

5.08 ESLICARBAZEPINE, Tablet 800 mg, Zebinix[®], Stada Pharmaceuticals Australia Pty Ltd

1 Purpose of submission

- 1.1 The submission requested an Authority Required (STREAMLINED) listing for eslicarbazepine acetate (ESL) for the treatment of intractable partial epileptic seizures, with or without secondary generalised seizures. ESL has not been previously considered by the PBAC. Lacosamide, perampanel and most recently brivaracetam (in 2017) have been PBS-listed for the target population.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis approach versus lacosamide (LAC). The key components of the clinical issues addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adjunctive therapy for patients aged above 16 years, with partial onset seizures (POS) with or without secondary generalisation
Intervention	Eslicarbazepine acetate (ESL) (tradenname: ZEBINIX) 800 mg tablet
Comparator	Lacosamide (LAC)
Outcomes	Patients achieving a $\geq 50\%$ reduction in 28-day seizure frequency, seizure freedom
Clinical claim	In patients aged 16 years and older with treatment-resistant POS with or without secondary generalisations, ESL is non-inferior compared with LAC at reducing seizure frequency and has comparable tolerability

Source: Table 1-1, p 13 of the submission.

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. The sponsor has requested TGA registration of ESL for use as monotherapy in adults, and as adjunctive therapy in adults, adolescents and children aged above 6 years with POS with or without secondary generalisation.
- 2.2 The PBAC noted the TGA Delegate informed the sponsor on 2 March 2021 that the submission did not require consideration by the Advisory Committee on Medicines (ACM).

3 Requested listing

- 3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – March 2021 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty Packs	Max. Qty Units	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ESLICARBAZEPINE eslicarbazepine acetate 200 mg tablet, 60 eslicarbazepine acetate 800 mg tablet, 30	NEW NEW	1 1	60 30	5 5	\$ [REDACTED]	Zebinix Stada Pharmaceuticals Australia Pty Ltd
Category / Program: General Schedule - Section 85						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction: <input checked="" type="checkbox"/> Authority Required – (Streamlined) [8770]						
Episodicity: Partial onset [blank]						
Severity: Intractable [blank]						
Condition: Intractable partial Eepilepsytic seizures						
PBS Indication: Intractable partial onset epileptic seizures						
Treatment phase: Initial treatment						
Treatment criteria: Must be treated by a neurologist						
AND						
Clinical criteria: The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent						
AND						
Clinical criteria: 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: 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.						
Restriction Summary number: 8814 / Treatment of Concept: 8815 (as at 1 January 2021)						
Category / Program: General Schedule - Section 85						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners – CTO						
Restriction: <input checked="" type="checkbox"/> Authority Required (Streamlined) [8815]						
PBS Indication: Intractable partial onset epileptic seizures						
Treatment phase: Continuing treatment						
Treatment criteria: Must be treated by a neurologist						
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.						
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.						

3.2 The ESC noted that the key trial, Study 304, excluded patients who were taking oxcarbazepine. This exclusion is not reflected in the proposed PBS restrictions.

- 3.3 The International League Against Epilepsy guidelines have implemented a new naming convention of ‘focal onset seizures’, and replaced the term ‘intractable’ with ‘drug-resistant’. The submission elected to use the old terminology, which was in use at the time the clinical data and PI for ESL was generated, and is consistent with previous PBAC Public Summary Documents (PSDs). The PBAC noted the accepted framework for diagnosing and classifying epilepsy has evolved and commented that terminology used in the restriction could appropriately reflect accepted clinical nomenclature and the intended use of these medicines.
- 3.4 The ESC noted that the requested restriction is narrower than the proposed TGA indication in terms of age, with the TGA proposed age requirement being at least 6 years of age and the PBS-listing requesting at least 16 years of age, to match the ESL clinical trial patient population. The PBAC noted there is no population criterion included in the PBS restriction for LAC, and the TGA indication for LAC specifies use in children 4 years and above. The Secretariat and the PBAC agreed that an age restriction is not required for ESL.
- 3.5 According to the draft PI, the recommended starting dose of ESL is 400 mg once daily, which should be increased to 800 mg once daily after one to two weeks. Based on individual response, the dose may be increased to 1,200 mg once daily. The submission only requested listing of the higher ESL strength of 800 mg, despite proposing to register a 200 mg strength tablet and outlining dosage adjustments that would result in doses other than 800 mg daily. The Secretariat queried the absence of the 200 mg strength, noting that such a strength would cater for adolescents, or for patients with renal impairment, or any patient requiring a dose other than 800 mg, through avoidance of halving/splitting tablets (which may lead to dose inaccuracy and general inconvenience). This was unaddressed in the sponsor’s pre-subcommittee response and pre-PBAC response.

4 Population and disease

- 4.1 Epilepsy is a derangement of brain function characterised by an enduring predisposition to generate epileptic seizures. It may arise from a variety of genetic, structural, metabolic, immune, and infectious causes. Epileptic seizures are generally characterised as brief episodes of involuntary movement that may involve part of the body (partial) or the entire body (generalised), and may be accompanied by loss of control of bowel or bladder function. Epilepsy is more likely to develop either early or late in life.
- 4.2 Most of the partial epilepsies are the result of a structural brain abnormality, even though this cannot always be identified. If imaging studies are normal, the cause remains unknown. These cases represent most cases of adult-onset epilepsy, although they are common in childhood as well.
- 4.3 There is no cure for epilepsy, however it is considered to be resolved for those who have remained seizure-free for 10 years, with no seizure medicines for the last 5 years,

or for individuals who had an age-dependent epilepsy syndrome but are past the applicable age.

