

**6.05 LACOSAMIDE,  
Tablet 50 mg, 100 mg, 150 mg, 200 mg,  
Oral solution 10 mg per mL, 200 mL  
Vimpat®,  
UCB Australia Proprietary Limited**

**1 Purpose of submission**

1.1 The submission requested that lacosamide is listed on the PBS General Schedule as an Authority Required (STREAMLINED) benefit for patients ( $\geq 4$  years of age) with idiopathic generalised epilepsy (IGE) with primary generalised tonic-clonic seizures (PGTCS).

1.2 Listing was requested on the basis of a cost-minimisation with perampanel (Table 1).

**Table 1: Key components of the clinical issues addressed by the submission**

Component	Description
Population	Adults and children aged $\geq 4$ years with idiopathic generalised epilepsy (IGE) with primary generalised tonic-clonic seizures (PGTCS)
Intervention	Vimpat® (lacosamide) tablets and oral solution; starting dose 100 mg/day (adults and adolescents weighing $\geq 50$ kg) or 2 mg/kg/day (children aged $\geq 4$ years) titrated to a maximum recommended dose of up to 400 mg/day (adults and adolescents weighing $\geq 50$ kg), 12 mg/kg/day (children $< 30$ kg) or 8 mg/kg/day (children 30-50 kg).
Comparator	Fycompa® (perampanel); starting dose 2mg/day titrated to a maintenance dose of up to 8 mg/day in adults and children aged $\geq 12$ years
Outcomes	Key outcomes are: <ul style="list-style-type: none"> <li>• 50% responder rate: percentage of subjects experiencing a 50% or greater reduction in PGTCS frequency relative to baseline.</li> <li>• Percentage change in seizure frequency: median % change from baseline in PGTCS frequency per 28 days during treatment.</li> <li>• Any treatment emergent adverse event (TEAE).</li> <li>• Discontinuation due to a TEAE.</li> <li>• Discontinuation due to a psychiatric TEAE.</li> </ul>
Clinical claim	In adults and children with IGE with PGTCS, lacosamide is non-inferior in terms of effectiveness and safety, compared to perampanel

Source: Table 1.1, p13 of the submission.

**2 Background**

**Registration status**

2.1 The submission was lodged under the TGA/PBAC Parallel Process. The Delegate recommended approval of the proposed indication, considering that sufficient data and justification were provided to support the registration of lacosamide. Approval for registration was granted on 12 March 2021. The TGA indication, with the addition for the treatment of PGTCS in patients with IGE (bolded) is provided below.

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

- monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.
- add-on therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 4 years and older.
- **add-on therapy in the treatment of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy aged 4 years and older.**

### 3 Requested listing

3.1 The requested listing for lacosamide is provided below. Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODCUT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
LACOSAMIDE					
lacosamide 50 mg tablet, 14	9333F	1	14	1	Vimpat
lacosamide 100 mg tablet, 14	9334G	1	14	1	Vimpat
lacosamide 150 mg tablet, 14	9336J	1	14	1	Vimpat
<b>Create new restriction summary number: [NEW] / Treatment of Concept: [NEW]</b>					
<b>Category / Program:</b> General Schedule - Section 85					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners ( <i>Note: the nurse practitioner prescribing icon is currently incorrectly attached to PBS item codes 9333F, 9334G, 9336J as at 1 January 2021</i> )					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – (STREAMLINED) [NEW CODE – NOT 7815]					
<b>Episodicity:</b> [blank]					
<b>Severity:</b> [blank]					
<b>Condition:</b> <i>Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures</i>					
<b>PBS Indication:</b> <i>Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures</i>					
<b>Treatment phase:</b> <del>Initial treatment</del> <i>Dose titration at the start of therapy, during therapy or to gradually cease treatment</i>					
<b>Treatment criteria:</b>					
Must be treated by a neurologist					
<b>OR</b>					
<del>Must be treated by a paediatrician</del>					
<b>Clinical criteria:</b>					
The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs <i>prior to when the drug is/was first commenced</i>					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be <i>(for initiating treatment)/have been (for continuing treatment)</i> in combination with at least one PBS-subsidised anti-epileptic drug <i>at the time the drug is/was first commenced</i>					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be for dose titration purposes					
<b>Population criteria:</b>					

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Patient must be aged 4 years or older
Patient must be aged in line with the age requirements specified in the approved Product Information for this drug
<b>Administrative Advice:</b> Special Pricing Arrangements apply
<b>Administrative Advice:</b> No applications for increased maximum quantities will be authorised.

MEDICINAL PRODUCT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
LACOSAMIDE					
lacosamide 50 mg tablet, 56	10293R	4	56	5	Vimpat
lacosamide 100 mg tablet, 56	9335H	1	56	5	Vimpat
lacosamide 150 mg tablet, 56	9337K	1	56	5	Vimpat
lacosamide 200 mg tablet, 56	9338L	1	56	5	Vimpat
lacosamide 10 mg/mL oral liquid, 200 mL	NEW (not 11694L)	2	2	5	Vimpat

<b>Create new restriction summary number: [NEW] / Treatment of Concept: [NEW]</b>
<b>Category / Program:</b> General Schedule - Section 85
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners - CTO
<b>Restriction:</b> <input checked="" type="checkbox"/> Authority Required – (STREAMLINED) [new code]
<b>PBS Indication:</b> Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures
<b>Treatment phase:</b> Initial treatment [blank]
<b>Treatment criteria:</b>
Must be treated by a neurologist or paediatrician if: (i) initiating treatment, (ii) titrating the dose; or
Must be treated by one of the following prescriber types if continuing established treatment: (i) medical practitioner, (ii) nurse practitioner
<b>OR</b>
<b>Treatment criteria:</b>
Must be treated by a paediatrician
<b>Clinical criteria:</b>
The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs prior to when the drug is/was first commenced
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be (for initiating treatment)/have been (for continuing treatment) in combination with at least one PBS-subsidised anti-epileptic drug at the time the drug is/was first commenced
<b>Population criteria:</b>
Patient must be aged 4 years or older
Patient must be aged in line with the age requirements specified in the approved Product Information for this drug
<b>Administrative Advice:</b> Special Pricing Arrangements apply
Apply the following administrative advice to the oral liquid only:
<b>Administrative Advice:</b> Requests for increases to the maximum quantity/units seeking up to 6 units (corresponding to the Product Information's maximum dose of 400 mg/day for this indication) are permitted.
Apply the following administrative advice to the tablets only:
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> <b>Continuing Therapy Only:</b> 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.

