5.09 LACOSAMIDE, Tablet 50 mg, 100 mg, 150 mg, 200 mg, Oral solution 10 mg/mL, 200 mL, Vimpat®, UCB Pharma

1 Purpose of Application

1.1 The purpose of the application was to request an extension to the existing Authority Required (Streamlined) listing for lacosamide for treatment of intractable partial onset epileptic seizures, in combination with two or more anti-epileptic drugs (AEDs), to include patients aged 4 – 15 years whose condition has not been satisfactorily controlled by other AEDs. The submission also sought to list an oral solution formulation of lacosamide.

1.2 The requested listing was on the basis of superior effectiveness compared with placebo (and standard care).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Children aged 4 - 15years with intractable partial onset (focal) epileptic seizures
Intervention	Lacosamide tablets and oral solution
Comparator	Placebo (plus standard of care)
Outcomes	Response rate (≥ 50% reduction in seizures), seizure frequency (partial seizures only), seizure freedom
Clinical claim	Lacosamide is more effective than placebo at decreasing seizure frequency in paediatric patients aged 4 - 15 years with intractable partial onset epileptic seizures. No clinical claim was made in terms of comparative safety.

Source: Table 1-1, p14 of the submission

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LACOSAMIDE				
Oral solution, 10 mg/mL 200 mL	2	2	$[redacted]	Vimpat® UCB Australia Proprietary Limited
Tablet, 50 mg, 14 tablets	4	5	$89.71	
Tablet, 100 mg, 56 tablets	1	5	$168.33	
Tablet, 150 mg, 56 tablets	1	5	$248.85	
Tablet, 200 mg, 56 tablets	1	5	$330.20	

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS indication:	Intractable partial epileptic seizures
Treatment phase:	Initial
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone

	☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, AND The condition 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.

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Continuing
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	Patient must have previously been treated with PBS-subsidised lacosamide.

Name, Restriction, Manner of administration and form	**Max. Qty**	**№.of Rpts**	**Dispensed Price for Max. Qty**	**Proprietary Name and Manufacturer**
LACOSAMIDE				
Tablet, 50 mg, 14 tablets	1	1	$30.74	Vimpat®
Tablet, 100 mg, 14 tablets	1	1	$50.40	UCB Australia Proprietary
Tablet, 150 mg, 14 tablets	1	1	$70.04	Limited

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS indication:	Intractable partial epileptic seizures
Treatment phase:	Initial
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, AND The condition 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 The treatment must be for dose titration purposes

2.1 The proposed restriction did not specify an age criterion. This is not consistent with the TGA approved indication which is for patients aged four years and older. The

submission justified not including an age criterion in the lacosamide restriction based on a similar criterion not being included in the perampanel restriction despite the TGA approved indication being for patients aged 12 years and older.

2.2 The proposed PBS restriction was narrower than the TGA approved indication because it required patients to have failed at least one first-line AED and at least two second-line adjunctive AEDs and start lacosamide in combination with two or more other AEDs (compared with "add-on therapy" in the TGA approved indication). If the restriction remains silent on age, the requested PBS restriction will be broader with respect to age than the TGA approved indication which is explicitly for patients four years and older.

3 Background

Registration status

3.1 Lacosamide was registered by the TGA on 20 July 2009 for add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

3.2 The TGA registered indication for lacosamide was extended on 14 August 2018 to:

"Vimpat (lacosamide) tablets and oral solution are indicated as:

- monotherapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.
- add-on therapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 4 years and older."

3.3 TGA registration was primarily based on extrapolation from adult safety and efficacy data using pharmacokinetic and dose-response studies in children. This was based on TGA, European Medicines Agency (EMA), and United States Food and Drug Administration (FDA) allowing extrapolation of drug efficacy, but not safety, from partial (focal) epilepsy trials in adults to children aged four years and older.

Previous PBAC consideration

3.4 At the November 2009 meeting, the PBAC recommended listing lacosamide tablets for patients aged 16 years and older with intractable partial epileptic seizures, 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 care (November 2009, PBAC Public Summary Document (PSD)). Lacosamide was listed on the PBS on 1 May 2010.

3.5 At the March 2011 PBAC meeting, the PBAC recommended listing lacosamide 15 mg per mL 200 mL oral solution on the PBS on a cost-minimisation basis compared with lacosamide tablets based on the defined daily dose. The formulation was not

PBS-listed and was a different strength to the 10 mg per mL, 200 mL oral solution being considered in this submission.

3.6 In November 2011, the PBAC rejected a submission seeking to extend the lacosamide PBS listing to include the treatment, in combination with a non-sodium channel target AED, of a patient with partial epileptic seizures which are not controlled satisfactorily by other AEDs (i.e. second line treatment).

3.7 In November 2012, the PBAC recommended a submission to amend the continuing restriction to allow prescribers to introduce lacosamide in combination with two other AEDs and then to remove the concurrent AEDs as a matter of clinical judgement, while maintaining the existing risk-share arrangement. The PBAC also recommended that the Authority Required listing be moved to an Authority Required (Streamlined) listing.

