PUBLIC SUMMARY DOCUMENT
Product: Lacosamide, tablets, 50 mg, 100 mg, 150 mg and 200 mg, Vimpat®
Sponsor: UCB Australia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To request an Authority Required (STREAMLINED) listing and to extend the current PBS listing to include the treatment, in combination with a non-sodium channel target anti-epileptic drug, of a patient with partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs.

2. Background

At the November 2009 meeting, the PBAC recommended listing lacosamide tablets as an Authority Required benefit for intractable epilepsy, as add-on treatment initiated by a neurologist in a patient who has failed previous therapy, on a cost-effectiveness basis compared with placebo plus standard background therapy. A Streamlined Authority was not considered suitable for use in this last-line setting. Listing was effective from 1 May 2010.

3. Registration Status

Lacosamide was registered by the TGA on 20 July 2009 for the indication:

- Add-on therapy, in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Treatment, initiated by a neurologist, of patients with partial epileptic seizures which are not controlled satisfactorily by other antiepileptic drugs in a patient aged 16 years or older, in combination with a non-sodium channel target antiepileptic drug.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Epilepsy is a common neurological condition, characterised by recurrent, unprovoked seizures, and produces significant morbidity in the general community.

In partial (focal) epilepsy, carbamazepine is generally considered first-line drug therapy. If seizures are still not controlled, a second drug is added to the first. Clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, sodium valproate, tiagabine, topiramate or zonisamide may be used. If a patient's seizures are not controlled after trying two or three different drug options, referral to a specialist epilepsy centre should be considered. Patients' refractory to drugs may be suitable for surgery.

The submission proposed that the place in therapy of lacosamide is as a second line anti-epileptic drug that must be given in combination with a non-sodium channel target anti-epileptic drug.

6. Comparator

The submission presented two "Stages" for which separate comparators are nominated.

Stage 1: Lamotrigine was nominated as the comparator, where the comparison of lacosamide + any AED versus lamotrigine + any AED was presented.

Stage 2: As the submission requested first-line add-on use for lacosamide to non-sodium AEDs, the nominated comparator for this sub-group was lacosamide + sodium AED to be used as a proxy for any first-line add-on AED (including lamotrigine) + any AED.

The PBAC did not accept that this, *see Recommendation and Reasons.*

7. Clinical Trials

The submission presented three randomised controlled trials (Trials SP667, SP754 and SP755) which compared lacosamide (200-600 mg/day) versus placebo and 12 lamotrigine trials, which compared lamotrigine (75-500 mg/day) versus placebo in patients with partial epilepsy.

The submission conducted meta-analyses of the three lacosamide and 12 lamotrigine trials and performed an indirect comparison using placebo as the common comparator.

The PBAC considered that the trials recruited subjects who were not entirely representative of those for whom PBS listing was requested, as only 20% of patients in the trial would have been representative of the requested population.

These trials had been published at the time of submission as follows:

Trial ID/First author	Protocol title/Publication title	Publication citation
Common reference - Placebo		
Lacosamide		
SP667		
Ben-Menachem E et al.	Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures.	Epilepsia (2007); 48(7): 1308-17.
SP754		
Chung S et al.	Lacosamide as adjunctive therapy for partial-onset seizures: A randomized controlled trial.	Epilepsia (2010); 51(6): 958-967.
SP755		
Halasz P et al	Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial.	Epilepsia (2009); 50 (3):443-453.
Lamotrigine		
Baulac M et al.	Randomised, double-blind parallel group study of add-on therapy in adults with partial seizures. A comparison of pregabalin, lamotrigine, and placebo as adjunctive therapy in patients with refractory partial-onset seizures.	Epilepsy Res (2010); 91(1):10-19.
Binnie C et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. Double-blind crossover trial of lamotrigine as add-on therapy in intractable epilepsy.	Epilepsy Res (1989); 4: 222-9.
Boas J et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. Controlled trial of lamotrigine for treatment-resistant partial seizures.	Acta Neurol Scand (1996); 94:247-52.