- 3.2 The eligible age range differed between the broader requested restriction for lacosamide (4 years or older) and the current restriction for perampanel (12 years and older). Thus, perampanel may not be the only anti-epileptic drug (AED) to be replaced by lacosamide. The age range requested for lacosamide was consistent with the proposed TGA indication and the lacosamide SP0982 trial population. Of note, the paediatric group (<18 years of age) represented only 20% of the total SP0982 study population. The sponsor emphasised in the pre-PBAC response that the population aged 4–12 years is a small, discreet and highly vulnerable group where there is a significant unmet clinical need for treatment options.
- 3.3 The proposed PBS restriction is narrower than the study population in trial SP0982, as the study included patients who had been maintained on a stable dose of 1 to 2 AEDs (non-benzodiazepine), or 1 benzodiazepine AED with 1 to 2 non-benzodiazepine AEDs, for the previous 28 days. In contrast, the proposed PBS restriction for initial treatment with lacosamide states that it is to be used as add on-therapy in patients who have failed at least 2 prior treatments and remain uncontrolled despite the use of 1 concomitant treatment.
- 3.4 The proposed TGA indication for lacosamide did not have a requirement for patients to have failed multiple AEDs, except for use as an add-on therapy. Thus, the proposed PBS restriction was narrower than the proposed TGA indication because it required patients to have failed to be controlled by at least two AEDs (treatment with lacosamide must be in combination with at least one PBS-subsidised AED or simply as an add-on therapy).
- 3.5 The evaluation noted that more than 50% of the study participants had no lifetime AEDs (defined as AEDs taken by the study participant at some point and stopped at least 28 days prior to Visit 1). The sponsor stated in the Pre-Sub-Committee Response (PSCR) and pre-PBAC response that the interpretation that more than 50% of the study participants had no lifetime AEDs is incorrect, and that it refers to the fact that a patient had not discontinued an AED in the 28 days before entering the trial. The PBAC noted that 45% of patients had at least one prior AED, and all patients were receiving one concomitant AED at trial entry; therefore, 45% of SP0982 trial patients failed to be controlled satisfactorily by at least two anti-epileptic drugs. The PBAC considered that Study SP0982 was adequately reflective of the refractory patient population targeted in the requested restriction.
- 3.6 Compared to the restriction for perampanel, which allows only a neurologist to initiate treatment and adjust dosing, the requested restriction for lacosamide included the additional option for prescribing by a paediatrician (in addition to a neurologist), noting the younger age range included in the target population for lacosamide. The sponsor maintained in the pre-PBAC response that the majority of generalised epilepsy occurs from childhood and patients are generally managed by a paediatrician. The sponsor stated that flexibility is required for prescribing by a neurologist or

paediatrician in the extended age group of 4 years or older. The PBAC agreed with the sponsor that lacosamide should be initiated by either a neurologist or paediatrician.

- 3.7 In the pre-PBAC response, the sponsor proposed a continuing treatment listing for the 50 mg strength with a maximum quantity of up to 4 packs. The Secretariat noted that 50 mg is intended as a titration dose (hence the 14 tablet pack size) and expected there would be very little use as an ongoing maintenance dose. Patients requiring such a low dose on a continuing basis would likely be young children and these patients would likely require the oral liquid presentation, not the tablet presentation. However, it was noted that prescribers are under no obligation to seek the maximum quantity of 4 packs for this strength, therefore the Secretariat advised that such a listing would have utility in that it could be used to facilitate both maintenance treatment and dose titration purposes.
- 3.8 The pricing of the comparator, perampanel 4 mg, 6 mg, 8 mg, 10 mg and 12 mg (for continuing treatment), is subject to a Special Pricing Arrangement (SPA) for the PGTCs indication. The current PBS published prices for perampanel were used in this submission. The submission requested a SPA for lacosamide for initial or continuing therapy.

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

## 4 Population and disease

- 4.1 Worldwide, an estimated 65 million people have epilepsy at any given time and over 250,000 Australians are currently living with epilepsy (Epilepsy Action Australia, 2020).<sup>1</sup> IGE represents 20% to 40% of all epilepsies.<sup>2</sup> Generalised tonic-clonic seizures (GTCS) are one seizure type in IGE and it is estimated that up to 74% of adults and children with IGE include GTCS as one of their seizure types.<sup>3</sup> PGTCs are clinically characterised by a sudden onset with an initial tonic phase, in which patients experience generalised muscle contraction and body stiffening, followed by a clonic phase of rhythmic jerking of the face and limbs.
- 4.2 Classification issues: In the first round TGA clinical evaluation report for lacosamide the clinical evaluator noted that the proposed indication of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy aged 4 years and older referred to:
- Primary: The epilepsy is the condition diagnosed first (not symptomatic of another previously diagnosed condition);

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<sup>1</sup> Epilepsy Action Australia. (2020). About Epilepsy: <https://www.epilepsy.org.au/about-epilepsy/>

<sup>2</sup> Colleran N, Connor TO, Brien JJO. Anti epileptic drug trials for patients with drug resistant idiopathic generalised epilepsy: A meta-analysis. *Seizure*. 2017;51:145-56.

Gupta S, Kwan P, Faught E, Tsong W, Forsythe A, Ryvlin P. Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: an analysis from the National Health and Wellness Survey. *Epilepsy & Behavior*. 2016;55:146-56.

<sup>3</sup> Gupta S, Kwan P, Faught E, Tsong W, Forsythe A, Ryvlin P. Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: an analysis from the National Health and Wellness Survey. *Epilepsy & Behavior*. 2016;55:146-56.

- Generalised tonic-clonic seizures: Bilateral and symmetric generalised motor seizures, that occur in an individual with loss of consciousness. The tonic-clonic seizure consists of a tonic (bilateral increased tone, lasting seconds to minutes) and then a clonic (bilateral sustained rhythmic jerking) phase, typically in this order, or sometimes with variations such as clonic-tonic-clonic and myoclonic-tonic-clonic); and
- Idiopathic: relating to, or denoting any disease or condition which arises spontaneously or for which the cause is unknown.

4.3 The clinical evaluator also stated that

“The proposed indication no longer exists in the presently accepted framework for diagnosing and classifying epilepsy. This creates a paradox: the sponsor, quite correctly, developed lacosamide using the framework available at the time, but in the interim the diagnostic framework has evolved. In the opinion of the Clinical Evaluator, it is possible to map the proposed indication to the currently used diagnostic framework. Experienced clinicians will be able to do this themselves. However, less experienced clinicians may require some guidance in the Product Information to enable this process, especially as, in the course of time, the older diagnostic framework recedes from collective memory”.

4.4 This issue raised by the clinical evaluator also appears to apply to the current PBS PGTCS restriction wording for perampanel.

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

## 5 Comparator

5.1 The submission nominated perampanel as the main comparator. Perampanel is listed on the PBS for the treatment of adults and children aged  $\geq 12$  years with refractory PGTCS whereas the requested listing for lacosamide is the treatment of adults and children aged  $\geq 4$  years.