3.8 In March 2015, the PBAC recommended the listing of lacosamide 50mg for continuation treatment with a quantity of 56 tablets. Lacosamide 50 mg in a pack of 14 tablets was previously only available for initial treatment on the PBS for titration purposes.

4 Population and disease

4.1 Epilepsy is a neurological condition characterised by recurrent seizures. Partial onset seizures ("focal" seizures) start in one region of the brain but may spread to other regions of the brain. People with epilepsy are at a higher risk of accidents and life-threatening events due to loss of consciousness and falls during seizures, irreversible brain damage, and status epilepticus (prolonged seizures). Children with epilepsy also have a higher risk of death.

4.2 AEDs are used to control seizures in patients with epilepsy. Patients typically start treatment with one AED (monotherapy). Patients may switch to another AED if the first AED does not provide adequate seizure control. If patients have tried several AEDs as monotherapy without good seizure control, two AEDs may be used together as adjunctive treatment. The stepwise approach to treatment in order to obtain seizure control is the same for adults and for children.

4.3 Lacosamide would provide an additional therapeutic option in the management of refractory partial onset epilepsy in patients aged less than 16 years. The ESC noted that there is a high unmet clinical need for additional treatment options in a highly refractory population of patients aged less than 16 years who have failed multiple AEDs and continue to experience seizures.

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

5 Comparator

5.1 The submission nominated placebo plus standard care as the main comparator.

Standard care could include numerous combinations of first and second-line AEDs. The submission's rationale was that there are no other medicines listed on the PBS for children with refractory partial onset epilepsy, and placebo (plus standard care) was considered the appropriate comparator at the November 2009 consideration of lacosamide for the same condition in patients aged 16 years and older. The ESC agreed that standard of care is the most appropriate comparator.

5.2 The submission considered perampanel was not an appropriate comparator because of a lack of clinical data supporting its use in patients aged 4 – 12 years, and the TGA approved indication for patients aged 12 years and older was based on studies with few adolescent participants. Perampanel is indicated for the adjunctive treatment of partial-onset seizures in adult and adolescent patients from 12 years of age with epilepsy. The ESC agreed that perampanel may be an appropriate comparator for the proposed population aged 12 years and older despite the lack of comparative data.

5.3 There are currently numerous medications listed on the PBS that can be prescribed for partial epileptic seizures in children which may also be alternative therapies to lacosamide in clinical practice**.** These could include phenobarbital, phenytoin, tiagabine, perampanel (>12 years) and vigabatrin. The Pre-Sub-Committee Response (PSCR) argued that, as lacosamide is last line pharmacological treatment, no other treatment is an appropriate comparator in this refractory population.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments noted that there is a significant need for an effective anticonvulsant for partial seizures in childhood in Australia.

Clinical trials

6.3 The submission was based on one head-to-head randomised, double-blind, placebo-controlled trial that compared lacosamide to placebo (N = 340) (SP0969) in patients aged 4 years to less than 17 years (referred to as 4 – 16 years for brevity) with uncontrolled partial onset epileptic seizures. The submission also presented several pharmacokinetic studies, 15 supplementary observational studies, and an indirect treatment comparison that compared lacosamide in patients aged 4 – 16 years with lacosamide in patients aged 16 years and older. The randomised trial SP0969 provided more robust evidence on the effectiveness and safety of lacosamide in the proposed

population than the observational studies and pharmacokinetic studies. The pharmacokinetic studies did not report clinical effectiveness or safety outcomes and were evaluated by the TGA.

6.4 The submission also used an indirect treatment comparison to claim that lacosamide provided a similar magnitude of outcomes in patients aged 4 – 15 years compared with patients aged 16 years and older and thereby justify the same price for lacosamide tablets.

6.5 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Lacosamide randomised trial (4 – 16 years)		
SP0969	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Subjects with Epilepsy ≥ 4 Years to <17 Years of Age with Partial Onset Seizures.	June 2017
	Farkas V, Steinborn B *et al*. Efficacy and tolerability of adjunctive lacosamide in children and adolescents with uncontrolled focal seizures: A randomized, double-blind, placebo-controlled trial.	46th Annual Meeting of the Child Neurology Society Annals of Neurology. 2017; 85: s287-290.
	Scheffer I, Bozorg A, *et al*. Tolerability and efficacy of adjunctive lacosamide in children and adolescents with focal seizures in context of presence or absence of sodium-channel blocking AEDs: post-hoc analysis of a randomized, double-blind, placebo-controlled trial.	70th Annual Meeting of the American Academy of Neurology (AAN) Neurology. 2018; 90(15, Supplement 1).
	Steinborn B, Stockis A, *et al*. Lack of pharmacokinetic interaction of lacosamide on carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate and valproic acid in children and adolescents with epilepsy: *Post-hoc* analysis of a randomized, double-blind, placebo-controlled trial.	70th Annual Meeting of the American Academy of Neurology (AAN) Neurology. 2018; 90(15, Supplement 1).
	Yuen N, Taeter C, *et al*. Tolerability of adjunctive lacosamide in paediatric patients aged 4 to <16 years with focal seizures: An interim pooled analysis of data from open-label trials.	32nd International Epilepsy Congress. Epilepsia 2017; 58 (supplement 5):s132.
Lacosamide randomised trials (age ≥ 16 years)		
SP667	A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-Group Trial to Investigate the Efficacy and Safety of SPM 927 (200 mg/day, 400 mg/day, 600 mg/day) as Adjunctive Therapy in Subjects with Partial Seizures with or without Secondary Generalization.	9th March 2005
	Ben-Menachem E, Biton V, Jatuzis D *et a*. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures.	*Epilepsia* 2007; 48(7):1308-17.
SP754	A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (400 and 600 mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization.	13th March 2007
SP755	A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400 mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization.	8th September 2006
	Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M *et al,* Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial.	*Epilepsia* 2009, 50 (3):443-453

