PUBLIC SUMMARY DOCUMENT
Product: Lacosamide, tablets, 50 mg, 100 mg, 150 mg and 200 mg, oral solution, 15 mg per mL, Vimpat®
Sponsor: UCB Australia Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

To request an Authority Required listing for treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs (AEDs) in patients who meet certain criteria.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Lacosamide tablets and oral solution were TGA registered on 20 July 2009 for use as 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

Treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs, and where:

(a) at least three anti-epileptic drugs have been unsuccessfully trialled, including at least two of the following adjunctive anti-epileptic drugs: lamotrigine, levetiracetam, topiramate, oxcarbazepine, tiagabine, and gabapentin; AND
(b) current treatment consists of at least 2 AEDs, including at least one adjunctive anti-epileptic 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. For many patients, existing antiepileptic drugs are either ineffective or produce unacceptable side-effects. Published reviews of the treatment of partial onset epilepsies define treatment refractory patients as having tried 3 or more anti-epileptic drugs without achieving seizure control.

Lacosamide would provide an additional therapeutic option in the management of refractory epilepsy.

6. Comparator

The submission nominated placebo plus standard care as the main comparator, which the PBAC considered appropriate. Standard care could include numerous combinations of first and second-line agents.

7. Clinical Trials

The submission presented three randomised trials, SP667, SP754 and SP755, comparing lacosamide (200 mg/day, 400 mg/day and 600 mg/day) with placebo in patients with partial onset epilepsy that is refractory to current treatment.

The below table provides the publication detail of the trials presented in the submission :

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
Ben-Menachem E, et al. (2007) (SP667)	Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures.	Epilepsia; 48(7): 1308-17.
Halasz P, et al (2009) (SP755)	Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial.	Epilepsia, 50 (3):443-453

8. Results of Trials

The primary outcomes of the trials were:

- 50% responder rate to treatment based on the percent change in seizure frequency (all types) per 4 week period in the baseline and maintenance phases, and
- Percent Reduction of Seizure Frequency over Placebo at Maintenance Endpoint.

For the first outcome listed above, there were statistically significant differences in favour of the lacosamide 400 mg/day treatment group compared to placebo in all three trials. Trials SP667 and SP755 also included a lacosamide 200 mg/day treatment group and although these groups had a higher proportion of responders than placebo, the difference in each trial was not statistically significant. The combined meta-analysis showed that a significantly larger proportion of patients treated with lacosamide (either 200 mg or 400 mg/day) experienced a 50% reduction in seizure frequency per 28 days from baseline to the maintenance phase compared to patients treated with placebo.

The results of the second primary outcome from the trials of percentage reduction of seizure frequency over placebo at the maintenance endpoint showed a statistically significant reduction in seizure frequency over placebo for the 400 mg/day lacosamide treatment group in all three trials. SP667 and SP755 included a 200 mg/day treatment group and both trials showed a reduction in seizure frequency with 200 mg/day, but only in trial SP755 did this reach statistical significance.

The submission presented meta-analyses of the randomised trials for a number of safety parameters.

Meta-analysis estimates of risk difference and relative risk for a number of safety parameters

Parameter	RD (LCM-PBO) (95%CI)	RR (LCM/PBO) (95%CI)
Total withdrawals LCM 200 or 400 mg/day vs placebo	0.08 (0.04, 0.13)	1.63 (1.20, 2.20)
Withdrawals due to adverse events LCM 200 or 400 mg/day vs placebo	0.09 (0.05, 0.14)	2.68 (1.67, 4.31)
Dizziness LCM 200 or 400 mg/day vs placebo	0.18 (0.04, 0.32)	3.04 (2.10, 4.39)
Headache LCM 200 or 400 mg/day vs placebo	0.03 (0.00, 0.07)	1.38 (0.95, 2.02)

Nausea LCM 200 or 400 mg/day vs placebo	0.06 (0.03, 0.08)	2.20 (1.05, 4.60)
Diplopia LCM 200 or 400 mg/day vs placebo	0.07 (0.05, 0.09)	4.43 (2.05, 9.57)

LCM: lacosamide; PBO: placebo; RD: risk difference; RR: relative risk; CI: confidence interval.

The reported adverse events of dizziness, nausea and diplopia were statistically significantly more frequently in patients treated with lacosamide compared to those treated with placebo, with the exception of 'headache'. There was no significant difference from placebo for the 200 mg/day group in total withdrawals (RD: 0.05, 95%CI: -0.01, 0.12), but the difference was significant at 400 mg/day (RD: 0.10, 95%CI: 0.05, 0.15). This was the same for withdrawals due to adverse events, which was not significantly different from placebo for the 200 mg/day treatment group (RD: 0.05, 95%CI: -0.04, 0.14) but were significantly different at 400 mg/day (RD: 0.12, 95%CI: 0.08, 0.16).