5.2 While perampanel is a relevant comparator, other AEDs may be substituted by lacosamide for patients in clinical practice who may not be considered suitable for perampanel. The age disparity for eligibility between the current perampanel listing ( $\geq 12$  years) and that requested for lacosamide ( $\geq 4$  years) may be one such factor that may result in the substitution of other AEDs. There are some AEDs that could be used in the proposed target population which may be less costly than the nominated comparator perampanel: lamotrigine, levetiracetam, topiramate and valproate.

5.3 The PBAC noted that while other AEDs could be considered comparators, as well as no treatment (placebo) with respect to last line therapy, it acknowledged the sponsor’s reasoning in the PSCR, that perampanel is the only other treatment specifically reimbursed for the same population, and the current perampanel price is weighted based on a mix of replacing other AEDs and no treatment (placebo)

(paragraph 7.1, perampanel Public Summary Document (PSD), July 2017). The PBAC further noted that both perampanel and lacosamide are likely to be added on top of another AED rather than replace it. The PBAC considered that perampanel is a reasonable comparator.

*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 the National Paediatric Medicines Forum (NPMF) via the Consumer Comments facility on the PBS website. The NPMF described a range of benefits of treatment with lacosamide specifically for paediatric patients, including easy dosing administration in children due to the number of strengths available. The NPMF considered that use of lacosamide would increase patient compliance and in turn reduce the number of presentations to hospitals and general practitioners for uncontrolled seizures. The PBAC noted the advice received from the NPMF was supportive of the evidence provided in the submission.

### ***Clinical trials***

6.3 The submission was based on an indirect comparison of lacosamide versus perampanel via placebo as the common reference. The following trials were presented:

- Study SP0982: a Phase III, randomised, double-blinded, placebo-controlled trial comparing lacosamide with placebo in IGE patients with uncontrolled PGTCs (n=242);
- Study 332: a Phase III, randomised, double-blinded, placebo-controlled trial comparing perampanel in patients with placebo in IGE patients with uncontrolled PGTCs (n=164). This trial was presented in previous perampanel submissions and was considered by the PBAC at the July 2016 and July 2017 meetings.

6.4 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Lacosamide trial</b>		
Study SP0982	<p>Clinical study report.</p> <p>A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy</p> <p>Vossler DG, Knake S, <i>et al.</i> Efficacy and safety of adjunctive Lacosamide in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial.</p> <p>A study to assess the safety and efficacy of lacosamide versus placebo (a pill without active medication) in patients with idiopathic generalised epilepsy who are already taking anti-epileptic medications (VALOR). NCT02408523.</p>	<p>September 2019</p> <p><i>Journal of Neurology, Neurosurgery &amp; Psychiatry</i> 2020; 91:1067-1075</p> <p>May 2020</p>
<b>Perampanel trial</b>		
E2007-G000-332 (Study 332)	<p>French JA, Krauss GL, <i>et al.</i> Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy.</p> <p>An efficacy and safety study of adjunctive perampanel in primary generalized tonic clonic seizures. NCT01393743.</p> <p>Krauss G, Wechsler RT, <i>et al.</i> Relationship between Perampanel exposure, seizure outcomes and treatment-emergent adverse events (TEAEs) in patients with primary generalized tonic-clonic (PGTC) seizures in idiopathic generalized epilepsy (IGE): a randomized, double-blind phase III study. (Abstract)</p> <p>O'Brien TJ, Steinhoff BJ, Yang H, Laurenza A, Patten A, Bibbiani F Efficacy of adjunctive Perampanel in idiopathic generalised epilepsy: subgroup analysis of patients with absence and myoclonic seizures in a double-blind placebo-controlled Phase 3 trial. (Abstract)</p> <p>Wechsler RT, French J, <i>et al.</i> Long-Term safety and efficacy of adjunctive Perampanel in patients with drug-resistant primary generalised tonic-clonic seizures in idiopathic generalised epilepsy: results of an open-label extension. (Abstract)</p>	<p><i>Neurology</i> 2015; 85(11):950-957</p> <p>August 2017</p> <p><i>Epilepsia</i> 2015; 56:132</p> <p><i>European Journal of Neurology</i> 2015; 22:343</p> <p><i>Epilepsia</i> 2016; 57(Suppl 2):168-169</p>

Source: Table 2.3, p35 of the submission.

6.5 The key features of the randomised trials included in the indirect comparison are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias <sup>a</sup>	Patient population	Outcome(s)	Use in modelled evaluation
<b>Lacosamide vs. placebo</b>						
Study SP0982	242 <sup>b</sup>	R, DB, MC Treatment: 24 weeks <sup>c</sup> Follow-up: 4-8 weeks <sup>d</sup>	Low	IGE patients with uncontrolled PGTCS	1) Time to second PGTCS during the 24-week treatment period 2) Seizure freedom for PGTCS during the 24-week treatment period 3) <b>50% and 75% PGTCS responder rates</b> 4) <b>PGTCS frequency per 28 days and changes from baseline</b>	NA
<b>Perampanel vs. placebo</b>						
Study 332	164 <sup>e</sup>	R, DB, MC Treatment: 17 weeks <sup>f</sup> Follow-up: 4 weeks <sup>g</sup>	Low	IGE patients with uncontrolled PGTCS	1) <b>Percent change from baseline in PGTCS frequency per 28 days during titration + maintenance phases</b> 2) <b>50% PGTCS responder rate in the maintenance period relative to baseline</b>	NA

Source: Table compiled during the evaluation, based on information provided in Sections 2.2 to 2.4 of the submission.

DB = double blind; IGE = idiopathic generalised epilepsy; MC = multi-centre; NA = not applicable; OS = overall survival; PFS = progression-free survival; PGTCS = primary generalised tonic-clonic seizure; R = randomised.

<sup>a</sup> Although the risk of bias within each trial was considered low, there was potential for bias in the indirect comparison, given issues with transitivity of the trials

<sup>b</sup> In Study SP0982, a total of 242 patients were randomised. Two randomised patients were subsequently excluded from the Full Analysis Set because they did not have at least one seizure diary assessment during the treatment period

<sup>c</sup> Including 6-week titration phase and 18-week maintenance phase.

<sup>d</sup> Including up to 4-week blinded taper period followed by a 30-day safety follow-up period (required for study participants not participating the extension study EP0012)

<sup>e</sup> In Study 332, a total of 164 patients were randomised. Two randomised patients were subsequently excluded from the Full Analysis Set: one patient in the perampanel arm did not receive treatment and one patient in the placebo arm did not have any post-baseline seizure data.

<sup>f</sup> Including 4-week titration phase and 13-week maintenance phase.

<sup>g</sup> Duration of follow-up for subjects not entering into an optional extension study.