Source: Table 2-4, pp42-44 of the submission

AED = Antiepileptic drug; CSR = clinical study report; LCM = lacosamide

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in Economic Evaluation
Lacosamide vs. placebo						
SP0969	340	R, DB, MC 113 days [a]	Low	4 -16 yrs partial-onset seizures uncontrolled after ≥ 2 AEDs	Δ partial seizure frequency, % pts with ≥ 50% partial seizure reduction AEs	No

Source: Compiled during the evaluation from Section 2 of the submission, p47-60; *figures in italics compiled during evaluation*
AE = adverse event; AED = Antiepileptic drug; DB = double blind; MC = multicentre; Pts = patients; R = randomised; yrs = years; Δ = change in;
[a] Median duration of treatment

6.7 The trial recruited patients who had uncontrolled partial seizures after two or more AEDs (sequentially or concurrently) and were on a stable regimen of one to three AEDs. The trial population differed from the proposed PBS population because PBS patients are required to:

- have failed to achieve adequate seizure control after treatment with at least three AEDs including at least two second-line adjunctive agents (compared with uncontrolled partial-onset seizures after ≥ 2 prior AEDs in trial SP0969); and
- have started lacosamide with two or more AEDs including a second line adjunctive AED (compared with 1 – 3 AEDs in trial SP0969 with 17% using only one concomitant AED).

6.8 The trial consisted of an eight-week baseline period, a six-week titration period, followed by a 10-week maintenance where patients used the lacosamide dose they used on the last day of the maintenance period.

Comparative effectiveness

6.9 The primary outcome in trial SP0969 was the change in 28-day partial onset seizure frequency. The results are presented in the table below.

Table 4: Results of change in POS frequency from baseline to maintenance in trial SP0969 (FAS) [a]

Analysis period	Lacosamide (N = 170)			Placebo (N = 170)			LS mean difference (95% CI) [b]	% POS reduction [d]
	mean baseline (SD)	mean end (SD)	LS mean change (SD)	mean baseline (SD)	mean end (SD)	LS mean change (SD)		
Baseline to maintenance	40.40 (76.03)	31.75 (80.87)	8.35 (0.11)	40.34 (107.17)	39.04 (113.06)	12.23 (0.10)	**0.68 [c] (0.56, 0.83)**	**31.7% (16.3, 44.3)**

Source: Table 2-15, p56 of the submission; Table 8-1, p108; Table 8-3, p113 of the study SP0969 CSR
ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; exp = exponential; FAS = Full Analysis Set; LS = least squares; POS = partial onset seizures; SD = standard deviation
[a] FAS included all randomised participants who received at least one dose and had one post-baseline assessment
[b] Analysed using ANCOVA with terms for treatment, pooled centre, and baseline seizure frequency
[c] Difference in LS Mean was calculated as the exp (LS mean lacosamide - LS mean placebo)
[d] Percent reduction over placebo was estimated as 100 x (1 - exp (LS mean lacosamide - LS mean placebo))

6.10 The ESC noted the high mean baseline seizure frequency in the trial population, further highlighting that the significant seizure burden experienced by these patients indicates an unmet clinical need for additional treatment options. The ESC considered the high baseline seizure frequency was reflective of the target PBS population.

6.11 There was a 31.7% (95% CI: 16.3, 44.3) reduction in partial onset seizure frequency from baseline to the end of the maintenance period in the lacosamide arm compared with the placebo arm. The trial SP0969 clinical study report (CSR) reported that the adjusted least square mean change from baseline in seizure frequency per 28 days was 8.35 in the lacosamide group and 12.23 in the placebo group and the least squares mean difference to be 0.68. The least squares mean change in 28-day seizure frequency from baseline for the placebo group differed substantially from the arithmetic difference (8.65 vs. 1.3), suggesting the statistical adjustment increased the difference.