- 4.4 Epilepsy is associated with a substantial burden of disease, with 2-3 times higher rates of mortality than the general population. In addition, there is a burden placed on patients and their families which includes physical and mental aspects, including increases in physical morbidity, as well as physical and mental comorbidities including depression, which has a prevalence of 23% in patients with epilepsy. Achieving successful remission of the disease decreased the risk of depression and anxiety, and improved QoL.¹
- 4.5 In Australia, it is estimated that 142,740 people were living with epilepsy in 2019–20.² Of these cases, about 60% have POS, and 30% of these people³ (about 25,700 people) will have a treatment-resistant form of POS, defined as a failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drugs (AEDs) (whether as monotherapies or in combination) to achieve sustained seizure freedom.⁴
- 4.6 The proposed line of therapy for ESL is ‘third line’, to provide an additional treatment option for patients with treatment-resistant POS. This is best summarised in the proposed clinical management algorithm, provided in Figure 1 below. The submission did not provide a source for this algorithm; the ESC noted it is inconsistent with the Australian eTG Complete Therapeutic Guidelines, which list lacosamide and perampanel as second-line treatments.⁵ The Pre-Sub-Committee Response (PSCR) argued that the clinical algorithm presented in the submission accurately reflects the treatment options consistent with the current PBS restrictions. However, the ESC advised ESL should not be considered a third-line treatment.

¹ Marson AG et. al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007 Mar 24;369(9566):1016-26.

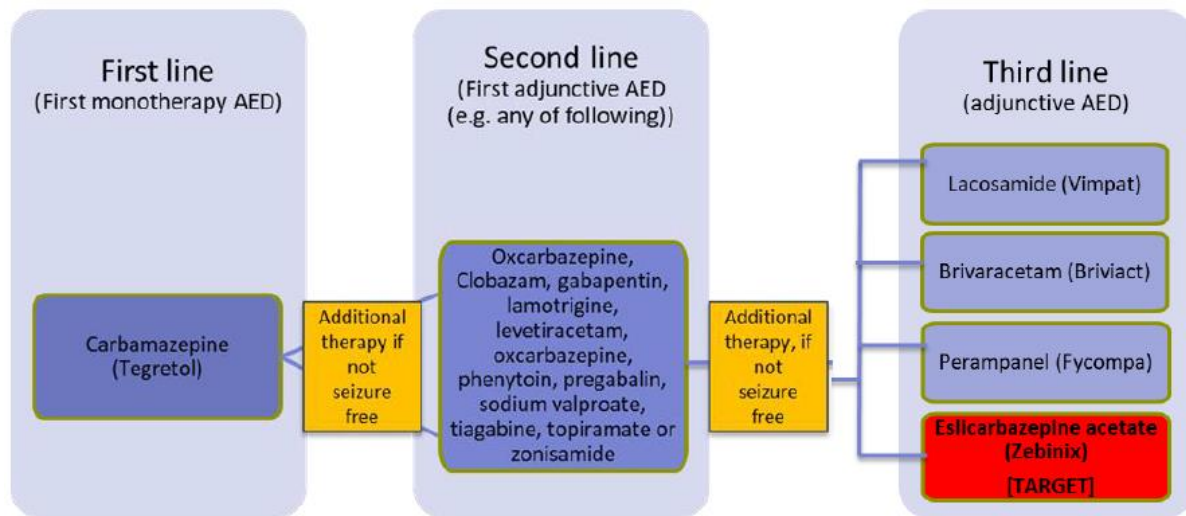
² Epilepsy Australia, 2019. The economic burden of epilepsy in Australia, 2019-2020.

³ National Institute of Neurological Disorders and Stroke, 2020. The Epilepsies and Seizures: Hope Through Research.

⁴ Kwan P, et. al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010 Jun;51(6):1069-77.

⁵ eTG Complete, by Therapeutic Guidelines. Management of focal (partial) epilepsies. Published November 2017.

Figure 1: Proposed clinical management algorithm



Source: Figure 1-7, p 27 of the submission.

- 4.7 ESL is a dibenzazepine which acts through blockade of voltage-gated sodium channels (VGSCs). Dibenzazepines are a well-established family (the carboxamides) of AEDs, which include carbamazepine and oxcarbazepine. ESL is structurally distinct from carbamazepine and oxcarbazepine, meaning that ESL metabolism does not generate epoxide metabolites which have been associated with side effects. However, the ESC commented that as a carboxamide, ESL is associated with adverse events such as sedation, hyponatraemia, as well as rash and severe cutaneous reactions in some Asian populations.
- 4.8 ESL has linear, dose-proportional pharmacokinetics, which means once-daily administration without regard to food is possible. The ESC noted that once daily administration is an advantage for ESL compared to LAC.
- 4.9 While the sponsor stated that drug monitoring is unnecessary, the ESC noted that ESL can induce hepatic CYP3A4, thereby reducing plasma concentrations of other drugs such as hormonal contraceptives, and considered that monitoring for drug interactions is necessary with ESL, as is the case with the other dibenzazepines.
- 4.10 The general therapeutic approach for treatment-resistant POS is to review past treatments, and assess patient compliance and whether the dose or frequency of therapies were adequate. Selection of an anti-seizure drug with a different mechanism of action than one previously tried, and combining drugs of different mechanisms may improve efficacy and tolerability of the regime⁶. No particular second- or third-line treatment is preferred; a meta-analysis of 70 randomised controlled trials (RCTs) of AEDs administered as add-on therapy in patients with treatment-resistant POS found

⁶ Sirven, J.I. Evaluation and management of drug-resistant epilepsy. UpToDate, Wolters Kluwer, Dec 20 2018.

that differences in efficacy were of too small a magnitude to allow conclusions about which antiseizure drug is more effective in this setting⁷. The placement of ‘second’ and ‘third’-line treatments in clinical use may differ from the sponsor’s treatment algorithm.