The extended assessment of comparative harms confirmed the safety conclusions of the direct randomised trials.

9. Clinical Claim

The submission described lacosamide as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo. The PBAC accepted this claim.

10. Economic Analysis

The submission presented a trial-based cost-per-responder analysis, which was based on direct randomised trials and using the primary outcome, 50% responder rate for the subgroup of the trial patient population who were representative of those for whom PBS listing is intended. The inputs into this estimation were the incremental cost of treatment with lacosamide (from the proposed PBS price and the mean dose of lacosamide) and the incremental increase in the proportion of responders to lacosamide in the post-hoc target subgroup (defined as patients with at least 50% reduction in seizure frequency).

The incremental cost per extra responder over 12 weeks for the subgroup population and the total population was calculated to be less than $15,000.

The economic evaluation was only for 12 weeks duration and this made the assessment of the cost-effectiveness of lacosamide difficult, as lacosamide is intended as a long-term maintenance therapy. A sensitivity analysis was conducted independently during the evaluation to determine a cost per additional seizure-free patient. This was calculated to be between $15,000 - $45,000. The PBAC considered that there should be a continuation rule incorporated in the listing

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in year 5. This estimate was considered uncertain.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5. The submission's estimate was considered uncertain, as it was based upon a number of uncertain assumptions, including the proportion of patients who would fulfil the requirements for lacosamide treatment, the potential uptake rate and compliance rate, the point of

withdrawal due to adverse events and lack of effect as well as the breakdown of the strengths of lacosamide dispensed dependent upon the maximum tolerated dose.

For PBAC's view see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of lacosamide on a cost-effectiveness basis compared with placebo plus standard background therapy as an authority required benefit for intractable epilepsy as add-on treatment initiated by a neurologist in a patient who has failed previous therapy. A streamlined authority was not considered suitable for use in this last-line setting.

Despite concerns about usage outside the intended population into 2nd line use, the PBAC recognised that there is a high clinical need for an effective treatment for intractable epilepsy, as highlighted in the hearing. Although other adjunctive anti-epileptic drugs have been listed on the basis of evidence from placebo-controlled, add-on studies, on a cost-minimisation basis compared with lamotrigine, lacosamide appears to be effective in heavily treated patients as more than 60% of patients in the trials had received seven prior treatments.

The PBAC noted that the economic analysis calculated an incremental cost/extra responder over 12 weeks (subgroup population) of less than $15,000 based on a 50% reduction in seizures (the primary outcome in the trials). The outcome of 50% responder rate is dependent on a patient's baseline seizure frequency and in a less severe population is of doubtful clinical relevance. However, although an outcome in epilepsy trials that is potentially more patient-relevant is the proportion of patients achieving a particular threshold such as, proportion of seizure-free patients), the PBAC recognised that in patients with intractable epilepsy, a 50% reduction in seizures was likely to be clinically important. Further, it would be unlikely for such patients to be seizure-free. Although an incremental cost-effectiveness ratio expressed in terms of QALYs gained was not provided in the submission, the PBAC considered that if the ICER per 50% responder were to be quality-adjusted, the resulting cost per QALY would most likely be within an acceptable range.

Recommendation:

LACOSAMIDE, tablets, 50 mg, 100 mg, 150 mg and 200 mg,14 tablet packs of 100 mg and 150 mg tablets, and oral solution 15 mg per mL, 465 mL

Restriction: <u>Authority Required</u>

Treatment, initiated by a neurologist, in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs in a patient aged 16 years or older with intractable epilepsy.

A patient must have trialled and failed to achieve satisfactory seizure control with:
(i) at least one first-line anti-epileptic agent; and
(ii) at least two second-line adjunctive anti-epileptic agents.

Continuing treatment, in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, of partial

epileptic seizures in a patient aged 16 years or older, who has previously been treated with PBS-subsidised lacosamide.

NOTE:
No applications for increased maximum quantities will be authorised for the 56 tablet packs of the 150 mg and 200 mg strengths.

Maximum quantity:	14	(50 mg)
	‡1	(100 mg (14) and 150 mg (14))
	56	(100 mg, 150 mg and 200 mg)
	1	(15 mg per mL)
Repeats:	1	(50 mg, 100 mg (14) and 150 mg (14))
	5	(100 mg, 150 mg, 200 mg and 15 mg per mL)

13. Context for Decision

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

14. Sponsor's Comment

The Sponsor has no comment.