6.12 The submission claimed there was a statistically and clinically relevant reduction in the partial onset seizure frequency per 28 days. The submission did not nominate a minimal clinically important difference (MCID) for change in 28-day partial-onset seizure frequency. Previous PBAC considerations have not used reduction in partial onset seizure frequency per 28 days.

6.13 Table 5 presents the median change in 28-day partial seizure frequency.

Table 5: Results of median change in 28-day partial seizure frequency

Analysis period	Lacosamide (N = 170)			Placebo (N = 170)		
	median baseline (range)	median end (range)	median change (range)	median baseline (range)	median end (range)	median change (range)
Baseline to maintenance [a]	10.41 (1.0, 625.0)	6.36 (0.0, 711.3)	-3.05 (-302.9, 210.4)	8.77 (0.9, 1,084.6)	8.71 (0.0, 1,067.2)	-1.55 (-318.7, 690.0)

Source: Table 2-15, p56 of the submission; Table 8-1, p108 of the study SP0969 CSR
CSR = clinical study report
[a] Primary outcome

6.14 The median unadjusted change from baseline in seizure frequency per 28 days was 3.05 and -1.55 seizures in the lacosamide and placebo groups, respectively. The submission did not present statistical analyses on the change in median 28-day partial seizure frequency.

6.15 Trial SP0969 also reported the responder rate – the proportion of patients with a 50% or greater reduction in 28-day partial onset seizure frequency from baseline to the maintenance period, and the seizure freedom rate. Response rate was the key effectiveness outcome considered by the PBAC in its consideration of brivaracetam (brivaracetam PSDs, July 2016, March 2017, and November 2017), perampanel (perampanel PSD, July 2014), and lacosamide for patients 16 years and older (lacosamide PSD, November 2009). At the November 2009 lacosamide consideration, the PBAC considered 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 the 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 (lacosamide PSD, November 2009). The results are presented in the table below.

Table 6: Results of dichotomous POS seizure outcomes from study SP0969 (FAS)

Outcome	Lacosamide	Placebo	Odds ratio (95% CI)	Unadjusted risk difference (95% CI)
Response rate (≥ 50% POS reduction)	90/170 (53%)	56/168 (33%)	**2.17 (1.39, 3.38)** [a]	**19.6% (9.3, 30.0)**
Seizure freedom	6/152 (4%)	9/154 (6%)	0.66 (0.23, 1.91)	-1.9% (-6.7, 2.9)

Source: Section 2.5.1.2.2, p56; Table 2-16, p57; Table 2-17, p57 of the submission; Table 8-4, p115; Table 8-8, p119; of the study SP0969 CSR; and calculated during the evaluation.
CI = confidence interval; CSR = clinical study report; FAS = Full Analysis Set; POS = partial onset seizures; **bold** = statistically significant
[a] Calculated from a logistic regression model with factors for treatment and pooled centre.

6.16 The proportion of responders was statistically significantly higher in the lacosamide arm than the placebo arm. There was no difference in the proportion of patients who were seizure-free between the two groups.

6.17 Lacosamide appeared to provide an improvement in partial-onset seizure frequency and response rate over placebo. However, the extent of the incremental benefit for the proposed PBS population may be overestimated because the PBS population will have failed treatment with more AEDs (≥ 3 AEDs including two second-line adjunctive AEDs) than the trial population (≥ 2 AEDs). Some previous studies have suggested that patients who have failed several AEDs were less likely to have 50% reduction in seizure frequency or seizure freedom (Schiller and Najjar, 2008; Camfield et al, 1997; Mohanraj and Brodie, 2006). The PSCR noted that in pre-clinical models of epilepsy, lacosamide demonstrated additive or synergistic effects when combined with other AEDs; however, the ESC considered that it was unclear if the efficacy of lacosamide was lower in patients who had failed 2 or more prior AED trials.

6.18 The submission did not present a subgroup analysis of the patients who better reflected the proposed PBS population (failed ≥ 3 AEDs including two second-line adjunctive AEDs), and therefore it is unknown whether patients in trial SP0969 who had failed three or more prior AEDs had similar outcomes to the broader trial population.

6.19 The submission presented an indirect treatment comparison that compared lacosamide in children (trial SP0969) with the lacosamide trials in the population aged 16 years and older (SP667, SP754, SP755) that were used to support the listing of lacosamide for this population.

