

5.14 LIGNOCAINE

5% patch: dermal, 30
Versatis[®], bioCSL Pty Ltd

1 Purpose of Application

- 1.1 To request Authority Required (STREAMLINED) listing for lignocaine 5% w/w dermal patch for the treatment of post-herpetic neuralgia (PHN).

2 Requested listing

- 2.1 The submission proposed two alternatives for consideration by the PBAC, referred to as Option 1 and Option 2. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics. Option 1 is the same as the pregabalin restriction.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LIGNOCAINE 5% patch: dermal, 30	2	5	\$ [REDACTED]	Versatis [®] CS

Option 1

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
Condition:	Postherpetic neuralgia
PBS Indication:	Postherpetic neuralgia
Restriction Level / Method:	<input 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 checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be refractory to treatment with other drugs.
Administrative Advice	<i>Continuing Therapy Only:</i> <i>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.</i>

Option 2

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

Condition:	Postherpetic neuralgia
PBS Indication:	Postherpetic neuralgia
Restriction Level / Method:	<input 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 checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be refractory to treatment with pregabalin, OR The patient must be unsuitable for or intolerant to treatment with pregabalin.
Administrative Advice	Continuing Therapy Only: <i>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.</i>

- 2.2 Listing was requested on a cost-effectiveness basis comparing treatment algorithms where lignocaine patch was PBS listed to an algorithm where lignocaine patch was not.
- 2.3 The sponsor stated a preference for Option 1, as this would allow more flexibility.
- 2.4 The wording of both proposed PBS-listings was ambiguous. Option 2 implicitly assumed that clinicians are aware that pregabalin is PBS-listed for neuropathic pain refractory to treatment with other drugs. The ‘other drugs’ were not specified in the pregabalin restriction nor the proposed listing. Expert opinion (six respondents) indicated a range of medications were considered as ‘other drugs’, from simple analgesics to opioids, adjuvant analgesics and tricyclic antidepressants (TCAs).
- 2.5 The Pre-PBAC Response indicated that the sponsor would be willing for the restriction to be Authority Required to manage the risk of leakage outside of the small PHN patient population.

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

3 Background

- 3.1 **TGA status:** Lignocaine patch was registered by the TGA for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (PHN) on 16 March 2012.
- 3.2 This drug has not previously been considered by the PBAC.

4 Clinical place for the proposed therapy

- 4.1 PHN is neuropathic pain that persists after the shingles rash has healed, generally in the original distribution of the rash.

- 4.2 For listing Option 1, the submission positioned lignocaine patch as an alternative treatment, alongside pregabalin and gabapentin in patients with PHN refractory to other drugs (e.g. analgesics and TCAs).
- 4.3 For Option 2, the submission proposed lignocaine patch as an option (as monotherapy or in combination with pregabalin), alongside pregabalin, opioids (including tramadol) and topical capsaicin for patients who fail or do not tolerate earlier-line therapies, including pregabalin. The submission stated that patients eligible for treatment under the more restrictive Option 2 would also be eligible for treatment under Option 1.
- 4.4 The ESC noted that in practice, when patients fail or do not tolerate these therapies clinicians will change treatment rather than add on new treatments. If the condition was refractory to treatment with pregabalin, a prescriber may be more likely to replace pregabalin with lignocaine, rather than prescribe lignocaine in combination with pregabalin.

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

5 Comparator

- 5.1 The submission nominated pregabalin as the active comparator (Option 1), and placebo as a proxy for best supportive care as an additional comparator (Option 2).
- 5.2 The clinical management algorithm identified opioids (including tramadol) and capsaicin as best supportive care. The economic model assumed that best supportive care comprised therapies of unknown or poor efficacy, accounting only for a 'placebo-response'.
- 5.3 The Evaluation suggested it is unclear whether other comparators including TCAs like amitriptyline and opioids could be appropriate comparators and whether the submission's various definitions and assumptions relating to best supportive care are reasonable.
- 5.4 The PSCR (p2) notes that pregabalin was proposed as the active comparator as it is currently prescribed in 38% of GP consultations for PHN (between its PBS listing and June 2014). This compares with 10% for amitriptyline and 3.4% for gabapentin.
- 5.5 The ESC agreed with the chosen comparators for each treatment option, noting that pregabalin is positioned after failure of other treatments and lignocaine is requesting the same place in therapy as pregabalin (Option 1).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed how the drug would be used in practice, addressed concerns regarding the model structure and addressed other matters in response to the Committee's questions. The clinician stressed the side effects related to other agents used for PHN (such as pregabalin) being a particular problem in the elderly due to risk of falls, and the relationship to the higher rate of discontinuations with these agents compared with lignocaine. A preference for listing restriction option 1 was indicated by the clinician.

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

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1) and health care professionals (3) via the Consumer Comments facility on the PBS website. The comments emphasised that lignocaine is associated with fewer side effects compared with alternative therapies.