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

5 Comparator

- 5.1 The submission nominated LAC as the main comparator, as it was the first to gain a PBS listing in the third-line treatment setting, and perampanel and brivaracetam were subsequently listed by presenting a comparison of efficacy and tolerability with LAC, and cost-minimised to LAC. In addition, LAC has the largest market share with approximately 56,396 prescriptions in 2019, compared to 17,640 for perampanel and 8,362 for brivaracetam. A risk-sharing arrangement (RSA) currently applies to lacosamide, brivaracetam and perampanel for intractable partial onset epileptic seizures.
- 5.2 The role of LAC as a third-line therapy is disputed; when the Epilepsy Society of Australia (ESA) advised the PBAC in the brivaracetam March 2017 PSD, it stated that it positioned lacosamide as second-line therapy. This sentiment is reinforced by the Australian eTG Complete Therapeutic Guidelines.⁸ Also, a recent review of the PBS restrictions on AEDs highlighted a difference in international prescribing practices and what it considered were outdated PBS restrictions,⁹ and urged the PBS to review the restrictions on well-tolerated AEDs including lacosamide and perampanel, suggesting that in practice most epileptologists ignore the PBS restrictions and follow the internationally recommended prescribing guidelines. However, consistent with the previous two PBAC recommendations in the third-line setting (perampanel in July 2014 and brivaracetam in November 2017), the PSCR maintained that LAC was the appropriate comparator for the submission, and that subsequent to these decisions, LAC has remained the most used treatment.
- 5.3 The ESC considered that both the proposed third-line therapy setting for ESL and the nominated comparator, LAC, were inappropriate. Of the current third-line therapies, LAC and perampanel both offer a novel drug class unavailable in first- or second-line therapies, which is desirable for patients who were unable to gain control after trying combinations of at least three different treatments from these earlier lines of therapy. In contrast, by the time patients qualify for ESL under the proposed PBS restrictions, they must have either tried and failed another dibenzazepine (such as carbamazepine or oxcarbazepine), or be currently taking one. The ESC considered that clinicians may

⁷ Costa J et. al. Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. *Epilepsia* 2011 Jul;52(7):1280-91.

⁸ eTG Complete, by Therapeutic Guidelines, November 2017. Management of focal (partial) epilepsies.

⁹ Gericke CA, O'Brien T.J. Pharmaceutical Benefits Scheme restrictions on anti-epileptic drug prescribing promote unsafe and outdated practice. *Med J Aust.* 2019 Jul; 211(2):55-57.e1.

be unlikely to forgo the opportunity to add a drug with a novel mechanism of action (such as LAC) in order to either retry a failed drug class or add an additional dibenzazepine to their patients' treatment regime. This particularly applies considering the lack of data suggesting ESL is meaningfully superior to placebo in this population, and thus it is unlikely that LAC will be replaced. The ESC considered a more appropriate comparator for ESL may be the other dibenzazepines.

- 5.4 With reference to the issue of likely prior use of dibenzazepines, the sponsor stated (pre-PBAC response) that the majority of patients (78.6%) in the 304 study had previously received carbamazepine (a dibenzazepine), and 38.9% and 42.4% concomitantly used carbamazepine in the 800 mg and 1,200 mg ESL treatment arms, respectively. The sponsor stated that prior and concomitant use of carbamazepine supported the relevance of ESL treatment for uncontrolled POS in later lines of treatment.
- 5.5 If treatment with ESL is substantially more costly than any of the alternative therapies (LAC, perampanel and brivaracetam, if positioned as a third-line treatment), the PBAC could only recommend listing ESL if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapies (National Health Act 1953, Section 101(3B)).

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 that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission was based on four placebo-controlled RCTs comparing ESL to placebo (301, 302, 303 and 304). Of these, only one, Study 304 aligned with the proposed treatment-resistant POS target population. The pooled results of the ESL Studies 301, 302 and 303 were presented to support the clinical effectiveness of ESL, however the patient population enrolled in these studies had limited prior use of AEDs (92.4% had 0 prior AEDs), and as such was not representative of the target population. Outcomes from Study 304 were compared in an indirect treatment comparison (ITC) to four placebo-controlled RCTs assessing the efficacy and safety of LAC in the treatment-resistant POS population.
- 6.4 Details of the trials presented in the submission are provided in the table below. The PBAC has considered evidence from three of the LAC trials previously (SP667, SP754 and SP755).

Public Summary Document – March 2021 PBAC Meeting

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 304	<p>ClinicalTrials.gov Identifier: NCT00988429: Efficacy and Safety of Eslicarbazepine Acetate (BIA 2-093-304) as Adjunctive Therapy for Refractory Partial Seizures in a Double-blind, Randomised, Placebo-controlled, Parallel-group, Multicentre Trial Protocol Number: BIA-2093-304. Clinical Study Report.</p> <p>Sperling MR, Abou-Khalil B, Harvey J, Rogin JB, Biraben A, Galimberti CA, Kowacs PA, Hong SB, Cheng H, Blum D, Nunes T, Soares-da-Silva P; 304 Study Team. Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: Results of a phase III, double-blind, randomized, placebo-controlled trial.</p>	<p>29 June 2012.</p> <p><i>Epilepsia</i>. 2015 Feb; 56(2):244-53.</p>
SP667	<p>Primary clinical study report - A multicentre, double-blind, randomised, 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. Schwartz Biosciences, Inc</p> <p>Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures</p>	<p>9 March 2005.</p> <p><i>Epilepsia</i> 2007; 48(7): 1308-17.</p>
SP754	<p>Primary clinical study report NCT00136019 - A multicentre, double-blind, randomised, 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. Schwartz Biosciences, Inc</p> <p>Chung S, Sperling MR, Biton V, Krauss G, Hebert D, Rudd GD, Doty P; SP754 Study Group. Lacosamide as adjunctive therapy for partial-onset seizures: a randomised controlled trial.</p>	<p>13 March 2007.</p> <p><i>Epilepsia</i>. 2010; 51(6):958-67.</p>
SP755	<p>Primary clinical study report NCT00220415 - A multicentre, double-blind, randomised, 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. Schwartz Biosciences GmbH.</p> <p>Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, Rosenow F, Doty P, Hebert D and Sullivan T. Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomised controlled trial.</p>	<p>8 September 2006</p> <p><i>Epilepsia</i> 2009; 50 (3):443-453.</p>
EP0008	<p>NCT01710657 – A Trial to Evaluate the Efficacy and Safety of Adjunctive Therapy With Lacosamide in Adults With Partial-Onset Seizures</p> <p>Hong Z, Inoue Y, Liao W, et al. Efficacy and safety of adjunctive lacosamide for the treatment of partial-onset seizures in Chinese and Japanese adults: A randomised, double-blind, placebo-controlled study.</p>	<p>Results posted February 2015.</p> <p><i>Epilepsy Res</i>. 2016;127:267-275.</p>

Source: Modified from Table 2-6, pp 38-39 of the submission.
SPM927 = lacosamide.

