAMETHASONE calcipotriol 0.05% + betamethasone (as dipropionate) 0.05%, foam spray, 60g	1	1	Enstilar® 50/500 foam spray Leo Pharma Pty Ltd

Episodicity:	Chronic
Severity:	Stable
Condition:	Plaque type psoriasis vulgaris
Restriction:	Restricted benefit
Clinical criteria:	The condition must be inadequately controlled by potent topical corticosteroid monotherapy
Administrative Advice	Note Continuing Therapy Only For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

9 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.

10 Sponsor's Comment

LEO Pharma welcomes the PBAC decision to recommend the listing of Enstilar® on the PBS.