Clinical trials

- 6.3 The submission was based on:
- An open-label head-to-head randomised non-inferiority trial comparing lignocaine patch to pregabalin (KF10004/03), referred to as the pivotal evidence. *The key data relied on from this trial are for the subgroup of patients with PHN.* Data from the overall population, including patients with diabetic polyneuropathy (DPN), are also presented below;
 - One enriched randomised withdrawal trial comparing lignocaine patch to placebo patch (Binder 2009);
 - One cross-over enriched randomised withdrawal trial comparing lignocaine patch to placebo patch (Galer 1999);
 - One head-to-head randomised trial comparing lignocaine patch to placebo patch (Galer 2002); and
 - Two supportive systematic reviews (Snedecor 2014, Wolff 2011).
- 6.4 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
<i>Lignocaine patch vs. pregabalin</i>		
KF10004/03 (PHN subgroup)	<p>KF10004/03/PHN (sub-report) CSR. Safety and efficacy of lidocaine 5% medicated plaster in comparison with pregabalin in postherpetic neuralgia and diabetic polyneuropathic pain. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in postherpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in postherpetic neuralgia and diabetic polyneuropathy. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy. Interim analysis from an open-label, two-stage adaptive, randomized controlled trial.</p> <p><u>Combination phase</u> Rehm S, Binder A, Baron R. Postherpetic neuralgia: 5% lidocaine medicated plaster, pregabalin, or a combination of both? A randomized, open, clinical effectiveness study.</p>	<p>25 September 2009</p> <p><i>Current Medical Research and Opinion</i> 2009a; 25(7):1663-76.</p> <p><i>Current Medical Research and Opinion</i> 2009b; 25(7): 1677-87.</p> <p><i>Clinical Drug Investigation</i> 2009c; 29(4):231-41.</p> <p><i>Current Medical Research and Opinion</i> 2010; 26(7):1607-19.</p>
<i>Lignocaine patch vs. placebo</i>		
Binder (2009)	<p>KF10004/01 CSR. A double-blind, multicentre, multiple-dose, enriched enrolment, randomized-withdrawal, parallel-group phase III study with Lido-Patch and corresponding placebo plaster in patients suffering from postherpetic neuralgia (PHN). Binder A, Bruxelle J, Rogers P, Hans G, Bösl I, Baron R. Topical 5% lidocaine (Versatis) medicated plaster treatment for postherpetic neuralgia: results of a double-blind, placebo-controlled, multinational efficacy and safety trial.</p>	<p>2 September 2005.</p> <p><i>Clinical Drug Investigation</i> 2009; 29(6):393-408.</p>
Galer (1999)	<p>KF10004/H32 CSR. A randomized, double-blind, cross-over study of the analgesic efficacy of lidocaine dds (dermal delivery system) compared to placebo dds in postherpetic neuralgia. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrolment study.</p>	<p>22 October 2004.</p> <p><i>Pain</i> 1999; 80(3):533-8.</p>
Galer (2002)	<p>KF10004/H31. Multicentre randomized, double-blind study of the analgesic efficacy and safety during 30 days of as needed use of topical lidocaine patches in patients with postherpetic neuralgia. Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Rowbotham MC, Davies PS, Galer BS. Multicentre, double-blind, vehicle-controlled trial of long term use of lidocaine patches for postherpetic neuralgia. Abstracts of the 8th World Congress of the International Association for the Study of Pain (Vancouver, British Columbia, Canada, August 17-22, 1996).</p>	<p>2 October 2004.</p> <p><i>Clinical Journal of Pain</i> 2002; 18(5):297-301.</p> <p>Abstract 184:274.</p>
Supportive systematic reviews		

Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Snedecor (2014)	Snedecor SJ, Suharshan L, Cappelleri JC, Sadosky A, Desai P, Jalundhwala Y, Botteman M. Systematic review and meta-analysis of pharmacological therapies for pain associated with postherpetic neuralgia and less common neuropathic conditions.	<i>International Journal of Clinical Practice</i> 2014; 68(7):900-18.
Wolff (2011)	Wolff RF, Bala MM, Westwood M, Kessels AG, Kleijnen J. 5% lidocaine-medicated plaster vs other relevant interventions and placebo for postherpetic neuralgia (PHN): a systematic review.	<i>Acta Neurologica Scandinavica</i> 2011; 123:295-309.

Source: Adapted from Tables B.2.3 (p68-9) and B.2.5 (p70) of the submission

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

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Lignocaine patch vs. pregabalin						
KF10004/03	311	Adaptive 2-stage, OL, R, MC, non-inferiority	High	DPN and PHN with NRS-3 >4	% achieved response at wk. 4 (reduction of ≥ 2 or an absolute value ≤ 4 on NRS-3); EQ-5D-5L	Not used
- PHN subgroup	98	4 wk. comparative, 8 wk. combination, 4 wk. downtitration	High	PHN with NRS-3 >4		% discontinue (AE), % add-on therapy in combination phase, utility value
Lignocaine patch vs. placebo patch						
Binder (2009)	71	Enriched, DB, R, MC, withdrawal; 8-wk OL run-in to determine response, 2 wk. DB	High	PHN NRS ≥ 4 & adequate response after 8-wk run-in	Time to exit due to lack of efficacy	Not used
Galer (1999)	33	Enriched, DB, R, CO withdrawal, 2 centres; each phase: 2-14d	High	PHN & adequate response (supply via OL CUP)	Time to exit due to lack of efficacy	Not used
Galer (2002)	167	DB, R, 2 centres; 2 single application sessions prior, 3 wks. in-house	High	Torso PHN ≥ 1 mth with allodynia	Pain relief : VAS & 6-point scale (single application sessions 1 and 2)	Not used

Source: Compiled during the evaluation using data from Tables B.2.6 (pp72-3), B.4.1 (pp82-3), and B.5.1 (pp89-90), and pp74-81 of the submission. Additional data from the CSR for Galer (2002) included.

Abbreviations: AE, adverse event; CO, cross-over; CUP, compassionate use program; DB, double blind; DPN, diabetic polyneuropathy; MC, multi-centre; NRS, 11-point numerical rating scale; NRS-3, recall of pain over the preceding 3 days; OL, open label; PHN, post-herpetic neuralgia R, randomised; VAS, visual analogue scale

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

Comparative effectiveness

Patients achieving reduction of ≥ 2 points or an absolute value of ≤ 4 on the NRS-3 scale at Week 4 (end of comparative phase) in Trial KF10004/03

	Lignocaine patch n/N (%)	Pregabalin n/N (%)	Lower limit CI ^a	p-value NI test ^a	RR (95% CI) ^b	RD (95% CI) ^b
Overall population (DPN and PHN)						
Per protocol – confirmatory	94/144 (65.3)	85/137 (62.0)	-9.15%	0.00656	1.05 (0.88, 1.26)	0.03 (-0.08, 0.14)
Full Analysis Set – supportive	101/152 (66.4)	91/148 (61.5)	-7.03%	0.00229	1.08 (0.91, 1.28)	0.05 (-0.06, 0.16)
PHN subgroup						
Per protocol	28/45 (62.2)	20/43 (46.5)	–	–	1.34 (0.90, 1.98)	0.16 (-0.05, 0.36)
Full Analysis Set	31/49 (63.3)	22/47 (46.8)	–	–	1.35 (0.93, 1.96)	0.16 (-0.03, 0.36)

Source: Adapted from Tables B.6.1 (p99) and B.6.2 (p99) of the submission

Abbreviations: CI, confidence interval; DPN, diabetic polyneuropathy; NI, non-inferiority NRS-3, recall of pain over the preceding 3 days on the 11-point numerical rating scale; PHN, post-herpetic neuralgia; RD, risk difference; RR, relative risk

^a p-value and confidence interval limit from a non-inferiority test of lignocaine patch versus pregabalin, with the non-inferiority margin set at 8%. The overall (combined) p-value was calculated as the product of the two p-values from the first and second stages of the trial, and has significance value of 0.0038.