6.5 The key features of the RCTs used in the ITC are summarised in Table 3 below.

Public Summary Document – March 2021 PBAC Meeting

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Eslicarbazepine acetate vs placebo					
Study 304	640	R, DB, MC 12 weeks of maintenance treatment	Low	Patients aged ≥ 16 years old with treatment-resistant POS	1) SSF over the maintenance period. 2) ≥ 50% reduction in SSF from baseline to maintenance. 3) Seizure freedom
Lacosamide vs placebo					
SP667	312 ^a	R, DB, MC 12 weeks of maintenance treatment	Low	Patients aged 18-65 years old with treatment-resistant POS	1) Reduction in seizure frequency from baseline to maintenance 2) ≥50% reduction in seizure frequency from baseline to maintenance 3) Seizure freedom
SP754	308 [†]	R, DB, MC 12 weeks of maintenance treatment	Low	Patients aged 16-70 years old with treatment-resistant POS	Same as SP667
SP755	485	R, DB, MC 12 weeks of maintenance treatment	Low	Patients aged 16-70 years old with treatment-resistant POS	Same as SP667
EP0008	548	R, DB, MC 12 weeks of maintenance treatment	Low	Patients aged 16-70 years old with treatment-resistant POS	1) Change in POS frequency from baseline to maintenance. 2) ≥ 50% reduction in POS frequency from baseline to maintenance. 3) Seizure freedom

Source: Modified from Table 2-7; Table 2-8, Table 2-9, Table 2-10 and Table 2-11, pp 43 – 46 of the submission.

DB = double blind; MC = multi-centre; POS = partial onset seizures; R = randomised; SSF = standardised seizure frequency.

^a Patients from the lacosamide 600 mg group have been excluded.

6.6 The risk of bias in Study 304 was considered low, however a high rate of discontinuations and missing data in the ESL 1,200 mg group compared to the other two groups was noted. From the safety population, 32.4% of the patients in the ESL 1,200 mg arm failed to complete the maintenance period, compared to 20% of the 800 mg group and 15.6% of the placebo group. This was primarily due to discontinuations, and the recording of ‘incomplete data’. Key reasons are summarised in Table 4 below.

Table 4: Summary of patient flow and reasons for discontinuation in Study 304

Parameter	Placebo	ESL 800 mg	ESL 1,200 mg
	n (% of patients randomised)		
Randomised	226 (100)	216 (100)	211 (100)
Randomised and received at least 1 dose of study drug (safety population)	224 (99.1)	216 (100)	210 (99.5)
ITT population	220 (97.3)	215 (99.5)	205 (97.2)
Entered maintenance period	212 (93.8)	201 (93.1)	184 (87.2)
Completed the double-blind period	189 (83.6)	173 (80.1)	142 (67.3)
Patients listed as 'not evaluable' ^a in the efficacy outcomes	8 (3.5)	15 (6.8)	22 (10.4)
Two most common reasons for discontinuation from the double-blind period^b			
Adverse event	9 (4.0)	21 (9.7)	45 (21.3)
Withdrawal by subject	7 (3.1)	7 (3.2)	12 (5.7)

Source: Data extracted from Table 9, p 92 of the Study 304 CSR.

ESL = eslicarbazepine acetate; ITT = intention-to-treat.

^a The "not evaluable" category includes subjects who discontinued during the titration period or who entered the maintenance period but have missing data. The submission was unclear about how these missing data were handled, and sensitivity analyses addressing them could not be located in the CSR.

^b Reasons for discontinuation from the double-blind period include subjects who discontinued from either the titration or maintenance periods. One subject was discontinued in the ESL 1,200 mg group for reason reported as 'lack of efficacy'. This reason on the case report form had been interpreted differently during the study depending on the protocol amendment in effect. Until Protocol Amendment No. 5, "lack of efficacy" required at least a 100% increase in seizure frequency.

Comparative effectiveness

6.7 The primary efficacy analysis of Study 304 was reduction in standardised seizure frequency (SSF), which reached statistical significance in the ESL 1,200 mg group but not in the ESL 800 mg group, as shown in Table 5 below.

Table 5: Primary efficacy analysis for Study 304 (ITT population)

Parameter	Placebo (N = 220)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)
	ANCOVA for SSF per 4 weeks over the 12-week maintenance period LS mean (95% confidence interval); p-value ^a	7.88 (6.98, 8.9)	6.54 (5.77, 7.4); p=0.058; n.s.
Log difference in LS mean (unadjusted 95% CI) SSF	–	-0.18 (-0.34, -0.02)	-0.26 (-0.42, -0.10)
≥ 50% reduction in seizures from baseline to maintenance period, n (%) ^b , Exact 95% CI for percentage of responders; p-value	49 (23.1%) (17.6%, 29.4%)	61 (30.5%) (24.2%, 37.4%); p=0.068	78 (42.6%) (35.4%, 50.1%); p<0.001
Seizure freedom and completed the maintenance period, n (%)	2 (0.9%)	4 (2.0%)	4 (2.2%)
Not evaluable ^c , n (% of ITT population)	8 (3.6%)	15 (7.0%)	22 (10.7%)

Source: Table 2-31 p 71, Table 2-35 pp 74-75 and Table 2-39 p 77 of the submission.