Note: **Bolded outcomes were compared between trials.**

6.6 There are transitivity concerns between the lacosamide (Study SP0982) and perampanel (Study 332) trials involved in the indirect comparison:

- The lacosamide trial included patients aged between 4 years and 12 years (7%); whilst the perampanel trial only enrolled subjects aged 12 years or above. The PSCR stated that the clinical benefits reported for patients aged 4-11 years are of a similar magnitude to those reported in adults and children aged 12-18 and that the total paediatric population efficacy is the same as that in the adult population. The sponsor also stated that the small sample size for 4-11 year old patients is reflective of the difficulty in enrolling younger patients in epilepsy trials, and emphasised the importance of the data with lacosamide in young children due to rarity of such trials.

- The most commonly used background AEDs varied across the trials. Valproate (53% vs. 34%) and levetiracetam (43% vs. 31%) were more frequently used in the lacosamide trial compared with the perampanel trial, respectively; whereas lamotrigine was more frequently used in the perampanel trial (39% vs. 30% in the lacosamide trial).
  - The lacosamide trial had a longer titration period (6 weeks vs. 4 weeks) and maintenance period (18 weeks vs. 13 weeks) than the perampanel trial. The PSCR stated that it is not possible to match the titration schedules for lacosamide and perampanel as their TGA recommended dosing schedules are different. The pre-PBAC response stated that the longer titration and maintenance period in the lacosamide trial biases the analysis against lacosamide, because there is a longer follow-up for a seizure to occur.
- 6.7 The differences across the trials outlined above may be reflected by the discrepancies in the event rates in the common reference arms of the clinical trials (Table 6 and Table 7). However, the direction and magnitude of the overall impact of the identified heterogeneities on the results of indirect comparison of lacosamide and perampanel cannot be reliably determined.
- 6.8 The submission stated that the July 2017 perampanel submission in IGE with PGTCs, which was based on indirect comparisons of perampanel versus lamotrigine and perampanel versus levetiracetam, did not nominate a non-inferiority margin. The lower confidence limit for the odds ratio (OR) of 50% PGTCs responder rate was 0.37 for perampanel versus lamotrigine, and 0.41 for perampanel versus levetiracetam. As the PBAC made a positive recommendation on the listing of perampanel for IGE with PGTCs, the non-inferiority margin was therefore set at 0.37 for the outcome of 50% responder rate in the current submission. However, the PBAC noted its previous decision was made based on the overall consideration of the clinical evidence. The PBAC did not accept the reasoning provided in the submission for the nominated non-inferiority margin.

### ***Comparative effectiveness***

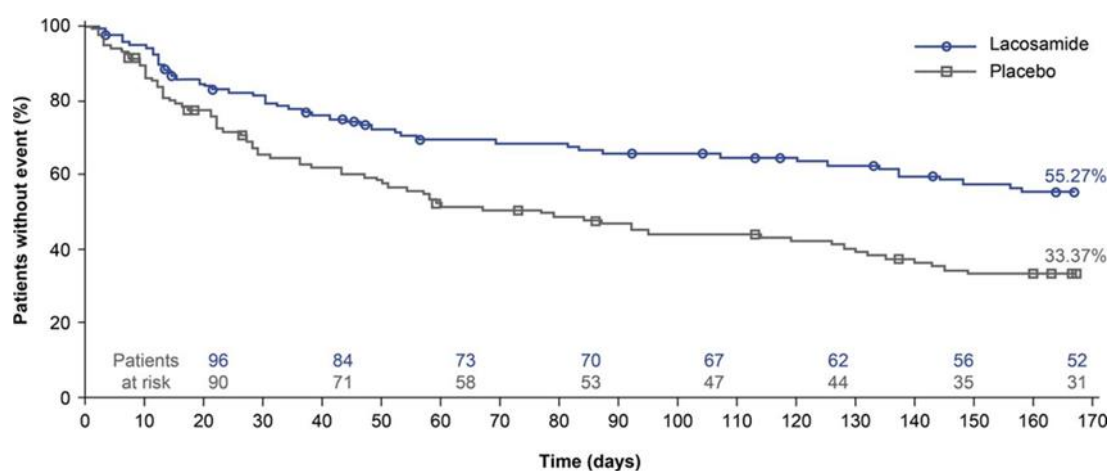
- 6.9 The results of the primary efficacy variable and the main secondary variables in the lacosamide trial are presented in Tables 4 and 5. Figure 1 shows the Kaplan-Meier curves for time to second PGTCs for lacosamide or placebo. Note that results of Study 322 (in terms of percent change of PGTCs frequency per 28 days from baseline and 50% responder rate) were presented in the previous perampanel submissions (Table 3 and Table 4, perampanel PSD, July 2016 PBAC meeting and Table 5 and Table 6, perampanel PSD, July 2017 PBAC meeting).

**Table 4: Analysis of time to second PGTCs (125 events) (FAS) in patients receiving lacosamide or placebo**

Study SP0982	Lacosamide n/N (%)	Placebo n/N (%)	Absolute difference	Hazard ratio (95% CI)
Events	49/118 (41.5%)	76/121 (62.8%)	21.3%	----
Median time to event (days) (95% CI)	NR (144, NR)	77 (49, 128)	NA	0.54 (0.38, 0.77)
<b>KM time to event estimates</b>				
At day 42 (1st 6 weeks)	74.9%	61.9%	13%	----
At day 84 (1st 12 weeks)	66.5%	47.7%	18.8%	----
At day 166 (treatment period)	55.3%	33.4%	21.9%	----

Source: Table 2.23, p77 of the submission and Table 8.1.1 Study SP0982 CSR-Additional tables, p304  
 CI=confidence interval; FAS=Full Analysis Set; HR=hazard ratio; KM=Kaplan-Meier; NA= not applicable; NR= not reached; PGTCs=primary generalised tonic-clonic seizure

**Figure 1: Kaplan-Meier estimates for time to second PGTCs (FAS) in patients receiving lacosamide or placebo**



Source: Figure 2.9 of the submission, p78  
 FAS=Full Analysis Set; PGTCs=primary generalised tonic-clonic seizure.  
 Kaplan-Meier estimates for time to second PGTCs (125 events) (FAS). One patient in the Lacosamide group was randomised after the 125th event and does not appear in this analysis. Symbols represent censored patients (patients who completed the treatment period without having a second PGTC). FAS, full analysis set; PGTCs, primary generalised tonic-clonic seizure.  
 Note: The numbers represent the number of study participants at risk at the start of the final day of each 3-week period.  
 Note: The symbols represent censored study participants.  
 Note: Study Participant SP0982-402-09600 (lacosamide) was randomised after the 125th event and does not appear in this graph.