^b Calculated by the submission using RevMan. The same approach was used during the evaluation to populate the table.

- 6.6 Non-inferiority between lignocaine patch and pregabalin was not demonstrated as the lower limit of the confidence interval (CI) (-9.15%) did not meet the pre-defined non-inferiority margin (-8%) and the combined p-value was more than the pre-defined critical value of 0.0038 (0.00656), based on the main analysis in the per protocol population of the pivotal Trial KF10004/03 (including DPN and PHN patients).
- 6.7 However, the lower limit of the CI of the supportive analysis in the full analysis set was -7.03%, which met the predefined non-inferiority margin of -8%.
- 6.8 The submission argued that the trial was underpowered to demonstrate non-inferiority, given that the pre-planned interim analysis estimated a sample size of 1,212 was required and the trial was stopped due to lack of feasibility.
- 6.9 The PSCR (p1) argued that the results for DPN patients are not relevant for PBAC consideration.
- 6.10 No combined p-value for the PHN subgroup was presented in the trial report. The submission argued that should the combined p-value for the PHN subgroup have been calculated, non-inferiority would have been demonstrated despite the lack of power. The submission further argued that overall response rates at week 4 were 'numerically higher' in the lignocaine patch arm versus pregabalin. Given that the trial failed the primary outcome, subgroup analyses and analyses of secondary outcomes are unreliable and should be interpreted with caution.

- 6.11 The submission calculated the proportion of ‘responders’ in the economic model using the proportions of patients who remained on monotherapy during the combination phase (allocated to monotherapy arm if NRS-3 \leq 4 points) (see the table of comparative benefits and harms for lignocaine patch and pregabalin). The post hoc analysis using this responder threshold presented in Section B of the submission suggested that more patients in the lignocaine arm remained on monotherapy during the subsequent combination phase compared to pregabalin, with the 95% CI not including the null value. However, the results used in the model were not consistent as the 95% CI of the modelled incremental difference included the null value. The post hoc exploratory results were fragile to the selected denominator. There were no differences between arms for the pre-specified responder thresholds of \geq 30% and \geq 50% reduction in pain.

Mean (SD) change in EQ-5D-5L (estimated health state) from baseline to week 4 (per protocol population) in Trial KF10004/03

	Overall population (DPN and PHN)			PHN subgroup		
	Lignocaine patch N=144	Pregabalin N=137	Statistical analysis	Lignocaine patch N=45	Pregabalin N=43	MD (95% CI)
Baseline	0.53 (0.294) n=142	0.56 (0.272) n=NR	-	0.61 (0.288) n=45	0.58 (0.319) n=42	-
Mean Δ at Wk. 4	0.12 (0.240) n=136	0.04 (0.235) n=NR	NE	0.12 (0.231) n=40	-0.00 (0.276) n=42	0.12 (0.01, 0.23) ^a

Source: Tables B.6.9 (109) of the submission; Table 11-24 (p159) and pp11-12 of the full CSR of KF10004/03; Baron (2009a)
Abbreviations: CI, confidence interval; DPN, diabetic polyneuropathy; MD, mean difference; PHN, post-herpetic neuralgia
^a Calculated in the submission using RevMan.

- 6.12 The submission claimed that lignocaine patch was ‘statistically significantly’ superior to pregabalin in terms of quality of life among PHN patients, with a patient relevant utility gain as measured by the EQ-5D-5L. While the data suggested a short-term gain in quality of life (4 weeks), the results were not robust given the small number of patients in the exploratory post hoc subgroup analysis from a trial that failed the primary endpoint and was at high risk of bias. In addition, the ESC noted that the range of utility values at baseline and at 4 weeks was from -0.18 to 1.0. This suggests considerable heterogeneity in quality of life, and also that the results may be sensitive to changes in quality of life for a small number of patients, which may not be robust. The submission presents a qualitative description of SF-36 results that suggests that improvements were observed in most dimensions across both treatments, but with no clear pattern of greater gain in quality of life for lignocaine compared with pregabalin.
- 6.13 The results of the primary outcomes of the placebo-controlled trials are presented below in the table of the comparative benefits and harms for lignocaine patch and placebo. In summary:
- **Binder (2009):** There was no statistically significant difference between treatment groups in the time to exit due to lack of efficacy for the main analysis in the full analysis set (median time to exit was 13.5 days for the lignocaine patch arm versus 9.0 days in the placebo arm; $p=0.1510$). However, the supportive analysis in the per protocol population found a statistically significant difference between arms in the median time to exit (14 days versus 6 days; $p=0.0398$).

- Galer (1999) (cross-over): The median time to exit for patients treated with lignocaine patches (>14 days) was statistically significantly longer than the median time of 3.8 days for those using placebo patches ($p < 0.001$).
- Galer (2002): There were no statistically significant differences between treatment groups for pain intensity reduction using visual analogue scale (VAS) (except at 2 hours during session 2) and pain relief scores (except at 10 hours during session 1). The submission stated that two of the three primary outcomes subsequently chosen by the trial report were only assessed during the in-clinic sessions. Therefore, the submission only presented one outcome as the primary outcome (pain relief using a 6-point scale after the in-house period of 21-24 days). There was a statistically significant difference between treatment groups in mean pain relief scale scores favouring lignocaine patch over placebo patch ($p = 0.021$).