Table 7: Comparison of responder rate for lacosamide – paediatric vs. adult

Trial type or estimate	Trial	n with event/N (%)	Common reference n with event/N (%)	Treatment effect (OR)	Treatment effect (RR)
Lacosamide (children) vs. placebo	SP0969	90/170 (52.9%)	56/168 (33.3%)	**2.25 (1.15, 3.50)**	**1.59 (1.23, 2.05)**
	Pooled	90/170 (52.9%)	56/168 (33.3%)	**2.25 (1.15, 3.50)**	**1.59 (1.23, 2.05)**
Lacosamide (adults) vs. placebo [a]	Pooled	NR	NR	NR	**1.70 (1.34, 2.15)**
	SP667	63/214 (29.4%)	17/96 (17.7%)	**1.94 (1.06, 3.54)**	**1.66 (1.03, 2.68)**
	SP754	71/201 (35.3%)	18/104 (17.3%)	**2.61 (1.45, 4.68)**	**2.04 (1.29, 3.23)**
	SP755	102/318 (32.1%)	33/159 (20.8%)	**1.80 (1.15, 2.83)**	**1.55 (1.1, 2.18)**
Indirect estimate of effect	–	–	–	NR	0.93 (0.66, 1.33)

Source: Table 2-19, p59 of the submission; indirect treatment comparison workbook
NR = not reported; OR = odds ratio; RR = relative risk; **bold** = statistically significant
[a] All adult patients in the adult trials. The November 2009 lacosamide submission also presented a *post-hoc* subgroup who met the proposed PBS criteria. The indirect treatment comparison with the adult subgroup is presented in Attachment 2.6.

6.20 The submission claimed the indirect treatment comparison demonstrated non-inferiority of the lacosamide benefit in the paediatric population when compared with the adult population and that the point estimates favoured the paediatric population over the adult population. However, the indirect treatment comparison violated the transitivity assumption because it compared a paediatric population treated with lacosamide vs placebo with a population aged 16 years and older treated with lacosamide vs placebo. As the placebo reference arms were not comparable, the indirect comparison was not a reliable way to demonstrate non-inferiority. Despite these limitations, the comparison may still provide PBAC with additional context that the magnitude of benefit from lacosamide treatment in children is likely to be similar to the magnitude of benefit seen in the adult population that has previously been accepted as cost-effective.

Comparative harms

6.21 Table 8 presents the summary of key adverse events (AEs) from the key trial.

Table 8: Summary of key adverse events in the trial SP0969

AE	Lacosamide N = 171	Placebo N = 172	RR (95% CI)
Any TEAE	122/171 (71%)	112/172 (65%)	1.1 (0.95, 1.27)
Drug-related TEAE [a]	58/171 (34%)	42/172 (24%)	1.39 (0.99, 1.94)
Serious TEAEs	11/171 (6%)	13/172 (8%)	0.85 (0.39, 1.85)
Drug-related serious TEAEs	6/171 (4%)	7/172 (4%)	0.86 (0.3, 2.51)
Severe TEAEs	7/171 (4%)	12/172 (7%)	0.59 (0.24, 1.45)
Discontinuations due to TEAEs	7/171 (4%)	12/172 (7%)	0.59 (0.24, 1.45)
Somnolence (drowsiness)	28/171 (16%)	11/172 (6%)	**2.56 (1.32, 4.98)**
Tremor	6/171 (4%)	0/172 (0%)	NE
Diplopia	8/171 (5%)	4/172 (2%)	2.01 (0.62, 6.56)
Decreased appetite	6/171 (4%)	1/172 (1%)	6.04 (0.73, 49.6)
Vertigo	6/171 (4%)	2/172 (1%)	3.02 (0.62, 14.74)
Suicidal ideation	3/171 (2%)	0/172 (0%)	NE
Irritability	4/171 (2%)	1/172 (1%)	4.02 (0.45, 35.63)

Source: Table 2-21, pp60-61 of the submission; Table 9-3, p137, Table 9-14, p163 of the study SP0969 CSR; and calculated during the evaluation; **bold** = statistically significant;
CI = confidence interval; CSR = clinical study report; NE = not estimable; RR = relative risk; TEAE = treatment-emergent adverse event
[a] Drug-related TEAEs were determined as per the investigator.

6.22 The submission considered that the frequency of treatment-emergent AEs was similar between the lacosamide and placebo arms. The submission also noted that fewer lacosamide patients discontinued treatment due to AEs (4% in lacosamide arm vs. 7% in placebo). Patients treated with lacosamide were significantly more likely to experience somnolence.

6.23 The submission considered the AE profile of lacosamide in trial SP0969 was broadly consistent with the studies in patients over 16 years. The TGA approved Product Information and the periodic benefit-risk evaluation report (PBRER) highlighted that decreased appetite, lethargy, abnormal behaviour, aggression, and vomiting were more frequently reported in children.

Benefits/harms

6.24 A summary of the comparative benefits and harms for lacosamide versus placebo (standard of care) is presented in the table below.

