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 2012

1. Purpose of Application

The submission sought the following changes:
1) Removal of the requirement in the continuation rule that patients be maintained on two or more other anti-epileptic drugs (AEDs) in combination with lacosamide;
2) Removal of reference to "…second line adjunctive agent…" from the restriction wording;
3) Changing the current Authority Required listing to Authority Required (Streamlined); and
4) Removal of the current Risk Share Arrangement.

2. Background

The PBAC has previously considered submissions for lacosamide.

In November 2009, the PBAC recommended listing lacosamide as an Authority required benefit for 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.

See lacosamide's November 2009 Public Summary Document for further details.

In November 2011, the PBAC rejected a submission seeking 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 (i.e. second line treatment).

See lacosamide's November 2011 Public Summary Document for further details.

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)
At initiation, in combination with two or more anti-epileptic drugs for the treatment of partial onset seizures and secondarily generalised seizures, in a patient with drug resistant epilepsy, aged 16 years or older.

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

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 lacosamide would be add-on treatment, in combination with two or more AEDs, for patients with partial epilepsy.

6. Comparator

The submission nominated topiramate as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission was based on an indirect comparison using three head-to-head randomised trials of lacosamide versus placebo and 10 head-to-head randomised trials of topiramate versus placebo. The three lacosamide trials (SP667, SP754, SP755) were the same trials presented in the two previous lacosamide submissions.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Lacosamide versus placebo		
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
Topiramate vs. placebo		
Ben-Menachem, E et al.	Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures.	*Epilepsia* (1996); 37(6): 539-543

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Faught, E et al.	Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages.	*Neurology* (1996); 46(6): 1684-1690
Guberman, A et al.	Low-dose topiramate in adults with treatment-resistant partial-onset seizures.	*Acta Neurologica Scandinavica* (2002); 106(4): 183-189
Korean Topiramate Study Group	Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial	*Epilepsia* (1999); 40(12):1767–74
Privitera, M et al.	Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600 mg, 800 mg, and 1,000-mg daily dosages.	*Neurology* (1996); 46(6): 1678-1683
Rosenfeld, W et al.	Placebo-controlled trial of topiramate as adjunctive therapy to carbamazepine or phenytoin for partial-onset seizures.	*Epilepsia* (1996); 37(5):153
Sharief, M et al.	Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy.	*Epilepsy Research* (1996); 25(3): 217-224
Tassinari, C et al.	Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy.	*Epilepsia* (1996); 37(8): 763-768
Yen, D et al.	A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy.	*Epilepsia* (2000); 41(9): 1162-1166
Zhang, L et al.	Topiramate as an adjunctive treatment for refractory partial epilepsy in the elderly.	*Journal of International Medical Research* 2001; 39(2): 408-415

8. Results of Trials

The table below summarises the main results of the indirect comparison of lacosamide and topiramate for 50% responder rate and withdrawal from treatment, the efficacy outcomes presented by the submission. The number of patients in each of the set of trials is included in the table below. Statistically significant results of the indirect comparisons are provided in bold text.

Summary of indirect comparison of lacosamide and topiramate – 50% responder rate

Outcome	Lacosamide vs. placebo	Topiramate vs. placebo	Indirect comparison
50% responder rate –subgroup analysis (N=658 for lacosamide and 971 for topiramate)			
Risk difference	0.18 (0.11, 0.26)	0.30 (0.24, 0.36)	**-0.12 (-0.22, -0.02)**
Relative risk	1.90 (1.39, 2.59)	3.12 (2.06, 4.72)	0.61 (0.36, 1.02)
50% responder rate – full analysis set (N=1092 for lacosamide and 1312 for topiramate)			
Risk difference	0.15 (0.10, 0.21)	0.31 (0.27, 0.36)	**-0.16 (-0.23, -0.09)**
Relative risk	1.65 (1.33, 2.04)	3.14 (2.30, 4.30)	**0.53 (0.36, 0.77)**
Treatment withdrawals – subgroup analysis (N=658 for lacosamide and 971 for topiramate)			
Risk difference	0.09 (0.03, 0.15)	0.10 (0.06, 0.14)	-0.01 (-0.09, 0.06)
Relative risk	1.78 (1.17, 2.71)	2.19 (1.41, 3.39)	0.81 (0.44, 1.49)
Treatment withdrawals – full analysis set N=1092 for lacosamide and 1312 for topiramate)			
Risk difference	0.09 (0.04, 0.13)	0.09 (0.03, 0.14)	0.00 (-0.07, 0.07)
Relative risk	1.72 (1.25, 2.37)	2.19 (1.48, 3.24)	0.78 (0.47, 1.30)

For PBAC's view, see Recommendation and Reasons.