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

Comparative harms

- 6.14 During the four-week comparative phase of Trial KF10004/03, more patients on pregabalin in the overall population (DPN and PHN) experienced treatment-emergent adverse events (descriptive p-value < 0.0001), and discontinued treatment due to adverse events compared to those who received lignocaine patches. *Post hoc* statistical analyses presented in the submission indicated that these differences were statistically significant in the PHN subgroup (see Table 5). The open-label design of the trial may have biased the reporting of adverse events. Additionally, patients who discontinued randomised pregabalin due to adverse events during the comparative phase were allowed to switch to lignocaine. This trial had an accelerated titration of the pregabalin dose which was not reflective of clinical practice and may have contributed to the increased side effects.
- 6.15 Limited safety data were available from the placebo-controlled trials. Many patients assessed for comparative data (lignocaine patch versus placebo patch) during the double-blind period were lignocaine patch treatment-experienced. Placebo patches can also induce localised skin reactions. Therefore, safety results were likely biased in favour of lignocaine patch.
- 6.16 Lignocaine patches were associated with localised application site reactions, but the frequency was unclear from the trial reports. The proportion of patients with skin reactions was reported as 12.4% in the TGA clinical evaluator report, apparently based on Hans (2009).

- 6.17 The majority of PHN cases occur in those aged over 70 years and the ESC considered the patches may be complicated to use in this patient group. In particular, the ESC was concerned about a patient's ability to cut the patches to size, frequent use on fragile skin and incorrect use which could result in a greater than intended dose of lignocaine being absorbed. The Pre-PBAC Response disagreed with the ESC, stating that safety concerns regarding patch application are not supported by the available clinical trial or post-marketing safety data. Furthermore, the Pre-PBAC Response argued that the potential safety and quality use of medicines concerns highlighted by ESC are relatively minor and manageable and should be interpreted in the context of the safety profile of pregabalin.
- 6.18 The commonly reported adverse events associated with pregabalin included dizziness, fatigue, headache, somnolence, and vertigo. The December 2014 Medicines Safety Update by the TGA included a reminder of the suicidality risk associated with pregabalin use.

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

Benefits/harms

- 6.19 A summary of the comparative benefits and harms for lignocaine patch versus pregabalin is presented in the following table.

Summary of comparative benefits and harms for lignocaine patch and pregabalin (PHN subgroup of Trial KF10004/03 during the comparative phase)

Trial	Lignocaine patch	Pregabalin	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Lignocaine patch	Pregabalin	
Benefits						
Patients achieving reduction of ≥ 2 points or an absolute value of ≤ 4 on the NRS-3 scale at Week 4 (PP)						
KF10004/03	94/144	85/137	1.05 (0.88, 1.26)	65.3	62.0	0.03 (-0.08, 0.14)
-KF10004/03 (PHN)	28/45	20/43	1.34 (0.90, 1.98)	62.2	46.5	0.16 (-0.05, 0.36)
Patients achieving $\geq 50\%$ reduction in pain (NRS-3) at Week 4 (PP)						
KF10004/03	56/144	44/137	NE	38.9	32.1	NE
-KF10004/03 (PHN)	16/45	9/43	1.70 (0.84, 3.43)	35.6	20.9	0.15 (-0.04, 0.33)
Post hoc: Patients achieving NRS-3 ≤ 4 points and remaining on monotherapy during the combination phase						
KF10004/03	NR	NR	NR	NR	NR	NR
-KF10004/03 (PHN) Sect B	25/50	14/48	1.71 (1.02, 2.89)	50.0	29.2	0.21 (0.02, 0.40)
-KF10004/03 (PHN) Sect D	NR	NR	NR	61.7	48.5	0.13 (-0.09, 0.35)
Harms						
	Lignocaine patch	Pregabalin	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Lignocaine patch	Pregabalin	
Treatment-emergent adverse events						
KF10004/03	29/155	71/153	NE	18.7	46.4	NE
-KF10004/03 (PHN)	5/50	25/45	0.46 (0.26, 0.81)	24.0	52.1	-0.28 (-0.47, -0.10)
Discontinuation due to adverse event						
KF10004/03	9/155	39/153	NE	5.8	25.5	NE
-KF10004/03 (PHN)	3/50	15/45	0.19 (0.06, 0.62)	6.0	31.3	-0.25 (-0.40, -0.11)

Source: Compiled during the evaluation using data from Tables B.6.1 (p99), B.6.2 (p99), B.6.3 (p100), B.6.4 (p101), B.6.15 (p108) and D.4.1 (p141) of the submission; Table 12-2 (p246) and p11 of the full CSR of KF10004/03; 6C - ModelData_VERSATIS_30Oct14.xlsx

^a 4 weeks duration of follow-up

Abbreviations: PHN, post-herpetic neuralgia; PP, per protocol; RD, risk difference; RR, risk ratio

- 6.20 On the basis of direct evidence presented by the submission, for every 100 patients with PHN treated with lignocaine patch in comparison to pregabalin:
- There were no differences in the proportions of patients who had an improvement in pain reduction over 4 weeks.
 - Approximately 21 more patients remained on lignocaine than remained on pregabalin after the initial trial period and had a pain score of ≤ 4 (measured using a scale where 0 is no pain and 10 is the worst pain imaginable) over a duration of 4 weeks.
 - Approximately 28 fewer patients with PHN would have treatment-emergent adverse events (side effects) over a 4 week duration of follow-up.
 - Approximately 25 fewer patients with PHN would discontinue treatment due to adverse events (side effects) over a 4 week duration of follow-up.
- 6.21 A summary of the comparative benefits and harms for lignocaine patch versus placebo is presented in the table below.