Table 9: Summary of comparative benefits and harms for lacosamide and placebo

Trial	Lacosamide n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Lacosamide	Placebo	
Benefits						
Response rate (50% or greater reduction in 28-day partial onset seizure frequency)						
SP0969	90/170	56/168	1.59 (1.23, 2.05)	53	33	0.20 (0.09, 0.3)
Seizure freedom						
SP0969	6/152	9/154	0.68 (0.25, 1.85)	4	6	-0.02 (-0.07, 0.03)
Change in 28-day partial seizure frequency: change from baseline to maintenance period						
	Lacosamide			Placebo		Mean difference*: Lacosamide vs. placebo (95% CI)
	N	Mean Δ baseline frequency	SD	N	Mean Δ baseline frequency	SD	
SP0969	170	8.35	0.11	170	12.23	0.10	0.68 (0.56, 0.83)
Harms						
	Lacosamide n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Lacosamide	Placebo	
Any treatment-emergent adverse event						
SP0969	122/171	112/172	1.10 (0.95, 1.27)	71%	65%	0.06 (-0.04, 0.16)
Somnolence						
SP0969	28/171	11/172	2.56 (1.32, 4.98)	16%	6%	0.10 (0.03, 0.17)

Source: Table 2-15 to 2-17, pp56-57; Table 2-21, pp60-61 of the submission; Table 8-1, p108; Table 8-3, p113, Table 8-4, p115; Table 8-8, p119; Table 9-14, p163 of the study SP0969 CSR; figures in italics calculated during evaluation

CI = confidence interval; CSR = clinical study report; RD = risk difference; RR = risk ratio; SD = standard deviation; Δ = change in

* Median duration of 113 days in trial SP0969

6.25 On the basis of direct evidence presented by the submission, for every 100 patients treated with lacosamide in comparison with placebo and over a median duration of 113 days:

- Approximately 20 additional patients would have a 50% or greater reduction in the frequency of partial onset seizures (per 28-days); and
- Approximately 10 additional patients would feel drowsy (somnolence).

Clinical claim

6.26 The submission described lacosamide as superior in terms of effectiveness compared with placebo based on seizure frequency outcomes. The magnitude of the seizure reduction benefit may be lower in the proposed PBS population because the PBS population will have failed treatment with more AEDs (≥ 3) than the trial population (≥ 2). Failure of more prior AEDs may be a poor prognostic factor for seizure control with a subsequent AED such as lacosamide; however, the ESC considered that the impact of this is unclear.

6.27 The submission did not explicitly make a claim related to the safety of lacosamide. The submission implicitly considered that the safety profile of lacosamide in the proposed population aged 4 – 15 years was acceptable on the basis of a similar safety profile to the population aged over 16 years, with the exception of infection-related AEs. Lacosamide may have worse safety in the population aged 4 - 15 years compared to

adults. Overall, lacosamide is likely to have an inferior safety profile compared with placebo. No safety data was presented in comparison to the >16 year age group.

6.28 The ESC concluded that, while the clinical trial population differed from the PBS population and there was a possible overestimation of the seizure reduction benefit, overall there were no significant clinical concerns identified.

6.29 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.30 The PBAC considered that lacosamide was likely to have inferior safety compared to placebo, but considered that the rate of potential harms were acceptable.

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

Economic analysis

6.31 The submission did not present an economic evaluation that compared lacosamide with placebo. The submission requested the current lacosamide AEMP (for the ≥ 16 years population) for the tablet formulation. This was not consistent with the PBAC guidelines (v5) which request an economic evaluation of substituting the proposed medicine for the main comparator in the context of the listing requested. The submission also requested a [redacted]% price premium above the current per-milligram AEMP for the oral solution.

6.32 The submission's rationale for requesting the same price for the tablet formulation in children as in adults was that lacosamide produced a similar magnitude of outcomes at the recommended dose in both populations. Lacosamide for the population aged 16 and older was recommended for PBS listing on a cost-effectiveness basis over placebo. The indirect treatment comparison presented in the submission of the magnitude of benefit in adults treated with lacosamide compared to children has limitations that may mean the economic approach is not justified. Despite these limitations, the ESC considered that as the claim of similar effectiveness of lacosamide in adults and children appeared to be reasonable, it was reasonable that the submission requested the same price for the tablet formulation. The submission requests a price premium of [redacted]% for the liquid formulation on the basis of unmet need and cost of goods.

6.33 Based on trial evidence, children treated with lacosamide were on a higher average daily dose (equivalent to 332mg per day for the average 41.5kg patient), compared to adult patients (equivalent to 316mg per day).

6.34 During the evaluation the cost per responder analysis from the November 2009 lacosamide submission was updated with data from trial SP0969.

Table 10: Results of the cost per responder analysis over 70 days based on AEMP pricing [a]

Component	Lacosamide	Placebo	Increment
Costs (over 10 weeks) [b]	$	$0	$
≥ 50% responder rate	0.529	0.333	0.196
Incremental cost/extra responder gained			**$**

Source: Constructed during the evaluation using lacosamide November 2009 Section D spreadsheet
AEMP = approved ex-manufacturer price
[a] Trial SP0969 maintenance phase
[b] Cost based on AEMP per milligram lacosamide as per the November 2009 analysis and 45.5% use of oral solution based on distributions from section 4 of the submission.
[c] Mean lacosamide dose of 331.8 mg from trial SP0969 maintenance phase: 8.0 mg/kg/day (average of median maintenance doses) × 41.48 kg = 331.8 mg/day

The redacted table shows incremental costs per extra responder gained of less than $15,000.