ANCOVA = analysis of covariance; CI = confidence interval; ESL = eslicarbazepine acetate; ITT = intent-to-treat; LS = least square, n.s. = not significant; SSF = standardised seizure frequency.

^a p-value for comparison to placebo.

^b Percentages calculated based on the number of subjects with non-missing data in the ITT population in each treatment group. If the full ITT population were used instead, the percentages would be: 22.3% (placebo), 28.4% (ESL 800 mg), and 38.0% (ESL 1,200 mg).

^c The Not Evaluable category includes subjects who discontinued during the titration period or who entered the maintenance period but have missing data. The submission was unclear about how these missing data were handled, and sensitivity analyses addressing them could not be located in the CSR.

Bold indicates statistically significant results.

- 6.8 The ‘Not Evaluable’ patients were removed from the ITC calculations, which had the effect of increasing the apparent efficacy of ESL; for example, the percentage of patients in the ESL 1,200 mg group with a ≥50% reduction in seizure frequency was 38% if the ITT population is used, and 43% after the ‘not evaluable’ patients were deducted from the calculation. Sensitivity analyses regarding the handling of the ‘not evaluable’ patients could not be located in the submission.
- 6.9 The submission nominated a minimal clinically important difference (MCID) of a decrease in seizure frequency of 28-30%, based on the assumption that a 1-unit decrease in the Clinical Global Impression of Improvement (CGI-I) scale was clinically meaningful, and applying this difference to the pooled efficacy curves of studies 301, 302 and 303. The elected MCID was poorly justified; furthermore, the results from Study 304 did not meet the nominated MCID for either the 800 mg or 1,200 mg dose.
- 6.10 The efficacy data from the four LAC trials used in the ITC are summarised in Table 6 below.

Table 6: Summary of results of the individual LAC versus placebo trials – overall patient population

Trial ID	≥50% Reduction in 28-day seizure frequency: n with event/N (%)		
	Placebo	Lacosamide 200 mg	Lacosamide 400 mg
SP667	21 /96 (22.00%)	35/107 (32.71%)	44 /107 (41.12%)
SP755	41 /159 (25.80%)	56/160 (35.00%)	64 /158 (40.50%)
SP754	19/104 (18.30%)	N/A	77 /201 (38.31%)
EP0008	36/183 (19.7%)	70/182 (38.5%)	88/179 (49.2%)
Seizure freedom: n with event/N (%)			
SP667	0 /96 (0%)	1 / 107 (0.93%)	5 /107 (4.67%)
SP755	3 /143 (2.10%)	5 /137 (3.60%)	3 /123 (2.40%)
SP754	0 / 96 (0%)	N/A	4 /160 (2.50%)
EP0008	0/183 (0%)	9/182 (4.7%)	10/179 (5.4%)

Source: Table 2-38, pp 76-77 and Table 2-40, p 78 of the submission.

N/A = not available; LAC = lacosamide.

Bold indicates statistically significant results.

6.11 As there are no direct head-to-head RCTs comparing ESL with LAC, an ITC was performed between Study 304 (ESL) and the four LAC studies, using placebo as the common reference. The efficacy outcomes for the ITC were based on those previously accepted by the PBAC (most recently in the brivaracetam November 2017 PSD), and consisted of two binary outcomes:

- Number and percentage of patients reporting a 50% reduction in 28-day seizure frequency;
- Seizure freedom.

6.12 A comparison of key factors that might influence the transitivity of the ITC is provided in Table 7 below. There were three differences which may influence the transitivity assumption:

- The prior AED use is difficult to directly compare due to differences in reporting, however two of the LAC trials reported approximately 50% of their cohort had tried ≥7 prior AEDs, suggesting their prior treatment exposure may have been greater than the ITT population mean of 5.7 prior AEDs in Study 304.
- The baseline seizure frequency per 28 days was substantially higher in Study 304 (17.9), compared to the LAC trials (10.5-13).
- The LAC trials had a greater number of concomitant AEDs at baseline than in Study 304. The group of patients from Study 304 who were taking 1 concomitant AED are not representative of the proposed PBS target population, who must be taking at least 2 concomitant AEDs. This may also bias the safety profiles in favour of ESL.

6.13 Considered together, the patients in Study 304 generally had greater baseline seizure frequency and fewer concomitant AEDs than patients in the LAC trials. These differences suggest patients in the LAC trials may have had better disease control at

Public Summary Document – March 2021 PBAC Meeting

baseline than the ESL patients, who may have been under-treated compared to the LAC cohorts. This means the Study 304 cohort may have been more responsive to the addition of an AED than the LAC cohorts, which may have biased the efficacy in favour of ESL.

Table 7: Comparison of select baseline demographics and disease characteristics in trials used for the ITC which may influence the transitivity