Jawad S et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. Controlled trial of lamotrigine for refractory partial seizures.	Epilepsia (1989); 30: 356-63.
Loiseau P et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures.	Epilepsy Res; (1990) 7(2): 136-145.
Matsuo F et al	Randomised, double-blind parallel group study of add-on therapy in adults with partial seizures. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. U.S. Lamotrigine Protocol 0.5 Clinical Trial Group.	Neurology (1993); 43(11): 2284-2291.
Messen-heimer J et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. Lamotrigine therapy for partial seizures: a multicenter placebo-controlled, double-blind, crossover trial.	Epilepsia (1994); 35: 113-21.
Naritoku D et al	Randomised, double-blind parallel group study of add-on therapy in adults with partial seizures. Lamotrigine extended-release as adjunctive therapy for partial seizures.	Neurology (2007); 69(16): 1610-1618.
Schachter S et al	Randomised, double-blind parallel group study of add-on therapy in adults with partial seizures (safety assessments only). Lamotrigine: A six-month, placebo-controlled, safety and tolerance study.	Journal of Epilepsy(1995); 8(3): 201-209.
Schapel G et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures.	J Neurol Neurosurg Psychiatry (1993); 56(5): 448-453.
Schmidt D et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. Add-on treatment with lamotrigine for intractable partial epilepsy: a placebo-controlled, cross-over trial.	Epilepsia (1993); 34 Suppl(2): 66.
Smith D et al	Randomised, double-blind crossover study of add-on therapy in adults with partial seizures. Outcomes of add-on treatment with lamotrigine in partial epilepsy.	Epilepsia (1993); 34(2): 312-322.

8. Results of Trials

The submission presented two outcomes to compare lacosamide and lamotrigine in Stage 1 – 50% responder rate and proportion of patients who are seizure-free. The results of the comparison are presented in the table below.

50% responder rate and proportion of patients who are seizure-free for the lacosamide 200/400mg combined group versus placebo, lamotrigine versus placebo and lacosamide versus lamotrigine

	Lacosamide v placebo Meta-analysis of 3 trials		**Lamotrigine v placebo Meta-analysis of 12 trials**		**Indirect: Lacosamide v lamotrigine**	
	RD (95% CI)	**RR (95% CI)**	**RD (95% CI)**	**RR (95% CI**	**RD (95% CI)**	**RR (95% CI)**
50% repsonder rate	**0.15 (0.10, 0.21)**	**1.65 (1.33, 2.04)**	**0.09 (0.05, 0.14)**	**1.58 (1.24, 2.01)**	0.06 (-0.01, 0.13)	1.04 (0.76, 1.44)
Propotion of patients seizure-free	0.02 (0.00, 0.03)	1.99 (0.66, 6.01)	-0.00 (-0.02,0.02)	0.87 (0.25, 3.08)	2.29 (0.43, 12.26)	0.06 (-0.01, 0.13)

50% responder rate
The lacosamide 200 mg and 400 mg treatment arms (pooled) were compared with the lamotrigine treatment arms in an indirect comparison.

The results of the meta-analyses of the lacosamide and lamotrigine trials demonstrated that treatment with both therapies results in a statistically significantly greater proportion of patients achieving a 50% reduction in seizure frequency compared with placebo. The results of the indirect comparison indicate that there is no statistically significant difference between lacosamide and lamotrigine, when both are used in combination with 'any AED'.

Proportion of patients seizure-free
The meta-analysis did not show a statistical difference compared to placebo for either the lacosamide or the lamotrigine combined estimates of treatment effect.

Patients in both the lacosamide and lamotrigine trials were refractory. In the lamotrigine meta-analysis, there were significant missing data, and the lack of difference observed for lamotrigine versus placebo may be as a result of the limited data available to inform the comparison, in addition to this not being a specified outcome in any of the lamotrigine trials.

For Stage 2, the submission presented a post-hoc analysis of the sub-group in the lacosamide trials that were consistent with the patient population for whom listing was sought (ie, those treated with lacosamide + non-sodium AED) versus lacosamide + sodium AED (which is used as a proxy for "any other first-line add-on AED + any AED). The results are presented in the table below.