6.35 The cost per responder was similar to the cost per responder of less than $15,000 over 12 weeks calculated for the population aged 16 years and older. The ESC considered that the cost per responder analysis constructed during the evaluation was informative and provided some support to the economic approach to the submission, however noted that there may be some uncertainty associated with the responder rate which has implications for the cost per responder estimated.

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

Drug cost/patient/year $ (oral solution); $2,781 (tablets)

6.36 Lacosamide would cost $ per year for a 40 kg patient using the oral solution (higher price per milligram) receiving a daily dose of 250 mg per day (6.3 mg/kg/day) with 100% adherence. This patient would use 23 lacosamide oral solution prescriptions at a DPMQ of $ (co-payment not removed).

6.37 Lacosamide would cost $2,781 per year for a 40 kg patient using the tablets (lower price per milligram) receiving a daily dose of 250 mg per day (6.3 mg/kg/day) with 100% adherence. This patient would use 13 lacosamide 100 mg prescriptions and 6.5 lacosamide 50 mg prescriptions per year at DPMQs of $168.33 and $89.71.

Drug cost/patient/year $ (oral solution); $3,763 (tablets)

6.38 Lacosamide oral solution would cost $ per year for a 41.5 kg patient (mean weight from trials) using the receiving a daily dose of 330 mg per day (8mg/kg/day; average dose in trials) with 100% adherence. This patient would use 30 lacosamide oral solution prescriptions at a DPMQ of $ (co-payment not removed).

6.39 Lacosamide would cost $3,763 per year for a 41.5 kg patient using the tablets (mean weight from trials) receiving a daily dose of 350 mg per day (8 mg/kg/day; average dose in trials) with 100% adherence. This patient would use 6.5 lacosamide 200 mg prescriptions per year and 6.5 lacosamide 150 mg prescriptions per year at DPMQs of $330.20 and $248.20, respectively (co-payment not removed).

Estimated PBS usage and financial implications

6.40 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate usage and financial implications.

6.41 The submission estimated that 0.65% of the population aged 4 – 15 years had epilepsy, of which 57% had partial onset epilepsy and 9.4% would be eligible for fourth line adjunctive treatment. These estimates could not be verified during evaluation as the clinical source was not provided by the submission. The submission assumed 65.5% of patients would use the oral solution and remaining patients would use tablets. The submission may have overestimated the prevalence of epilepsy, and use of the oral solution, because incidence of epilepsy and treated epilepsy increases over childhood (Hollingsworth and Eadie, 2010, Wallace et al, 1998). The daily dose of lacosamide attributed to patients using tablets in the financial estimates was lower than the minimum therapeutic doses in the Product Information (after adherence assumptions). The submission assumed patients weighing 30 – 50 kg and over 50 kg would use a daily dose of 150 mg daily (3.8 mg/kg/day) and 195 mg, respectively. This was lower than the therapeutic dose of 4 mg/kg/day for patients weighing 30 – 50 kg and 200 mg daily for patients weighing over 50 kg.

6.42 The submission did not include the use of titration packs.

Table 11: Estimated use and financial implications

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of lacosamide						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Tables 4-12 to 4-14, p93-94 of the submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

[a] Assuming 65.5% of patients use the oral solution (13.71 scripts/year) and patients using tablets use 9.78 scripts/year and 75% adherence

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year.

6.43 The submission estimated that lacosamide will cost the PBS and RPBS less than $10 million each year to Year 6, resulting in a total cost to the PBS and RPBS of less than $10 million (net of patient co-payments). The net cost to the PBS and RPBS may be higher or lower because:

- the prevalence of epilepsy in children may be lower (decrease cost);
- there is existing use of lacosamide outside of the PBS restriction in patients aged less than 16 years, with PBS prescription claim data provided by the DUSC

secretariat indicating that 105 patients aged 4-15 years received lacosamide in the 2017-18 financial year (decrease cost);

- there may be substitution of the existing use of other AED's outside of their PBS restriction in patients aged less than 16 years (decrease cost);
- the lacosamide dose used by patients using the tablet formulation is likely to be higher than estimated (increase cost); and
- patients starting lacosamide may be older (and heavier) than assumed in the submission because the prevalence of epilepsy increases over childhood and patients require sufficient opportunity to use earlier lines of treatment (increase cost).

6.44 Overall, ESC considered that the financial implication of extending the listing of lacosamide to include children aged 4-15 years is uncertain but likely to be small, particularly as many of these patients are likely to already be accessing PBS-subsidised lacosamide.

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

Financial Management – Risk Sharing Arrangements

6.45 The submission requested that the agreed market estimates for younger patients aged 4 - 12 years, inclusive, are added to the market caps in the current risk share arrangement.

7 PBAC Outcome

7.1 The PBAC recommended an extension to the existing Authority Required (Streamlined) listing for lacosamide, and a new listing for lacosamide oral liquid, for treatment of intractable partial epileptic seizures in combination with two or more anti-epileptic drugs (AEDs), to include patients aged 4 – 15 years. The PBAC were satisfied that lacosamide provides, for some patients, a significant improvement in efficacy over placebo.