Table 5: Responder status for reduction in PGTCS frequency (FAS) in patients receiving lacosamide or placebo

SP0982	Lacosamide N=119	Placebo N= 121	Relative risk (95% CI) <sup>a</sup>	Risk difference (95% CI) <sup>a</sup>
<b>Titration period</b>				
50% responder n (%)	65 (54.6)	53 (43.8)	1.25 (0.96, 1.62)	10.8% (-1.8%, 23.4%)
75% responder n (%)	56 (47.1)	44 (36.4)	1.29 (0.96, 1.75)	10.7% (-1.7%, 23.1%)
<b>First 12 weeks of the treatment period<sup>b</sup></b>				
50% responder n (%)	82 (68.9)	63 (52.1)	<b>1.32 (1.07, 1.63)</b>	<b>16.8% (4.7%, 29.0%)</b>
75% responder n (%)	56 (47.1)	37 (30.6)	<b>1.54 (1.11, 2.14)</b>	<b>16.5% (4.3%, 28.6%)</b>
<b>24-weeks treatment period<sup>b</sup></b>				
50% responder n (%)	81 (68.1)	56 (46.3)	<b>1.47 (1.17, 1.85)</b>	<b>21.8% (9.6%, 34.0%)</b>
75% responder n (%)	68 (57.1)	44 (36.4)	<b>1.57 (1.19, 2.08)</b>	<b>20.8% (8.4%, 33.1%)</b>

Source: Table 2.27 of the submission, p83

FAS=Full Analysis Set; PGTCS=primary generalised tonic-clonic seizure

Note: Percentages were based on the number of study participants in the FAS.

Note: A 50% or 75% responder was a study participant experiencing  $\geq 50\%$  or  $\geq 75\%$ , respectively, reduction in PGTCS frequency per 28 days from the combined baseline to the period of interest.

<sup>a</sup> Relative risk and risk difference were calculated during the evaluation using R software.

<sup>b</sup> Including titration period

Statistical significance is indicated by **bold** type.

- 6.10 Overall, the risk of developing a second PGTCS during the 24-week treatment period was significantly lower in the lacosamide arm compared with the placebo arm. The risk of developing a second PGTCS in the lacosamide treatment arm decreased over Days 42, 84, and 166 of the SP0982 study period (Table 4). For the first 12 weeks of treatment, and by the end of the whole treatment period, there were higher rates of patients in the lacosamide treatment arm who experienced  $\geq 50\%$  and  $\geq 75\%$  reductions in PGTCS frequency, compared to placebo (Table 5). Regarding the other secondary efficacy variables, for the 24-week treatment period, there was a higher median percent change from baseline in the “PGTCS frequency per 28 days” in the lacosamide arm compared to the placebo arm (-77.92% and -43.24%, respectively).
- 6.11 Although all the age sub-groups seem to benefit from lacosamide compared to placebo in terms of the primary efficacy variable, the confidence intervals in the paediatric age groups were very wide because of the small number of study participants of these age groups. A similar trend was observed for the secondary efficacy variable (50% responder status). Overall, the evaluation considered the data in the paediatric group, especially for those children aged less than 12 years, should be interpreted with caution.
- 6.12 The results of the indirect comparison of lacosamide with perampanel in terms of 50% PGTCS responder rate are presented in Table 6.

**Table 6: Indirect comparison results for 50% PGTCs responder rate**

	Trial ID	Active n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	Relative risk (95% CI)	Risk difference (95% CI)
Lacosamide vs. placebo	Study SP0982 <sup>a</sup>	81/119 (68.1%)	56/121 (46.3%)	2.47 (1.46, 4.18)	1.47 (1.17, 1.85)	0.22 (0.10, 0.34)
Perampanel vs. placebo	Study 332 <sup>b</sup>	52/81 (64.2%)	32/81 (39.5%)	2.75 (1.45, 5.19)	1.63 (1.19, 2.23)	0.25 (0.10, 0.40)
<b>Indirect estimate of effect adjusted for the common reference (lacosamide vs. perampanel)</b>				0.90 (0.39, 2.06) p=0.805	0.91 (0.61, 1.34) p=0.615	-0.03 (-0.22, 0.16) p=0.768

Source: Table 2.63, p121 of the submission

CI = confidence interval; PGTCs = primary generalised tonic-clonic seizure

Note: Within individual trials, an odds ratio >1, a relative risk > 1 and a risk difference >0 favoured active treatment (for comparison of lacosamide or perampanel vs. placebo). For indirect comparison, an odds ratio <1, a relative risk <1 and a risk difference <0 favoured perampanel (for indirect comparison of lacosamide vs. perampanel).

<sup>a</sup> SP0982: ≥50% reduction in PGTCs frequency/28 days during titration + maintenance phases (Weeks 1-24) vs. baseline

<sup>b</sup> Study 332: ≥50% reduction in PGTCs frequency/28 days during maintenance phase (Weeks 5-17) vs. baseline.

6.13 The 50% PGTCs responder rate was reported during the titration + maintenance phases in Study SP0982 (6 + 18 weeks) and during the maintenance phase in Study 332 (13 weeks). No statistically significant difference was observed between lacosamide and perampanel on the 50% PGTCs responder rate (Table 6). The submission also presented an indirect comparison for the median percent reduction in PGTCs frequency per 28 days from baseline. The indirect comparison showed no statistically significant difference between lacosamide and perampanel (-3.4% (-21.6%, 14.8)).

### **Comparative harms**

6.14 There were numerically more treatment-emergent adverse events (TEAEs), serious TEAEs, severe TEAEs, discontinuation due to TEAEs and drug-related TEAEs in the lacosamide arm of Study SP0982 compared to the placebo arm. However, the risk difference was statistically significant for “any TEAEs” only (risk difference (95% CI): 14.0% (2.9%, 25%)). No deaths due to TEAEs were reported. The most common TEAEs reported in the lacosamide arm (compared to the placebo arm) were nervous system disorders (48% versus 30%), nausea (10% versus 6%), vomiting (6% versus 1%), ear and labyrinth disorders (7% versus 2%). The overall incidence of TEAEs leading to discontinuation was low (6.6%), including 9.1% in the lacosamide arm and 4.1% in the placebo arm. The most common TEAEs leading to lacosamide discontinuation were nervous system disorders (3.3%), psychiatric disorders (1.7%) and investigations abnormalities (1.7%). There was a lower number of study participants with an increase in days with absence seizures (3 and 8 patients) but a higher number with increase in days with myoclonic seizures (6 and 3 patients) in the lacosamide and placebo arms, respectively. A similar trend was observed regarding seizure worsening for days with absence and myoclonic seizures.