Summary of comparative benefits and harms for lignocaine patch and placebo

Benefits							
Time to exit due to lack of efficacy^a							
	Lignocaine patch	Placebo patch	Absolute Difference	HR (95% CI)			
Binder (2009)							
Failed	9/36	16/35	-	Post hoc data driven: 3.12 (1.202, 8.075) ^b			
Median in days (range)	13.5 (2-14)	9.0 (1-14)	NS (log-rank test)	-			
Galer (1999); CO trial							
Failed	NR	NR	-	NR			
Median in days (95% CI)	> 14 (14.0, > 14.0)	3.8 (3.0, > 14)	>10.2	-			
Continuous Outcome I: change from baseline in pain relief scale score (6-point categorical scale^c)							
	Lignocaine patch			Placebo patch			Mean difference^d: Lignocaine patch vs. placebo (95% CI)
	n	Mean Δ baseline	SD	n	Mean Δ baseline	SD	
Galer (2002)	100	2.6	1.3	50	2.1	1.0	0.50 (0.12, 0.88)
Harms							
	Lignocaine patch	Placebo patch	RR (95% CI)	Event rate/100 patients^e		RD (95% CI)	
				Lignocaine patch	Placebo patch		
Treatment-emergent adverse events							
Binder (2009)	2/36	1/35	NR	5.6	2.9	NR	
Galer (1999)	13/32	11/32	1.18 (0.63, 2.23)	41	34	NR	
Galer (2002)	NR	NR	NR	NR	NR	NR	
Discontinuation due to adverse event							
Binder (2009)	0/36	1/35	NR	0	2.9	NR	
Galer (1999)	NR	NR	NR	NR	NR	NR	
Galer (2002)	2/108	1/53	NR	1.8	1.9	NR	

Source: Compiled during the evaluation using data from Tables B.6.17 (p111), B.6.23 (p116), B.6.24 (p116), B.6.25 (p118), B.5.27 (p118) and B.6.30 (p120), and p111 of the submission; p70 of the CSR for Binder (2009)

Abbreviations: CO, cross-over; NR, not reported; NS, not statistically significant; RD, risk difference; RR, risk ratio

^a decreased pain relief by ≥ 2 categories on the 6-item scale (worse, no pain relief, slight, moderate, a lot, complete) on two consecutive treatment days

^b adjusted for baseline Short Form McGill Pain Questionnaire (SF-MPQ) sensory sub-scores at randomisation, baseline allodynia and PHN duration

^c Six-point scale: 0 = worse pain, 1 = no change, 2 = slight relief, 3 = moderate relief, 4 = a lot of relief, and 5 = complete relief

^d 3 weeks duration of follow-up

^e Max 2 weeks of exposure for the enriched withdrawal studies (Binder 2009 and Galer 1999); data from Galer (2002) related to 3-week in-house period

- 6.22 On the basis of direct evidence presented by the submission, the comparison of lignocaine patch and placebo resulted in:
- No differences in the time to exit due to lack of efficacy for 50% of patients for one trial (Binder 2009).
 - Approximately >10.2 days difference in the time to exit due to lack of efficacy for 50% of patients for one cross-over trial (Galer 1999).
 - Approximately a 0.5 reduction in pain relief scale score (6-point categorical scale) over a 3 week duration of follow-up. The submission did not indicate what difference was considered to be clinically meaningful.
- 6.23 On the basis of direct evidence presented by the submission, for every 100 patients treated with lignocaine patch in comparison to placebo:

- There were no clear differences in treatment-emergent adverse events (side effects) or discontinuations due to adverse events (side effects).

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

Clinical claim

- 6.24 The submission described lignocaine patch as at least non-inferior in terms of comparative efficacy (response) but superior in terms of quality of life, and superior in terms of comparative safety compared to pregabalin. The ESC considered these claims were not adequately supported.
- 6.25 The submission described lignocaine patch as superior in terms of comparative efficacy and non-inferior in terms of comparative safety compared to placebo. The ESC considered these claims were not adequately supported.
- 6.26 The PBAC considered that the claims of non-inferior comparative effectiveness and superior quality of life compared to pregabalin and superior comparative effectiveness compared to placebo were not adequately supported by the data.
- 6.27 The PBAC considered that the claims of superior comparative safety compared to pregabalin and non-inferior safety compared with placebo were not adequately supported by the data.

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

Economic analysis

- 6.28 The submission presented a modelled economic analysis. The type of economic evaluation presented was a cost-utility analysis. This was not consistent with the clinical evidence, as the clinical claims were inadequately supported. The economic evaluation also modelled superior efficacy in terms of pain management (i.e. more pregabalin-treated patients required additional therapy due to lack of efficacy), which was inconsistent with the clinical claim of at least non-inferior efficacy.
- 6.29 The model compared treatment algorithms where lignocaine patch was PBS listed to an algorithm where lignocaine patch was not. Therefore, the model had a mix of 'treatment' states and health states. The model considered the two alternative PBS-restrictions as separate arms. The same main comparator arm was used.
- 6.30 All patients started the model on lignocaine patch for Option 1; and on pregabalin for Option 2 and the main comparator arms. Subsequently, patients in the 'initial pregabalin' or 'initial lignocaine patch' states switch treatment states due to adverse events or add therapy due to lack of efficacy (based on the availability of lignocaine patch and pregabalin).

Patients in the main comparator arm were able to add best supportive care to pregabalin, but a corresponding treatment state was not available for lignocaine patch treatment states. Patients in a subsequent-line treatment state (switched from

or added to initial treatment) who discontinued irrespective of reason switch to best supportive care.

- 6.31 Net benefits in the lignocaine patch arms (Option 1 and Option 2) were achieved through having fewer patients in the treatment states with lower utility values, including 'initial pregabalin' for two cycles (due to the assumption of gradual utility gain), 'best supportive care' and 'pregabalin plus best supportive care'.

Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 4 weeks of a randomised comparative phase with a subsequent non-randomised 8 week combination phase in the trial
Outcomes	Quality adjusted life years (QALYs)
Methods used to generate results	Markov cohort expected value analysis. 'Tunnel' states used to maintain 'memory' of duration in a particular treatment state.
Cycle length	4 weeks
Transition probabilities	Comparison of the clinical management algorithm with the patient flow of Trial KF10004/03 to initiate treatment related transition probabilities. Long-term studies used to inform subsequent transition probabilities (Hans 2009 and Stacey 2008b). Review of four cohort studies identified in Kawai (2013) to inform the probability of PHN resolution: Bouhaissira (2012) to inform the probability of PHN resolving during first 12 months of the model; Helgason (2000) to inform the model beyond 12 months.
Discount rate	5% for costs and outcomes
Half-cycle correction	Applied to benefits, but not costs as drug costs are assumed to accrue at the beginning of the cycle

Source: constructed during the evaluation

Key drivers of the model

Description	Method/Value	Impact
Utility gain with treatment (lignocaine patch, pregabalin, lignocaine patch + pregabalin states)	0.12; based on the post hoc mean change in EQ-5D-5L from baseline at Week 12 (Trial KF10004/03, PHN subgroup). Utility gain for 'initial pregabalin' state achieved over 3 cycles, and over 1 cycle for the remaining treatment states.	High, favours lignocaine patch
Utility gain for best supportive care and pregabalin + best supportive care states	0.03; adjusted for placebo-response ($\geq 30\%$ pain reduction) in 24.3% based on 3 pregabalin trials.	High, favours lignocaine patch
Model structure	The submission claimed that the model structure closely aligned with the patient pathway through Trial KF10004/03. The lignocaine patch arm for Option 1 appeared to be largely based on the lignocaine patch arm of the trial, but included additional switching to pregabalin. The pregabalin arm of the trial was used as the basis for the lignocaine patch arm for Option 2. The main comparator arm appeared to be constructed based on assumption of no effective alternative treatment. A key driver of the model was the highly uncertain assumption of switching from and adding therapies subsequent to the initial therapy.	High, favours lignocaine patch

Source: constructed during the evaluation

- 6.32 There were issues with the model, particularly the model structure, including:
- The economic evaluation effectively modelled an additional line of therapy for each option rather than provide head-to-head comparisons between lignocaine patch and the comparator. This resulted in inconsistencies between the clinical data and the modelled benefit. The data to populate the transition probabilities

are from the combination phase of the pivotal trial, which does not capture the alternatives in the model. The use of these data is particularly not appropriate for Option 2, where patients are assumed to be refractory to pregabalin. The PSCR (p3) identified that a similar modelled algorithm approach was accepted for pregabalin. The ESC considered that whilst a comparison of different algorithms with and without the new treatment may have been considered appropriate for pregabalin in the context of significant clinical need and few viable alternatives, this was not the case for lignocaine which is seeking to be considered as an alternative treatment to pregabalin. Also, the model is not adequately supported by the trial data. In this instance a direct comparison of lignocaine versus the comparator for the two options is more appropriate.

- Option 1 and Option 2 were modelled together, assuming that Option 2 can be proxied by assuming that all patients start the model on pregabalin and are allowed to transition to different treatment states with the availability of lignocaine patch (based on the pregabalin arm of the trial). The ESC considered that this approach did not fully capture the differences between whether lignocaine is listed or not. For example, some patients may start on BSC due to already discontinuing pregabalin due to intolerance or a lack of efficacy.
- The treatment algorithm in the model was not consistent with the clinical trial algorithm and was unlikely to reflect clinical practice. There were missing treatment states and likely transitions between treatment states. The model did not adequately capture the probability of concomitant therapy at reduced doses following drug-related (or treatment-related) adverse events, nor did it allow for re-trial of therapies or for adequate cycling through therapies. The submission acknowledged that while all switches between/addition of therapies in the model happened with lignocaine patch and pregabalin, and vice versa, this is unlikely given the presence of alternative treatments in practice.
- The model included a 'pregabalin plus best supportive care' state (which incurs pregabalin cost with no additional benefit) without a corresponding 'lignocaine patch plus best supportive care' state. This introduced bias in favour of lignocaine patch.
- The modelled population included patients with pain one month post herpes zoster, based on the assumptions to derive the probability of self-resolution of PHN. This was inadequately justified. Pregabalin and lignocaine patches are for subsequent-line therapies (therefore unlikely to be initiated at the point of PHN diagnosis). It also appears improbable that patients one month post-rash would have exhausted all treatment options as implied by the utility value of the best supportive care state. This also appears to be inconsistent with the inclusion criteria for the trial, which required patients to have PHN for at least three months post rash. The PSCR (p4) provides a sensitivity analysis based on a 3-month definition for PHN, assuming slower rates of PHN resolution, and this variable had little impact on the ICER.
- The assumption that there were no other effective treatment options was inadequately justified. It appears improbable that patients would persist with treatments with little benefit. The main comparator arm appeared to be constructed based on the assumption of no effective alternative treatment.
- The time horizon may be appropriate to model long-term chronic patients. However, the model assumed that patients eligible for treatment were

experiencing pain one month after acute herpes zoster. There were limited data to extrapolate beyond the trial duration.

- The trial-based inputs were not robust, given the small number of PHN patients included in Trial KF10004/03 (which failed its primary outcome). These data may be subject to bias due to the open-label trial design, particularly the trial-based probability of discontinuation due to adverse events in the pregabalin arm. Differences in pain responses that may not be statistically significantly different were modelled.
- The application of transition probabilities was poorly documented and did not appear to entirely correspond with the description in the submission.

Results of the economic evaluation (Option 1)

Component	Lignocaine patch	Pregabalin	Increment
Costs	\$ [REDACTED]	\$725	\$ [REDACTED]
QALYs	3.0713	3.0198	0.0515
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Table D.5.1 (p194) of the submission

Results of the economic evaluation (Option 2)

Component	Lignocaine patch	Comparator	Increment
Patients with pain refractory to pregabalin (comparator: pregabalin)			
Costs	\$ [REDACTED]	\$725	\$ [REDACTED]
QALYs	3.0664	3.0198	0.0466
Incremental cost/extra QALY gained			\$ [REDACTED]
Sensitivity analysis: Patients unsuitable for pregabalin (comparator: best supportive care)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	3.0405	3.0021	0.0384
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Table D.5.2 (p194) of the submission and additional results calculated using the model

- 6.33 The redacted tables above show ICERs in the range of \$15,000/QALY - \$45,000/QALY
- 6.34 The results were not reasonable, given the flawed model structure and the various inadequately justified and/or uncertain inputs. The results were highly biased in favour of lignocaine patch. The ESC was of the view that the model structure cannot be relied upon.
- 6.35 The model was most sensitive to the assumed utility values for the various treatment/health states, in particular 'best supportive care' and 'pregabalin plus best supportive care' states. Halving the treatment-related utility gain resulted in the doubling of the incremental cost-effectiveness ratios (ICERs). The model was also highly sensitive to increasing the 'placebo-response' for the 'best supportive care' and 'pregabalin plus best supportive care' states (therefore was dependent on the inadequately justified assumption of no other effective treatment in practice).