7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of lacosamide would be acceptable at an equivalent price to lacosamide for intractable partial seizures in adults.

7.3 The PBAC accepted the clinical place for lacosamide in patients aged 4 – 15 years and noted that there is a high unmet clinical need for additional treatment options in this highly refractory population.

7.4 The PBAC accepted placebo plus standard of care as the appropriate comparator.

7.5 While the population in trial SP0969 was not directly representative of the target PBS population, the PBAC accepted that there was a clinically meaningful reduction in seizure frequency for patients treated with lacosamide in a population with a high

mean baseline seizure rate. The magnitude of clinical response to treatment in patients aged 4 – 15 years was similar to the response seen in the adult population indicating that age is not a treatment effect modifier and further supporting PBAC's conclusion that lacosamide provides a significant improvement in efficacy over placebo.

7.6 The PBAC considered that the comparative harm over placebo was acceptable in this population for whom there are no alternative treatment options.

7.7 The PBAC noted that no economic model was provided in the submission, but accepted that as the clinical benefit reported for patients aged 4 - 15 years were of a similar magnitude to those reported in adults, and the submission proposed the same DPMQ for lacosamide tablets regardless of age, the PBAC concluded that it was reasonable to accept the cost-effectiveness of lacosamide in this expanded population.

7.8 The PBAC considered that the requested [redacted]% price premium for lacosamide oral liquid was appropriate, noting that an oral liquid formulation provides a suitable treatment option in children.

7.9 The PBAC considered that the financial estimates may be slightly overestimated, noting that 105 patients aged 4 - 15 years received lacosamide under the existing PBS listing in the 2017-18 financial year. The PBAC considered that the financial estimates should be reduced by at least 105 patients in year 1 to ensure these patients are not double counted. The PBAC also noted that current utilisation of PBS subsidised lacosamide for intractable partial epileptic seizures in adults is lower than previously estimated, and that a risk sharing arrangement is currently in place with utilisation to date being below current financial caps despite some existing use of lacosamide in patients less than 16 years. As such, the PBAC considered that the extension of the lacosamide listing to include patients aged 4 - 15 years could be mostly incorporated into the existing RSA financial caps. The PBAC considered that a modest increase in the current subsidisation cap may be appropriate by any amount the updated financial estimates exceed the current projected shortfall in the RSA caps.

7.10 The PBAC advised that lacosamide is suitable for prescribing by nurse practitioners for continuing therapy only.

7.11 The PBAC noted that the Early Supply Rule currently applies to the tablet formulation of lacosamide. The PBAC advised that due to variability in dosing, the oral liquid formulation of lacosamide should be exempt from the Early Supply Rule.

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended.

8 Recommended listing

8.1 Amend existing listings as follows:

Item codes 9335H, 9337K, 9338L

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
Tablet 100 mg, 56 tablets	1	5	
Tablet 150 mg, 56 tablets	1	5	Vimpat®
Tablet 200 mg, 56 tablets	1	5	UCB Australia

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS indication:	Intractable partial epileptic seizures
Treatment phase:	Initial
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, AND The condition 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.
Population criteria:	~~Patient must be aged 16 years or older~~
Administrative advice	No application for increased maximum quantities will be authorised for the 56 tablet packs of the 150mg 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.

Item codes 10293R, 9335H, 9337K, 9338L

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
Tablet 50 mg, 14 tablets	4	5	Vimpat® UCB Australia
Tablet 100 mg, 56 tablets	1	5	
Tablet 150 mg, 56 tablets	1	5	
Tablet 200 mg, 56 tablets	1	5	

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Continuing
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously been treated with PBS-subsidised lacosamide.
Population criteria:	~~Patient must be aged 16 years or older~~
Administrative advice	No application for increased maximum quantities will be authorised for the 56 tablet packs of the 150mg 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.

Item codes 9333F, 9334G, 9336J

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
LACOSAMIDE			
Tablet, 50 mg, 14 tablets	1	1	Vimpat®
Tablet, 100 mg, 14 tablets	1	1	UCB Australia Proprietary
Tablet, 150 mg, 14 tablets	1	1	Limited

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS indication:	Intractable partial epileptic seizures
Treatment phase:	Initial
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, AND The condition 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 The treatment must be for dose titration purposes
Population criteria:	~~Patient must be aged 16 years or older~~
Administrative advice:	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.

8.2 Add new item as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
LACOSAMIDE Oral solution 10mg/mL, 200mL	6	5	Vimpat® UCB Australia

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS indication:	Intractable partial epileptic seizures
Treatment phase:	Initial
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, AND The condition 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.
Administrative advice	No application for increased maximum quantities will be authorised for the oral liquid. 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.

Category/Program:	General Schedule, Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Continuing
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously been treated with PBS-subsidised lacosamide.
Administrative advice	No application for increased maximum quantities will be authorised for the oral liquid. Continuing therapy only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.