6.15 Results of indirect comparison for TEAEs are summarised in Table 7.

Table 7: Indirect comparison of TEAEs

	Trial ID	Active n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	Relative Risk (95% CI)	Risk difference (95% CI)
<b>Any TEAE</b>						
Lacosamide vs. placebo	Study SP0982	96/121 (79.3%)	79/121 (65.3%)	2.04 (1.15, 3.64)	1.22 (1.04, 1.42)	0.14 (0.03, 0.25)
Perampanel vs. placebo	Study 332	67/81 (82.7%)	59/82 (72.0%)	1.87 (0.88, 3.95)	1.15 (0.97, 1.36)	0.11 (-0.02, 0.24)
<b>Indirect estimate of effect adjusted for the common reference (lacosamide vs. perampanel)</b>				1.09 (0.42, 2.82) p=0.852	1.06 (0.84, 1.33) p=0.638	0.03 (-0.14, 0.20) p=0.704
<b>Discontinuation due to a TEAE</b>						
Lacosamide vs. placebo	Study SP0982	11/121 (9.1%)	5/121 (4.1%)	2.32 (0.78, 6.89)	2.20 (0.79, 6.14)	0.05 (-0.01, 0.11)
Perampanel vs. placebo	Study 332	9/81 (11.1%)	5/82 (6.1%)	1.93 (0.62, 6.02)	1.82 (0.64, 5.20)	0.05 (-0.04, 0.14)
<b>Indirect estimate of effect adjusted for the common reference (lacosamide vs. perampanel)</b>				1.21 (0.25, 5.83) p=0.816	1.21 (0.28, 5.24) p=0.801	0.00 (-0.11, 0.11) p=0.992
<b>Discontinuation due to a psychiatric TEAE</b>						
Lacosamide vs. placebo	Study SP0982	2/121 (1.7%)	1/121 (0.8%)	2.02 (0.18, 22.54)	2.00 (0.18, 21.77)	0.01 (-0.02, 0.04)
Perampanel vs. placebo	Study 332	5/81 (6.2%)	3/82 (3.7%)	1.73 (0.40, 7.50)	1.69 (0.42, 6.83)	0.03 (-0.04, 0.09)
<b>Indirect estimate of effect adjusted for the common reference (lacosamide vs. perampanel)</b>				1.16 (0.07, 19.61) p=0.916	1.19 (0.07, 18.85) p=0.904	0.02 (-0.09, 0.06) p=0.646
<b>Serious TEAE<sup>a</sup></b>						
Lacosamide vs. placebo	Study SP0982	8/121 (6.6%)	4/121 (3.3%)	2.07 (0.61, 7.07)	2.00 (0.62, 6.47)	0.03 (-0.02, 0.09)
Perampanel vs. placebo	Study 332	6/81 (7.4%)	7/82 (8.5%)	0.86 (0.28, 2.67)	0.87 (0.30, 2.47)	-0.01 (-0.09, 0.07)
<b>Indirect estimate of effect adjusted for the common reference (lacosamide vs. perampanel)</b>				2.42 (0.45, 12.87)	2.30 (0.48, 11.10)	0.04 (-0.06, 0.14)

Source: Table 2.65, p122 and Table 2.43, p99 of the submission; Table 5, p7 of the Perampanel Public Summary Document, July 2016 PBAC meeting.

CI = confidence interval; TEAEs = treatment-emergent adverse events

Note: Within individual trials, an odds ratio >1, a relative risk > 1 and a risk difference >0 favoured placebo (for comparison of lacosamide or lacosamide vs. placebo). For indirect comparison, an odds ratio >1, a relative risk > 1 and a risk difference >0 favoured perampanel (for indirect comparison of lacosamide vs. perampanel).

<sup>a</sup> Indirect comparisons performed during the evaluation.

6.16 The point estimates of indirect ORs for any TEAEs, serious TEAEs, discontinuation due to TEAEs, and discontinuation due to psychiatric TEAEs all consistently favoured perampanel. The wide confidence intervals for most of the indirect estimates of safety outcomes, which contained clinically meaningful differences, indicated that the indirect comparisons were statistically underpowered.

### Clinical claim

6.17 The submission presented the clinical evidence of lacosamide efficacy and safety (in patients with uncontrolled idiopathic generalised epilepsy with primary generalised tonic-clonic seizures, ≥4 years of age) based on data from Study SP0982.

6.18 The submission described lacosamide as non-inferior to perampanel in terms of both effectiveness and safety. The key issues were:

- The non-inferiority claim relied upon a common reference-adjusted indirect comparison of the lacosamide and perampanel trials where there were differences in the baseline risks of the patients, in the background AEDs in the common reference groups, in the outcome measure and analysis, and in the trial duration. While these differences may be reflected by the observed difference in the number of events in the common reference (placebo) arms, the direction and magnitude of their impact on the indirect comparison cannot be reliably determined (paragraph 6.7).
  - The submission did not provide any clinical justification for the non-inferiority margin nominated in the submission (0.37), based on the lower CI for the OR of 50% PGTCs responder rate for perampanel versus lamotrigine in IGE with PGTCs (paragraph 6.8). A non-inferiority margin was also not nominated for perampanel in IGE with PGTCs (July 2017).
- 6.19 The PBAC and the ESC noted the transitivity concerns raised by the evaluation but acknowledged the challenges in conducting indirect comparisons in this population. The PBAC considered that the claim of non-inferior comparative effectiveness of lacosamide compared to perampanel was reasonable.
- 6.20 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.21 The submission presented a cost-minimisation analysis based on a claim of non-inferiority of lacosamide compared to perampanel.
- 6.22 The equi-effective doses were estimated as a daily dose relativity of lacosamide to perampanel of 50:1. The submission claimed that equi-effective doses were derived from respective Australian PI's, data from clinical trials, and PBS usage statistics. Twice-a-day dosing of lacosamide 50 mg, 100 mg, 150 mg and 200 mg is equal to once daily dosing of perampanel 2 mg, 4 mg, 6 mg and 8, 10, 12 mg, respectively. The proposed equi-effective doses in the submission are primarily based on the Therapeutic Relativity Sheet equi-effective doses for lacosamide and perampanel in partial onset seizures POS.<sup>4</sup>
- 6.23 The cost-minimisation analysis, based on the published approved ex-manufacturer price (AEMP) for perampanel, is presented in Table 8. The proposed listing the oral solution was requested at the same price as the current PBS listing of lacosamide oral solution for POS, and is therefore not included in the table.

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<sup>4</sup> See <https://www.pbs.gov.au/pbs/industry/pricing/pbs-items/therapeutic-relativity-sheets#N03> and paragraph 6.20, perampanel, July 2014 PSD.