Given the small number of patients informing the utility values, and the heterogeneity in individual utility values (see paragraph 6.12), this suggests that the modelled utility gains are not robust.

- 6.36 The Pre-PBAC Response [p3] presented additional multiway sensitivity analyses of the economic model to address the key concerns of the ESC.

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

Drug cost/patient/day

Drug cost (DPMQ)/patient/day	Drug cost/patient/day
Lignocaine patch 1.71 patches/day (Sect E and D; KF10004/03 PHN subgroup dosing)	\$ [REDACTED]
Lignocaine patch 1.03 patches/day (US data from IMS Health 2006)	\$ [REDACTED]
Pregabalin 481.4mg/day (Sect D; KF10004/03 PHN subgroup dosing; assumed only 150mg and 300mg strengths dispensed)	\$ [REDACTED]
Pregabalin 186mg/day (Sect D sensitivity analysis; 10% Medicare sample data, assumed only 75mg and 150mg strengths dispensed and BD dosing)	\$ [REDACTED]
Pregabalin 193mg/day (Sect E; BEACH data 2013-14 distributions across strengths assumed BD dosing)	\$ [REDACTED]
Pregabalin 150mg/day (75mg strength ~ 50% of dispensed scripts, DUSC Oct 14 pregabalin review, assumed BD dosing)	\$ [REDACTED]

Source: Compiled during the evaluation. Daily costs provided given the methods used to estimate the extent of utilisation.
Abbreviations: BD, twice daily; DPMQ, dispensed price for maximum quantity

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

Estimated PBS usage & financial implications

- 6.37 This submission was not considered by DUSC. The submission used a mixed epidemiological and market share approach. At year 5, the estimated number of patients would be less than 10,000 for Option 1 (or less than 10,000 for Option 2) and the net cost to the PBS would be \$10 - \$20 million (or less than \$10 million for Option 2).

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Option 1					
Estimated extent of use					
Total patient yrs. on therapy					
Scripts ^a					
Estimated net cost to PBS/RPBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Cost-offset from pregabalin	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Option 2					
Estimated extent of use					
Total patient yrs. on therapy					
Scripts ^a					
Estimated net cost to PBS/RPBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Cost-offset from pregabalin	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$

Source: Adapted from Tables E.2.5 (p223), E.2.8 (p225), E.2.11 (p227), E.2.14 (p228), E.2.15 (p229), E.2.16 (p229), E.2.19 (p230), E.3.16 (p237), E.3.17 (p238), E.3.18 (p238), E.4.2 (p240), and E.4.3 (p241) of the submission; 6E - Section E VERSATIS November 2014 PBAC submission.xlsx

^a Assuming 10.4 per patient per year as estimated by the submission.

- 6.38 The redacted table above shows that at Year 5, the estimated number of scripts dispensed would be 50,000 – 100,000 for Option 1 and 10,000 - 50,000 for Option 2 and that the net cost to the PBS/RPBS would be \$10 - \$20 million for Option 1 and less than \$10 million for Option 2.
- 6.39 The limitations in the estimates included the assumption that only the incident PHN population were eligible to initiate treatment in a given year (resulting in a likely underestimate of the eligible population and an overestimation of the rate of PHN self-resolution), the reliance on modelled outputs to determine average duration of therapy (see economic analysis), the inconsistencies in approach between Section D and Section E (utilisation estimates for Option 1 required modelled outputs for both Option 1 and 2), and the assumed uptake rates.
- 6.40 The PSCR (p4) agreed that the ‘...assumption that only the incident population initiate treatment in Year 1 may underestimate patients eligible for treatment in the first few years’ but that the financial implications of listing lignocaine will remain below \$20 million even at 80% uptake rate’. This sensitivity analysis examined the financial implications if the Year 1 to 5 uptake rates increased to 50%, 58%, 65%, 73%, and 80%, respectively, compared with the base case of 40%, 43%, 45%, 48% and 50%. The net cost to the PBS in this scenario was estimated to be \$10 - \$20 million in Year 5.
- 6.41 The PSCR (p6) provided private unit sales data for lignocaine, with less than 10,000 units sold in 2014, as requested by the Commentary. It was unclear whether a unit equates to a pack of 30 patches.

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

Financial Management – Risk Sharing Arrangements

- 6.42 The Pre-PBAC Response stated that the sponsor is willing to work with the PBAC and the Department in designing an appropriate Risk Share Agreement to manage any remaining uncertainty in the financial implications of listing lignocaine on the PBS.

Quality Use of Medicines

- 6.43 The submission claimed that pregabalin was sub-optimally dosed in practice based on commissioned BEACH and 10% Medicare sample analyses. This claim was inadequately supported.
- 6.44 There is the potential for usage outside the requested PBS listings among patients who do not meet the criteria of refractory pain. Additionally, there is the potential for usage among patients with peripheral neuropathic pain conditions other than PHN. The PSCR and Pre-PBAC Response noted that the sponsor is willing to work with the PBAC to minimise such usage by amending the restriction to Authority Required.