The safety evidence presented by the submission was based on the full analysis population. There were few between-group differences observed, with a statistically significantly greater occurrence of dizziness associated with lacosamide compared to topiramate and a statistically significantly greater occurrence of somnolence and thinking abnormally associated with topiramate. Overall, the occurrence of adverse events in the lacosamide and topiramate trials matched what is expected for these drugs, with no unexpected events or between-group differences. The submission did not provide safety evidence relative to the identified post-hoc subgroup.

9. Clinical Claim

The submission described lacosamide as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety compared to topiramate. The PBAC considered this claim was not adequately supported.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis, based on the non-inferiority claim for lacosamide compared to topiramate. The cost-minimisation approach was not valid given that the data presented did not support the claim of non-inferiority.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost savings per year to the Government of less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered that the submission's claim that only an additional 10% of patients would access the listing under the proposed changes was not reasonable. The PBAC recalled

previous DUSC advice that at best 78% of patients currently initiated on lacosamide comply with the current, highly restrictive last-line PBS restriction. The PBAC therefore considered that the number of additional patients who would access lacosamide could be significant.

The PBAC considered also that by removing the requirement under the continuation rule for patients to remain on two other AEDs, this would allow patients to use lacosamide as eventual dual or monotherapy. The PBAC noted the advice of the sponsor's clinical expert during the hearing that the requirement to keep a patient on two additional AEDs in order to preserve their eligibility to access lacosamide was not clinically appropriate. The clinical expert advised that given the substantial burden of treatment-related toxicity from AEDs, it was considered clinically appropriate to remove ineffective AEDs from a patient's regimen as early as practicable. The PBAC considered this reasonable.

The PBAC noted that the submission nominated topiramate as the main comparator. The evidence provided to justify this choice was the advice of the sponsor's Advisory Board (of which nine of the ten members nominated topiramate) and the "SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial." (*Lancet* 369: 1000–1015).

The PBAC did not consider the input of the sponsor's Advisory Board to be convincing. The PBAC noted also that the SANAD study was designed to examine whether new AEDs should be first-line treatment and replace existing first-line agents. The SANAD study was not designed to rank AEDs into second- and subsequent lines of therapy, and this was consistent with the advice of the sponsor's clinical expert, who advised that neurologists, in the context of lacosamides's current PBS restriction and its reference to first and second line therapies, do not consider treatments to be clearly separated into first-, second- or subsequent-line options. Moreover, the PBAC noted that the selection of topiramate as a comparator was complicated by it having multiple indications for epilepsy (beyond the partial onset seizures shared with lacosamide) as well as an indication for migraine. The multiple indications for topiramate are responsible for its relatively high price compared with other AEDs.

The submission presented an indirect comparison using three head-to-head randomised trials of lacosamide versus placebo and 10 head-to-head randomised trials of topiramate versus placebo. The three lacosamide trials (SP667, SP754, SP755) were also presented in the two previous lacosamide submissions. A post-hoc subgroup analysis was used to minimise differences between the lacosamide and topiramate trials, and to form a population more closely aligned with the requested restriction.

The submission claimed non-inferiority to topiramate for key clinical outcomes of 50% reduction in seizure frequency, treatment withdrawal (any cause) and safety. The PBAC noted that the non-inferiority margin of 21-30% was based on guidelines for initial monotherapy, not the requested third-line listing and was therefore inappropriate. In addition, the PBAC noted that results for efficacy (i.e. proportion of patients who were responders) indicated that topiramate is statistically superior to lacosamide. A recent meta-analysis by Costa et al 2011 found that topiramate is the most effective AED, with lacosamide being less efficacious than other AEDs; the PBAC noted, however, that these results were from trials that did not specifically examine add-on therapy in third line. Lastly, the PBAC noted that the absolute risk difference between lacosamide and topiramate for the submission's efficacy

outcome of 50% responder rate that is considered non-inferior (0.16) is similar to the difference found between lacosamide and placebo (0.15). The PBAC therefore considered that the data supporting a claim of non-inferiority to topiramate were not robust.