**Table 8: Proposed cost-minimised prices (published ex-manufacturer)**

Lacosamide				Perampanel			
Strength	Pricing Quantity	Cost minimised EMP	Daily cost of treatment	Strength	Pricing Quantity	Published AEMP	Daily cost of treatment
50 mg (14 or 56 units)	14	\$18.28	\$2.61	2 mg (14 units)	7	\$18.28	\$2.61
100 mg (14 or 56 units)	14	\$36.56	\$5.22	4 mg (28 units)	28	\$146.22 <sup>a</sup>	\$5.22
150 mg (14 or 56 units)	14	\$54.83	\$7.83	6 mg (28 units)	28	\$219.34 <sup>a</sup>	\$7.83
200 mg (56 units)	56	\$292.42	\$10.44	8 mg (28 units)	28	\$292.42 <sup>b</sup>	\$10.44
200 mg (56 units)	56	\$292.42	\$10.44	10 mg (28 units)	28	\$292.42 <sup>b</sup>	\$10.44
200 mg (56 units)	56	\$292.42	\$10.44	12 mg (28 units)	28	\$292.42 <sup>b</sup>	\$10.44

Source: Table 3.3, p141 of the submission

AEMP = approved ex-manufacturer price; EMP = ex-manufacturer price

<sup>a</sup> Special Pricing Arrangement applies, which was not acknowledged by the submission.

<sup>b</sup> Special Pricing Arrangement applies.

- 6.24 The sponsor acknowledged the special pricing arrangements (SPA) for perampanel 8 mg, 10 mg and 12 mg only. However, the SPA applies to all perampanel strengths for continuing treatment, including 4 mg and 6 mg. There is no SPA for the treatment initiation dosage, perampanel 2 mg. The sponsor requested a SPA for lacosamide for initial and continuing treatment.
- 6.25 The cost-minimisation approach established that the cost per patient for treatment with lacosamide would be no more than the cost per patient of perampanel (see Drug cost/per patient/per year). The cost per patient takes into account the equi-effective doses of lacosamide and perampanel based on dose relativity of 50:1. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.
- 6.26 A different economic analysis could be performed for children aged 4-11 years. This population is not eligible for perampanel therefore, perampanel is not a comparator to lacosamide in this population, and the cost-minimisation is not applicable. The sponsor stated in the PSCR that the requested listing is for patients who are refractory to other treatment options evidenced as continued seizures, and the clinical evidence demonstrates that lacosamide is as effective in seizure control for this younger age group as the older patients. The sponsor stated that the submission proposed the same DPMQ for lacosamide tablets regardless of age, and it is reasonable to accept the cost-effectiveness of lacosamide in this slightly expanded paediatric population in whom there remains a high clinical need. The ESC considered that a cost utility analysis in this population is unlikely to be informative.

**Drug cost/patient/year \$4,398 (200 mg tablets)**

- 6.27 Lacosamide would cost \$4,398 per year for a patient receiving a daily dose of 400 mg per day with 100% adherence (same cost as for perampanel 8 mg once daily).

### Estimated PBS usage & financial implications

- 6.28 This submission was not considered by DUSC.
- 6.29 The submission presented a mixed epidemiological and market share approach to estimate the financial impact of extending the current PBS listing of lacosamide to include patients aged from 4 years old with IGE and PGTCs who have failed treatment with at least two AEDs. An epidemiological approach was used to estimate the number of patients aged between 4 and 11 years and a market share approach was used to determine the number of scripts for patients aged 12 years and above. In addition, the submission used an epidemiological approach to estimate the current number of eligible patients to compare with the currently treated patients and forecast uptake for patients aged between 4 and 11 years. The use of a mixed approach is reasonable in this circumstance.
- 6.30 The submission estimated the net impact to the PBS/RPBS to be low (Table 9) and expected it to be reduced with further price reductions of lacosamide. A large proportion of this increase would be due to the paediatric patients who would be expected to use the lacosamide oral liquid, which would incur a proportionally larger cost.

**Table 9: Estimated use and financial implications using published prices**

	2021	2022	2023	2024	2025	2026
<b>Estimated extent of use</b>						
Total number of patients treated <sup>a</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed <sup>a</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of lacosamide</b>						
Cost to PBS/RPBS less copayments	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
<b>Estimated financial implications for perampanel</b>						
Cost to PBS/RPBS less copayments	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>

Source: Compiled during evaluation using Tables 4.2.4 p85, Table 4.2.6, p86 and Table 4.4.1, p90 of the submission

<sup>a</sup> The total number of the patients is calculated during the evaluation by adding the approximate number of patients ≥12 years (which is calculated by dividing estimated annual scripts in Table 4.8, p149 of the submission by 13), and the number estimated paediatric patients aged 4-11 years (Table 4.4, p147).

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

- 6.31 A proportion of lacosamide use will be in patients aged 4-11 years; perampanel is not listed for this population and will not be substituted, resulting in a net financial cost to the PBS/RPBS. The sponsor stated in the PSCR that a small net cost can be expected for this population of < 500 to < 500 patients per year (Years 1 to 6, respectively), totalling one third (33%) of all lacosamide scripts.
- 6.32 The submission estimated that 0.40% of the population aged 4 – 11 years had epilepsy, of which 18% had IGE, 66.7% with PGTCs and 12.1% would be eligible for drug-

refractory adjunctive treatment. The submission assumed 15% of patients would use the oral solution (which was 65.5% for lacosamide POS) and remaining patients would use tablets. There were uncertainties in the estimation of prevalence of epilepsy, proportion of patients with IGE, IGE with PGTCS, and refractory patients, which the submission addressed by sensitivity analysis. However, the uptake rate is the major source of uncertainty, since this assumption is based on perampanel PGTCS uptake rate in 2 full years (24%).

### **Financial Management – Risk Sharing Arrangements**

- 6.33 The submission did not propose any RSA. The RSA in place for the nominated comparator, perampanel, for the treatment of IGE with PGTCS (paragraph 6.63, perampanel PSD, July 2017) was not acknowledged in the submission.
- 6.34 Lacosamide is already listed for the treatment of intractable partial epileptic seizures and there is a price-volume based RSA in place for lacosamide, in conjunction with brivaracetam and perampanel, for this indication.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of lacosamide for the treatment of patients with idiopathic generalised epilepsy (IGE) with primary generalised tonic-clonic seizures (PGTCS). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of lacosamide would be acceptable if it were cost-minimised against perampanel.
- 7.2 The PBAC considered that there is an unmet clinical need in this patient population, and noted that up to 30% of patients who are treated with currently available AEDs have insufficient seizure control or unacceptable drug tolerability. The PBAC acknowledged the Consumer Comment from the National Paediatric Medicines Forum, that the PBS listing of lacosamide would particularly benefit paediatric patients by allowing easy dosing administration in children due to the number of strengths available.
- 7.3 The PBAC noted the accepted framework for diagnosing and classifying epilepsy has evolved and noted that the sponsor is committed to working with the Department of Health to ensure terminology used in the restriction wording appropriately reflects accepted clinical nomenclature and the intended use of these medicines.
- 7.4 The PBAC considered that the lacosamide restriction should specify initiation by either a neurologist or paediatrician, rather than a neurologist only, to allow prescribing flexibility in generalised epilepsy, which often occurs from childhood.
- 7.5 The proposed clinical place of lacosamide was accepted by the PBAC as add on-therapy in patients who have failed at least 2 prior treatments and remain uncontrolled despite the use of 1 concomitant treatment. The PBAC considered that