50% responder rate for the lacosamide 200/400mg combined group versus placebo. For the sub-group, complement and total trial populations of the lacosamide and lamotrigine trials

Outcome: 50% responder rate				
	LCM 200/400 combined group n/N, (%)	**Placebo n/N, (%)**	**Relative Risk (95% CI)**	**Risk Difference (95% CI)**
Sub-group: Lacosamide added to only non-sodium AED - (with non-Na)				
SP667	22/47 (46.8%)	5/22 (22.7%)	2.06 (0.90, 4.72)	0.24 (0.01, 0.47)
SP754	20/36 (55.6%)	3/19 (15.8%)	**3.52 (1.20, 10.35)**	**0.40 (0.17, 0.63)**
SP755	26/50 (52.0%)	8/26 (30.8%)	1.69 (0.90, 3.19)	0.21 (-0.01, 0.44)
Pooled	68/133 (51.1%)	16/67 (23.9%)	-	-
Meta-analysis of sub-group using random effects model			**2.05 (1.30, 3.23)**	**0.28 (0.15, 0.41)**
Chi-square heterogeneity			P=0.51	P=0.48
I^2 statistic			0%	0%
Complement sub-group: Lacosamide added to at least one sodium AED				
SP667	57/167 (34.1%)	16/74 (21.6%)	1.58 (0.97. 2.56)	0.13 (0.01, 0.24)
SP754	57/165 (34.5%)	16/85 (18.8%)	**1.84 (1.13, 2.99)**	**0.16 (0.05, 0.27)**
SP755	94/268 (35.1%)	33/133 (34.8%)	**1.41 (1.01, 1.98)**	**0.10 (0.01, 0.20)**
Pooled	208/600 (34.7%)	65/292 (22.3%)	-	-
Meta-analysis of complement using random effects model			**1.55 (1.22, 1.97)**	**0.13 (0.06, 0.19)**
Chi-square heterogeneity			P=0.69	P=0.76
I^2 statistic			0%	0%
Meta-analysis of total lacosamide RCT population			**1.65 (1.33, 2.04)**	**0.16 (0.10, 0.23)**
Test for treatment effect variation			P=0.29	P=0.03
I^2 statistic			11%	78%
Comparison of sub-group to complement			1.32 (0.79, 2.22)	**0.16 (0.01, 0.30)**

Meta-analysis of total lamotrigine RCT population	**1.58 (1.24, 2.01)**	**0.09 (0.05, 0.14)**
Comparison of sub-group to total lamotrigine RCT population	1.30 (0.78, 2.17)	**0.19 (0.05, 0.33)**
Comparison of complement to total lamotrigine RCT population	0.98 (0.70, 1.38)	0.04 (-0.04, 0.12)

* The random effects model was analysed using RevMan

More patients in the non-sodium sub-group (proposed PBS listing) achieved a ≥50% reduction in seizure frequency compared to the complement subgroup (lacosamide + sodium AED), 51.1% versus 34.7% respectively, however this was only statistically significantly different when analysing the results by risk difference (0.16 (95% CI: 0.01, 0.30)).

For PBAC's view of these results, see Recommendation and Reasons.

The comparison of adverse events in the lacosamide and lamotrigine trials demonstrated that lacosamide and lamotrigine have comparable adverse event profiles, but there may be an increase in the incidence of dizziness and a decrease in the incidence diplopia for lacosamide compared with lamotrigine. The types of adverse reactions identified in the extended assessment of comparative harms were generally consistent with those identified in the shorter-term trials, including mainly CNS-related effects such as dizziness, fatigue, somnolence and headache.

9. Clinical Claim

For Stage 1, in a comparison of lacosamide + any AED versus lamotrigine + any AED, the submission described lacosamide as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over lamotrigine.

For Stage 2, in a comparison of lacosamide + non-sodium AED versus lacosamide + sodium AED (which is also used as a proxy for any first-line add-on AED + AED), the submission described lacosamide + non-sodium AED as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over lacosamide + sodium AED.

The PBAC considered that the evidence presented did not support the claim of superior clinical efficacy of lacosamide in combination with a non-sodium AED over lamotrigine in combination with any AED.

10. Economic Analysis

A stepped economic evaluation was presented.

The time horizon of the model was 120 days in the base case, however the submission provided a sensitivity analysis in which the time horizon was extended to 52 weeks.