	ESL Study	LAC studies			
Study	Study 304	Ben-M	Chung	Halasz	Hong
N	650	312	305	477	544 (FAS)
Demographic baseline characteristics					
Age, mean (range), years	38.5 (16-71)	40 (18-68)	38.8 (16.0-71.0)	37.8 (16-70)	32.5
Seizure Type at baseline, n (%)^a					
Simple partial	231 (35.5)	122 (39)	114 (37)	186 (38)	185 (34)
Complex partial	515 (79.2)	278 (89)	256 (84)	426 (88)	525 (96)
Partial-onset with secondary generalisation	179 (27.5)	229 (73)	129 (42)	382 (79)	350 (64)
Other disease characteristics					
Disease duration, years	21.4	24.5 ^c	24.8	22	17.7
Mean seizure frequency in the 4 weeks prior	17.9	11-13 ^c	12.7 ^b	10.6 ^b	10.5 ^b
PRIOR AED	(mean)	Number of AEDS: n (%)			
Mean	5.7	Approx. 50% had tried ≥ 7 AEDs in their lifetime	1-3: 54 (17.7) 4-6: 108 (32.8) ≥7: 146 (47.9) NR: 5 (1.6)	1-3: 142 (29.8) 4-6: 156 (32.7) ≥7: 174 (36.5) NR: 5 (1.0)	0: 40 (7.4) 1: 89 (16.4) 2: 119 (21.9) 3: 104 (19.1) ≥4: 192 (35.3)
Range (25 th -75 th percentiles)	1-22 (3-8)				
Concomitant AEDs use (%)					
Carbamazepine	34.9%	NR	24.9% ^c	47.8%	47.6%
Valproate	18.5%		16.9% ^c	32.8%	45.4%
Levetiracetam	24.4%		39.1% ^c	19.8%	23.9%
Lamotrigine	22.9%		36.1% ^c	30.5%	21.7%
Oxcarbazepine	-		21.4% ^c	NR	15.8%
Topiramate	-		18.2% ^c	28.2%	15.3%
Zonisamide	-		14.7% ^c	NR	NR
Total concomitant AEDs at baseline, n (%)					
1 AED	183 (28.2)	16% ^c	54 (17.7)	63 (13.2)	121 (22.2)
2 AEDs	462 (71.1)	84% ^c	164 (53.8)	238 (49.9)	231 (42.5)
3 AEDs	1 (0.2)	-	87 (28.5)	176 (36.9)	192 (35.3)

Source: Data modified from Table 2-53, p 103 of the submission; additional data extracted from respective LAC study publications. AED = anti-epileptic drug; ESL = eslicarbazepine acetate; FAS = full analysis set; LAC = lacosamide; NR = not reported.

^a Patients could have more than one response for any seizure classification.

^b Weighted mean of median baseline seizure frequency per 28 days.

^c Pooled data which included the LAC 600 mg group.

Note: The submission table included the 600 mg groups from the SP667 and SP754 LAC studies; these data have been removed from the above table, which is limited to the 200 mg and 400 mg LAC groups, unless otherwise specified.

6.14 The results of the nominated efficacy outcomes of the ITC are provided in Table 8. A risk ratio >1 favours ESL. The submission claimed that as there were no p-values <0.05, it could be concluded there were no significant differences between ESL and LAC for either of the nominated comparisons. The submission used this evidence to support

the claim of ESL non-inferiority to LAC in terms of these efficacy outcomes. This was not a valid interpretation of this evidence; the fact that CIs are wide enough to traverse 1 does not necessarily mean that there is no difference between these treatments. The ITC indicates that the true value likely lies within the range of the 95% CIs, but the ITC lacks the power to be more certain of the true value. The outcome of seizure freedom was highly uncertain, due to the low event rate in the RCT data.

Table 8: Comparison of numbers of the three groups used to generate the efficacy outcome of the ITC

	ESL, n/N (%)	Placebo (pooled), n/N (%)	LAC, n/N (%)	RR (95% CI)	p-value
50% responders at 28 days					
ESL 800 mg vs LAC 200 mg	61/201 (30%)	166/754 (22%)	161/449 (36%)	0.82 (0.55, 1.23)	0.339
ESL 1,200 mg vs LAC 400 mg	78/184 (42%)		273/645 (42%)	0.93 (0.64, 1.34)	0.683
Seizure Freedom					
ESL 800 mg vs LAC 200 mg	4/201 (2%)	5/730 (0.7%)	20/426 (5%)	0.65 (0.07, 6.16)	0.710
ESL 1,200 mg vs LAC 400 mg	4/184 (2%)		22/569 (4%)	0.53 (0.06, 5.08)	0.583

Source: Constructed during the evaluation, from Table 2, p 5 & Table 4, p 7 of the ITC Report.
ESL = eslicarbazepine acetate; LAC = lacosamide; RR = risk ratio.

- 6.15 It is more appropriate to have pre-specified a non-inferiority margin which is consistent with previous PBAC considerations for 50% responders at 28 days. Most recently, the brivaracetam resubmission (March 2017 PSD) proposed a non-inferiority margin of 0.62 to 0.68 based on the accepted lower 95% CIs of the zonisamide November 2007 and perampanel July 2014 submissions. The zonisamide submission was for a different line of therapy, and 13 years ago when the treatment options for this condition were more limited. Brivaracetam had a lower 95% CI of 0.66, which was accepted in the Nov 2017 PSD. The ESC noted that neither of the lower 95% CIs for the ESL vs LAC comparison of 50% responders at 28 days (0.55 for ESL 800 mg vs LAC 200 mg, and 0.64 for ESL 1,200 mg vs LAC 400 mg) satisfied a non-inferiority margin of 0.66.
- 6.16 The submission described ESL as non-inferior in terms of effectiveness compared with LAC in third-line treatment of treatment-resistant POS. The ESC agreed with the evaluation that this therapeutic conclusion is not adequately supported by the submitted evidence because: (i) the ESL 800 mg group failed to achieve statistical significance in primary and secondary outcomes; (ii) Study 304 failed to demonstrate a benefit of ESL over placebo which met the sponsor-nominated MCID; (iii) the transitivity concerns about baseline characteristics may have biased the ITC in favour of ESL; and (iv) the ITC generated wide confidence intervals, was not performed with a pre-specified non-inferiority margin, and did not satisfy a margin previously accepted by the PBAC.