7 PBAC Outcome

- 7.1 The PBAC rejected the request to list lignocaine patch for the treatment of patients with PHN on the basis of uncertain cost effectiveness compared with pregabalin. The PBAC considered that there was a mismatch between the restriction, the clinical treatment algorithm, the model, and the clinical trial data.
- 7.2 The PBAC considered that there is a potential clinical need for the lignocaine patch for the treatment of PHN and acknowledged the safety and quality use of medicine issues relating to the use of systemic for this condition. However, the PBAC considered that the submission did not provide a confident basis that recommending lignocaine at the requested price would be cost-effective.
- 7.3 The PBAC considered that the proposed clinical treatment algorithm and the wording of the two suggested restrictions were ambiguous and inconsistent with current primary care advice, which is based on the therapeutic guidelines (Australian Family Physician, Neuropathic pain: A management update, Volume 42, No.3, March 2013 Pages 92-97). Current primary care advice for PHN places lignocaine as a first line treatment along with TCAs, gabapentin and pregabalin. Recommended second line therapies for PHN are opioids and tramadol.
- 7.4 While noting that the wording for the restriction Option 1 was based on the current restriction for pregabalin, the PBAC considered that it would be beneficial if the criterion “must be refractory to other drugs” was more specific for both pregabalin and lignocaine. It would be informative for a future proposed restriction for lignocaine to be informed by advice from general practitioners.

- 7.5 The PBAC considered that pregabalin was not the only reasonable comparator for the requested Option 1 listing. TCAs and gabapentin were also considered to be likely alternative treatments options to lignocaine, in line with current primary care advice.
- 7.6 The PBAC noted the ESC's concerns regarding the complexities of administration of lignocaine patch. However, the PBAC noted that TCAs and pregabalin have a worse side-effect profile in the elderly and the option to choose lignocaine before these drugs would be preferable.
- 7.7 The PBAC considered that there was a mismatch between the clinical trials and the requested restriction. For instance, patients in the pivotal trial KF10004/03 were not required to have pain refractory to other drugs (as per the requested restriction Option 1) and were not allowed to use concomitant adjuvant pain medications during the comparative phase (which was inconsistent with current clinical practice). In addition, the placebo controlled trial populations are not applicable to the requested PBS population for restriction Option 2 as patients were not required to be inadequately controlled on, or unable to tolerate, pregabalin. Furthermore, two of the three trials included lignocaine patch treatment-experienced patients.
- 7.8 The pivotal trial KF10004/03 presented the results of an open-label head-to-head randomised non-inferiority trial comparing lignocaine patch to pregabalin. The key data relied on from this trial are for the subgroup of patients with PHN. The primary outcomes were the proportion that achieved a response at week 4 (reduction of ≥ 2 or an absolute value ≤ 4 on NRS-3) and change in patient utility (measured using EQ-5D-5L).
- 7.9 The PBAC noted that non-inferiority between lignocaine patch and pregabalin was not demonstrated based on the pre-defined non-inferiority margin for the PHN and DPN population in the pivotal trial (see paragraph 6.6). The PBAC also noted that no combined p-value for the PHN subgroup was presented in the trial report. Given that the trial failed the primary outcome, the PBAC considered that subgroup analyses and analyses of secondary outcomes are unreliable and should be interpreted with caution.
- 7.10 The PBAC noted that the submission claimed that lignocaine patch was 'statistically significantly' superior to pregabalin in terms of quality of life among PHN patients, (measured by the EQ-5D-5L). While the data suggested a short-term gain in quality of life (4 weeks), the PBAC considered that the results were not robust given the small number of patients informing the exploratory post hoc subgroup analysis from a trial which failed the primary endpoint and was at high risk of bias. In addition, the PBAC agreed with the ESC that the range of utility values at baseline and at 4 weeks (from -0.18 to 1.0) suggests considerable heterogeneity in quality of life.

- 7.11 The PBAC considered that while lignocaine patch appeared to be associated with fewer adverse events and discontinuations due to adverse events, compared to pregabalin during the first 4 weeks, differences in the safety profile were likely to be overestimated due to the open-label design of the trial and that patients who discontinued pregabalin due to adverse events during the comparative phase were allowed to switch to lignocaine and rapid up-titration
- 7.12 The PBAC noted the quality of the data for lignocaine versus placebo was poor. Two of the three trials evaluating pregabalin versus placebo failed to demonstrate differences between treatment groups for the a priori primary outcomes. The claimed non-inferiority in terms of safety compared to placebo is unlikely to be realised in clinical practice, as placebo patches may induce localised application site reactions due to the patch and/or excipients.
- 7.13 The economic evaluation relied on Trial KF10004/03 (PHN subgroup) for both alternative requested PBS listings, despite the lack of a best supportive care or placebo arm of the trial. There were small numbers of PHN patients included in the trial, which was at high risk of bias and failed its primary outcome. The PBAC acknowledged that the economic model was flexible (see paragraph 6.33) but noted the ESC concerns that the model could not be relied upon for the reasons outlined in paragraph 6.32. The PBAC considered the problems with the data used to inform the model and the algorithm being different to the proposed restrictions and treatment guidelines were the key reasons the model was unreliable.
- 7.14 The PBAC noted that the financial and utilisation estimates relied on modelled outputs to inform the extent of lignocaine patch and pregabalin usage, and therefore were subject to the issues relating to the model. The PBAC noted the potential for usage among patients with peripheral neuropathic pain conditions other than PHN (e.g. diabetic peripheral neuropathy), or who do not meet the criteria of refractory pain.
- 7.15 The PBAC considered that a major resubmission would be required to seek listing of lignocaine for PHN on the PBS. The resubmission should present a revised model that addresses the issues outlined in paragraph 6.32. Alternatively, the PBAC considered that the evidence presented in the submission may be sufficient to recommend listing of lignocaine on a cost-minimisation basis to pregabalin, although alternative comparators eg TCAs should also be considered.
- 7.16 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

bioCSL is disappointed with the outcome but welcomes the PBAC's acknowledgement of the potential clinical need for VERSATIS which offers a topical treatment option for post herpetic neuralgia, a debilitating condition occurring predominantly in the elderly. bioCSL considers undue weight was placed on the results of the pivotal trial not meeting the pre-defined non-inferiority outcome in the overall per-protocol trial population which included patients with diabetic polyneuropathy, a condition for which VERSATIS is not registered in Australia. bioCSL also notes that the differences in safety profile between VERSATIS and pregabalin reflect the topical versus systemic nature of the two therapies.