The economic evaluation presented an incremental cost/extra responder gained over 120 days analysis, which was less than $10,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net total financial cost to the PBS was estimated by the submission to be less than $10 million in Year 5. The estimate was considered uncertain given the likely use in combination with sodium AEDs.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered that the requested restriction was inappropriate. The PBAC noted that the requested restriction was inconsistent with currently PBS listed first line add-on antiepileptic drugs (AEDs) and with the way that AEDs are prescribed in clinical practice. The PBAC considered that clinicians do not make decisions about which AED to use in the treatment of epilepsy based on distinguishing between sodium channel blocking (sodium) and non-sodium channel blocking (non-sodium) AEDs. Further, the PBAC considered there is ambiguity about the definition of AEDs in relation to whether their mechanism of action is based on blocking sodium channels or not, as some AEDs may have multiple/various mechanisms of action, some of which may be attributed to blocking sodium channels e.g. topiramate and sodium valproate.

The PBAC noted that the submission first compared lacosamide in combination with any AED to lamotrigine in combination with any AED. The PBAC considered that this may have been an appropriate comparator if the submission had been claiming non-inferiority to lamotrigine as add-on to first line treatment of epilepsy. However, the submission claimed superior clinical efficacy of the comparison of lacosamide + non-sodium AED versus lacosamide + sodium AED. The PBAC noted that this comparison is a proxy for any first line add-on AED treatment (including lamotrigine) in combination with any AED, but the PBAC did not accept this proxy comparator.

Firstly, the PBAC noted that the comparison of lacosamide in combination with a sodium AED with any first-line add-on AED (including lamotrigine) with any AED has not been specifically established as cost effective. The comparison was also considered inappropriate to inform the proposed cost effectiveness of lacosamide in combination with a non-sodium AED. Further, if the rationale for superior efficacy of lacosamide in combination with a non-sodium AED is followed, based on a synergistic effect of the combination of different mechanisms of action (sodium and non-sodium), then a comparison of a sodium and non-sodium AED (such as lamotrigine in combination with a non-sodium AED) would have followed the submission's rationale. However, as noted above, the PBAC did not consider the classification of AEDs as sodium and non-sodium channel blocking as appropriate for the intended use as part of an unambiguous PBS restriction.

The PBAC noted that the submission presented an indirect comparison of three lacosamide trials and twelve lamotrigine trials in combination with other AEDs with placebo as the common reference. The PBAC considered that the results of the meta-analysis expressed as 50 % responder rate suggest non-inferiority of lacosamide to lamotrigine in combination with any AED. However the PBAC noted that the results for placebo show different 50 % responder rates across the two sets of trials (15.7% for the lamotrigine trials and 22.6% for the lacosamide trials), which may reflect the fact that the lamotrigine trials were published mainly in the 1990s and the lacosamide trials were completed 2005-2007. In turn, this suggests that management of patients might have improved over this period, which would reduce the comparability of the trial populations and affect the indirect comparison of the

drugs. The PBAC also noted that for the outcome, 'proportion of patients seizure-free', results of the meta-analysis did not show a statistical difference compared to placebo for either the lacosamide or the lamotrigine combined estimates of treatment effect.

In addition to these major issues with the requested restriction and the comparison presented in the submission, the PBAC considered that the results for the second stage of the comparison of the subgroup of lacosamide in combination with non-sodium AEDs were uncertain as the analysis was post hoc, consisted of subgroups representing a small proportion of the pooled total trial population (18 %) and was not supported by the statistical tests for treatment effect variation across the proposed subgroup and its complement from the trials.

The PBAC considered the problems with the requested restriction, comparator and clinical data analysis flowed into the economic evaluation. The PBAC noted that the economic evaluation presented a cost per responder gained analysis (over 120 days). Presentation of an incremental cost per QALY would be more informative considering the less severe epileptic population for whom listing was sought and the number of AEDs currently PBS listed for first line add-on or second line treatment.

The PBAC considered that the utilisation estimates presented in the submission are uncertain. In addition to the potential for extensive use beyond the requested restriction, the PBAC considered that both the extent to which lacosamide would substitute for other AEDs currently PBS listed and the pattern of substitution were uncertain.

The PBAC therefore rejected the submission on the basis that the evidence presented did not support the claim of superior clinical efficacy of lacosamide in combination with a non-sodium AED over lamotrigine in combination with any AED, and on the basis of an inappropriate requested restriction and therefore comparator.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

UCB will continue working with the PBAC in order to make Vimpat available to Australian patients who can benefit from this treatment.