- the lacosamide trial participants were adequately reflective of the refractory patient population targeted in the requested restriction.
- 7.6 The PBAC noted that while lacosamide may substitute for other AEDs or placebo in clinical practice, perampanel was the appropriate main comparator as it was most likely to be replaced.
  - 7.7 The PBAC noted the transitivity concerns between the lacosamide and perampanel trials involved in the indirect comparison, in terms of patient age ( $\geq 4$  years for lacosamide and  $\geq 12$  years for perampanel), background AEDs, and titration/maintenance periods. However, the PBAC acknowledged the challenges in conducting indirect comparisons in this population in terms of both the therapeutic area and the difficulty of enrolling younger patients in epilepsy trials.
  - 7.8 The PBAC noted significantly more patients treated with lacosamide achieved a 50% reduction in PGTCs frequency over 24 weeks compared to patients treated with placebo [risk difference 21.8% (95% CI: 9.6, 34.0)]. The PBAC noted that no statistically significant differences were observed between lacosamide and perampanel in the indirect comparison for the 50% PGTCs responder rate. The PBAC noted the point estimate for all effect measures favoured perampanel and the confidence intervals were wide. However, the PBAC noted there were transitivity issues between the lacosamide and perampanel trials that may impact on interpretation of the indirect comparison (paragraph 7.7). The PBAC considered that, overall, the claim of non-inferior comparative effectiveness of lacosamide compared to perampanel was reasonable.
  - 7.9 The PBAC considered lacosamide to be non-inferior to perampanel for comparative safety, noting that serious TEAEs were low in both trials, and no statistical differences were observed between lacosamide and perampanel.
  - 7.10 The PBAC noted the unmet need in this patient population for treatment options, particularly in the 4-11 year old age group, and overall considered the clinical evidence supported listing.
  - 7.11 The cost-minimisation analysis, based on a claim of non-inferiority of lacosamide compared to perampanel, was accepted by the PBAC. The equi-effective doses were estimated as a daily dose relativity of lacosamide to perampanel of 50:1, where twice-a-day dosing of lacosamide 50 mg, 100 mg, 150 mg and 200 mg is equal to once daily dosing of perampanel 2 mg, 4 mg, 6 mg and 8, 10, 12 mg, respectively. While the PBAC noted a different economic analysis could be performed for the 4-11 years age group, it considered a cost-utility analysis would be unlikely to be informative and accepted the same DPMQ for lacosamide regardless of age. The PBAC accepted the same price for lacosamide oral solution as the current PBS listing of lacosamide oral solution for POS.

- 7.12 The epidemiological and market share approach to estimate usage was considered by the PBAC to be reasonable, despite noting that the epidemiological inputs and uptake rate in the population aged 4-11 years were uncertain. The PBAC noted there will be a small financial impact associated with lacosamide usage in the 4-11 years paediatric population, in which perampanel is not listed and will not be substituted.
- 7.13 The PBAC indicated that lacosamide would be required to join the existing RSA with perampanel in IGE with PGTCS.
- 7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because lacosamide is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over perampanel, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines - Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.15 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 Add indication (14229 - idiopathic generalised epilepsy with primary generalised tonic-clonic seizures) as follows:

MEDICINAL PRODUCT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
LACOSAMIDE					
lacosamide 100 mg tablet, 14	9334G	1	14	1	Vimpat
lacosamide 150 mg tablet, 14	9336J	1	14	1	Vimpat
Max Qty multiplier = 1, Repeat increases: nil					
<b>Attach new restriction summary number: [NEW] / Treatment of Concept: [NEW CODE 1]</b>					
<b>Category / Program:</b> General Schedule - Section 85					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [NEW CODE 1 – NOT 7815]					
<b>PBS Indication:</b> Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures					
<b>Treatment phase:</b> Dose titration at the start of therapy, during therapy or to gradually cease treatment					
<b>Treatment criteria:</b>					
Must be treated by a neurologist; or					
Must be treated by a paediatrician					
<b>Clinical criteria:</b>					
The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs prior to when the drug is/was first commenced					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be (for initiating treatment)/have been (for continuing treatment) in combination with at least one PBS-subsidised anti-epileptic drug at the time the drug is/was first commenced					

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<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be for dose titration purposes
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.

MEDICINAL PRODUCT, medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
LACOSAMIDE					
lacosamide 50 mg tablet, 14	10293R	4	56	5	Vimpat
lacosamide 100 mg tablet, 56	9335H	1	56	5	Vimpat
lacosamide 150 mg tablet, 56	9337K	1	56	5	Vimpat
lacosamide 200 mg tablet, 56	9338L	1	56	5	Vimpat
Max Qty multiplier = 1, Repeat increases: nil					
lacosamide 10 mg/mL oral liquid, 200 mL	NEW (not 11694L)	2	2	5	Vimpat
Max Qty multiplier = 3, Repeat increases: nil					

Attach new restriction summary number: [NEW] / Treatment of Concept: [NEW CODE 2]

<b>Concept ID</b>	<b>Category / Program:</b> General Schedule - Section 85
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners - CTO
	<b>Restriction:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [New code 2]
	<b>PBS Indication:</b> Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures
	<b>Treatment phase:</b> [blank]
	<b>Treatment criteria:</b>
	Must be treated by a neurologist; or
	Must be treated by a paediatrician; or
	Patient must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion
	<b>Clinical criteria:</b>
	The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs prior to when the drug is/was first commenced
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be (for initiating treatment)/have been (for continuing treatment) in combination with at least one PBS-subsidised anti-epileptic drug at the time the drug is/was first commenced
	<b>Administrative Advice:</b>
	<b>Continuing Therapy Only:</b> 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.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply
	<i>Apply the following administrative advice to the oral liquid only:</i>
	<b>Administrative Advice:</b> Requests for increases in the maximum quantity (packs) up to 3 times that stated may be authorised.
	<i>Apply the following administrative advice to the tablets only:</i>
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.

	<b>Administrative Advice:</b> For dose titration involving the 100 mg or 150 mg strength, refer to the dose titration listing for these strengths with pack sizes of 14 units. Avoid prescribing a 'broken' quantity under this listing.
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***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

The sponsor had no comment.