The submission offered a price reduction based on using the average dose in the Therapeutic Relativity Sheets for topiramate (300 mg/day) and the average from the trials for lacosamide (316 mg/day).

The PBAC noted that this lower price, cost-minimised against topiramate, did not take into account the multiple indications of topiramate, including migraine, primary generalised tonic-clonic epileptic seizures, and seizures of the Lennox-Gastaut syndrome. The PBAC considered that, as the data did not support a claim of non-inferiority with topiramate, a cost-minimisation analysis against topiramate was inappropriate.

The PBAC considered that the estimated number of patients was likely to double despite the submission's claim that the extension to the listing would encompass only the 10% of patients not eligible due to current restrictions. The PBAC noted also that the estimated number of packs dispensed has increased significantly from 2009 submission. The PBAC was therefore concerned with estimated number of packs dispensed.

The PBAC noted that the claimed cost savings are associated with the cost difference between the requested listing and the current listing; however the underlying costs to the PBS remain. Furthermore, projected cost savings in Year 4 and 5 are dependent on the removal of the current risk-sharing arrangement. The PBAC noted that claimed cost savings included a reduction in PBS prescriptions processing, which was not considered appropriate. Estimates calculated during the evaluation indicate a cost of less than $10 million in Year 1, increasing to $10 - $30 million in Year 5, for a total cost of $30 - $60 million for the first 5 years under the requested extension to listing. Overall the PBAC considered the financial risk to the Commonwealth to be substantial. The PBAC noted that the current risk share agreement contained a cap and considered that the removal of the cap would be inappropriate.

The PBAC noted the advice of the sponsor's clinical expert that in practice no one AED was considered to be superior over another by a significant margin. The PBAC concurred with this advice and considered that there was therefore no justification of a price advantage of a comparable margin for lacosamide.

The PBAC therefore rejected the submission's proposed restriction changes to allow the use of lacosamide earlier in the treatment algorithm on the basis that the evidence presented did not support the claim of non-inferior clinical efficacy of lacosamide to topiramate, and on the basis that at the requested price the revised restriction would expose the Commonwealth to significant financial risk.

The PBAC noted that the meta-analysis by Costa et al. (2011) demonstrated the non-inferiority of lacosamide to lamotrigine for safety and efficacy, and therefore considered that as the proposed changes would place lacosamide as a clinical alternative to lamotrigine this would be appropriate at a price equivalent to lamotrigine.

The PBAC therefore recommended that, at the current price and while maintaining the existing risk-share arrangement, the continuing restriction be amended to allow prescribers to

introduce lacosamide in combination with two other AEDs and then to remove the concurrent AEDs as a matter of clinically judgement.

The PBAC also recommended that a Streamlined Authority Required indication would be reasonable while maintaining the existing risk-share arrangement. Any further broadening of the initiation criteria would require a price reduction to a point equivalent with lamotrigine.

Recommendation:
LACOSAMIDE, tablets, 50 mg, 100 mg, 150 mg and 200 mg

Amend the current restriction to the following:

Restriction:

Authority Required *(STREAMLINED)*
Initial treatment of intractable partial epileptic seizures

- Must be treated by a neurologist;
- The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent;
- Patient must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents; and
- Patient must be aged 16 years or older;
- The treatment must be for dose titration purposes (For the 100 mg, 14, and 150 mg, 14, pack sizes only)

Authority Required *(STREAMLINED)*
Continuing treatment of intractable partial epileptic seizures

- Patient must have previously been treated with PBS-subsidised lacosamide; and
- Patient must be aged 16 years or older

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

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 believes that the differences between the current submission's estimates of use, the 2009 submission's estimates of use and the current use of locasamide, were misinterpreted.

The sponsor will continue to work with the PBAC to ensure that treatment alternatives are made available to patients with uncontrolled seizures. The sponsor welcomes changes to the wording of the PBS restriction and would welcome further changes that the sponsor believes would better reflect current clinical practice.