Comparative harms

6.17 A summary of various treatment emergent adverse events (TEAEs) in Study 304 is provided in Table 9 below.

Table 9: TEAEs affecting ≥5% of patients, TEAEs leading to discontinuation in ≥2% of patients, all serious TEAEs, and deaths (safety population), Study 304

	Number (%) of patients		
	Placebo (n = 224)	ESL 800 mg (n = 216)	ESL 1,200 mg (n = 210)
Any TEAE	125 (55.8)	145 (67.1)	163 (77.6)
Dizziness	19 (8.5)	34 (15.7)	55 (26.2)
Somnolence	12 (5.4)	16 (7.4)	36 (17.1)
Nausea	11 (4.9)	16 (7.4)	32 (15.2)
Headache	17 (7.6)	20 (9.3)	24 (11.4)
Vomiting	3 (1.3)	6 (2.8)	23 (11.0)
Diplopia	4 (1.8)	14 (6.5)	22 (10.5)
Vertigo	1 (0.4)	6 (2.8)	15 (7.1)
Fatigue	6 (2.7)	8 (3.7)	11 (5.2)
Potentially related TEAE	83 (37.1)	111 (51.4)	140 (66.7)
TEAEs leading to discontinuation	18 (8)	26 (12.0)	54 (25.7)
Dizziness	1 (0.4)	11 (5.1)	19 (9.0)
Nausea	0	3 (1.4)	13 (6.2)
Vomiting	0	0	8 (3.8)
Ataxia	0	1 (0.5)	8 (3.8)
Dysarthria	0	0	5 (2.4)
Somnolence	2 (0.9)	2 (0.9)	5 (2.4)
Serious TEAEs	7 (3.1)	14 (6.5)	3 (1.4)
Deaths ^a	1 (0.4)	1 (0.5)	0

Source: Table 2-45, p 87 of the submission; data modified to correct the safety population numbers in the table.

ESL = eslicarbazepine acetate; TEAE = treatment-emergent adverse event.

^a Data are based on the double-blind, placebo-controlled period.

6.18 An ITC was performed between Study 304 and the four LAC studies, using placebo as the common reference. The outcomes consisted of three safety outcomes:

- Withdrawal due to AE
- Dizziness
- Somnolence

6.19 Limiting the safety comparison to withdrawal due to AE and two individual TEAEs did not provide a comprehensive comparison of the safety data, particularly when the individual TEAE profiles of ESL and LAC may differ. A more appropriate comparison may include categories such as 'Any TEAE' and 'serious adverse events', as well as up to 12 individual TEAEs.

6.20 The safety outcomes of the ITC are provided in Table 10 below. A risk ratio less than 1 favours ESL. The submission stated these results favoured the claim that ESL has a similar (non-inferior) tolerability profile when compared to LAC. Similar to the efficacy claim, this is not a reasonable interpretation of these data. All of the upper 95% CIs are greater than 1, with upper CIs for withdrawal due to AE and somnolence being greater than 3, indicating that the CIs are very wide and may not be able to be meaningfully interpreted.

Table 10: Indirect comparisons of ESL and LAC for safety outcomes

	Estimated effect Treatment / Placebo		Risk ratio		
	ESL	LAC	Indirect comparison ESL / LAC		
			Estimate	95% confidence interval	P-value
ESL 800 mg versus LAC 200 mg					
Withdrawal due to AE	1.50	1.17	1.28	0.54, 3.07	0.575
Dizziness	1.86	2.01	0.92	0.48, 1.77	0.805
Somnolence	1.38	1.86	0.74	0.26, 2.08	0.570
ESL 1,200 mg versus LAC 400 mg					
Withdrawal due to AE	3.20	2.97	1.08	0.57, 2.04	0.817
Dizziness	3.09	3.46	0.89	0.50, 1.58	0.700
Somnolence	3.20	2.01	1.59	0.72, 3.53	0.255

Source: Table 2-61, p 107 of the submission.

AE = adverse event; ESL = eslicarbazepine acetate; LAC = lacosamide.

6.21 The PSCR and pre-PBAC response argued that ESL is a well-tolerated treatment with a manageable adverse event profile that is comparable to the profile of LAC. The ESC noted that the PSCR provided raw tabulated data in support of this statement, and considered these data would need to be included in the ITC to allow for appropriate interpretation. The pre-PBAC response provided a naïve comparison for additional AEs that were not included in the original submission.

Clinical claim

6.22 The submission described ESL (both 800 mg and 1,200 mg doses) as non-inferior in terms of effectiveness and safety compared with LAC in the third-line treatment of treatment-resistant POS. This claim was not supported by the evidence submitted.

6.23 The key issues were:

- The proposed line of therapy and comparator was inappropriate, and ESL is unlikely to displace LAC (paragraph 5.3). The ESC considered there was no evidence that ESL would confer any substantial benefit to any subgroup of patients with medically refractory epilepsy in the third-line setting; after having tried and failed another dibenzazepine clinicians may be unlikely to forgo the opportunity to add a drug with a novel mechanism of action.
- Study 304 failed to demonstrate a robust benefit of ESL over placebo. Only the 1,200 mg group was able to demonstrate a statistically significant difference to placebo for the primary and secondary efficacy outcomes (paragraph 6.7). The

1,200 mg group had a higher rate of discontinuations and missing data than the other groups, which may have affected the internal validity and biased the results of Study 304 (paragraph 6.6). The pre-PBAC response commented that for the LAC studies presented to the PBAC in November 2009, only the higher dose (LAC 400 mg) achieved a statistically significant higher response versus placebo (in terms of reduction in seizure frequency $\geq 50\%$ relative to baseline) for this highly refractory patient population.

- The ITC suffered from transitivity concerns (paragraph 6.12); the patients in Study 304 had greater baseline seizure frequency and fewer concomitant AEDs than patients in the LAC trials, suggesting they may be under-treated and more responsive to the addition of another AED compared to the LAC cohorts.
- The ITC did not pre-specify a non-inferiority margin, and the lower 95% CIs for 50% responders at 28 days for ESL 800 mg vs LAC 200 mg and ESL 1,200 mg vs LAC 400 mg were 0.55 and 0.64, respectively; both values are outside the lower 95% CI of 0.66 in the brivaracetam submission (brivaracetam PSD, November 2017, Table 2).
- The PBAC noted the ITC for safety outcomes had wide confidence intervals, where ESL may cause approximately half or up to three times as many adverse events as LAC, and considered that these data cannot be confidently interpreted. Further, the ESL cohort were on fewer concomitant AEDs than patients in the LAC studies, which may bias the ITC in favour of ESL.

6.24 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was not adequately supported by the available data.

Economic analysis

6.25 The submission estimated that ESL 800 mg daily is equi-effective to LAC 200 mg daily (4:1), and ESL 1,200 mg daily is equi-effective to LAC 400 mg daily (3:1), based on the recommended doses used in the trials and the respective Australian PI. The submission applied the dosage proportions of LAC utilisation to calculate the split between the ESL 800 mg and 1,200 mg doses. This is not reasonable, because the utilisation distribution of LAC doses does not apply to the potential distribution of ESL doses.

6.26 The submission claimed that the proposed equi-effective doses are valid because they are trial-based; however, the ESL dose was allocated to patients on trial entry, and therefore does not apply to clinical practice. The sponsor did not provide further analysis of the actual doses received in the clinical trials (e.g. mean dosage used, treatment duration etc). The ESC noted that real-world data from Villaneuva et al. (2017) is broadly consistent with the expected dosing presented in the submission, however it does not mitigate all uncertainty around the equi-effective doses and the cost-minimisation approach. The pre-PBAC response acknowledged there is no long-term utilisation and dosing patterns of ESL in practice in Australia, but maintained that

the trial-based approach used to determine a price of ESL is appropriate. The PBAC considered there is limited evidence that identifies the distribution of ESL doses (between 800 mg and 1,200 mg) that would be expected to occur in clinical practice.

- 6.27 The submission presented a cost-minimisation analysis using the approved ex-manufacturer price (AEMP) for LAC 100 mg and 200 mg tablet strengths (Table 11). The submission calculated a weighted AEMP of \$216.78 for LAC based on PBS utilisation statistics 2015–2019. This approach omits consideration of other lacosamide products: 50 mg tablets, 150 mg tablets and the oral solution. The simplistic low dose/high dose allocation does not accurately reflect the distribution of LAC doses, nor the weighted mean dose of LAC used in practice. The ESC considered that the simplified dose utilisation estimates based on only two strengths of LAC was uncertain.

Table 11: Results of the cost minimisation analysis conducted by the submission

		LAC	ESL	Source/calculation
A	Ex-manufacturer price 100 mg and 200 mg	\$216.78 ^a	\$ [REDACTED]	LAC = (51.75% * \$146.24) + (48.25% * \$292.42) ESL = D / C
B	Days per pack	28	25.17 ^b	LAC = pack size (56) / 2 ESL = (30 * 51.75%) + (20 * 48.25%)
C	Scripts per year	[REDACTED]	[REDACTED]	LAC = 365.25 / B ESL = 365.25 / B
D	Cost per year	\$ [REDACTED]	\$ [REDACTED]	LAC = A * C ESL = LAC

Source: Table 3-3 of the submission.

AEMP = approved ex-manufacturer price; ESL = eslicarbazepine acetate; LAC = lacosamide.

^a Based on the weighted average AEMP of LAC 100 mg and 200 mg strengths; derived using item numbers 9335H (200 mg/day) and 9338L (400 mg/day).

^b Based on the weighted average usage of ESL 800 mg/day (pack lasts 30 days) and 1,200 mg/day (pack lasts 20 days).

- 6.28 ‘The number of prescriptions per year’ was calculated as < 500, and the 28 ‘days lasted per pack’ was obtained by dividing the number of tablets in LAC continuing treatment pack (56) by the number of tablets required for recommended LAC daily dosing (2 tablets per day), which are both likely overestimated assuming 100.0% adherence. The AEMP cost of LAC per year was calculated as \$ [REDACTED] (= \$216.78 * <500).
- 6.29 The ESL 800 mg tablet cost minimised AEMP price was calculated to be \$ [REDACTED]. This is not reasonable since the equi-effective doses (paragraph 6.25) are not adequately supported, and no data were provided on the distribution of ESL doses (paragraphs 6.25 to 6.26), or all LAC tablet strengths (paragraph 6.27).
- 6.30 The submission did not include any additional costs or cost-offsets in the cost-minimisation analysis, which is reasonable.
- 6.31 The PBAC noted that the cost-minimisation approach must establish that the cost per patient for treatment with ESL would be no more than the cost per patient of LAC. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy. 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.

Drug cost/patient/year: \$ [REDACTED]

6.32 This is based on the proposed DPMQ of \$ [REDACTED] for ESL 800 mg tablet, 30 tablets per pack, which is sufficient for a 30 day supply (< 500 scripts per year, as calculated by the submission). It is assumed that the cost/patient/year of treatment with ESL and LAC is the same (based on AEMP), but this is highly uncertain given the concerns in calculations of equi-effective doses (paragraphs 6.25 to 6.27).

Estimated PBS usage & financial implications

6.33 This submission was not considered by DUSC. The submission used a market-share approach to predict the likely use and financial impact of listing of ESL on the PBS.

Table 12: Key inputs for financial estimates

Parameter	Value	Source	Comment
Market Size	Total services each year (Jan 2015 – Dec 2019) for currently listed medicines (LAC, PER BRV) for intractable POS	PBS Usage Statistics	
Average annual increase in services for intractable POS	2016: 13.4% 2017: 16.22% 2018: 17.98% 2019: 25.16% 2020: 8.89% 2021 (Year 1): 11.19% 2022 (Year 2): 10.06% 2023 (Year 3): 9.14% 2024 (Year 4): 8.38% 2025 (Year 5): 7.73% 2026 (Year 6): 7.17%	<u>2016 – 2019:</u> based on PBS usage statistics (Medicare Australia) <u>2020 - 2026:</u> Forecast calculation by Microsoft Excel FORECAST.ETS Formula using PBS usage statistics for 2016-2019	The submission has not adequately justified the annual increase in services for intractable POS treatment over 2016-2019. No rationale was provided for the decrease in growth rate in 2020 and onwards.
Treatment utilisation of eslicarbazepine acetate			
Uptake rate (as substitution for LAC)	Year 1: 4.0% Year 2: 6.0% Year 3: 8.0% Year 4: 10.0% Year 5: 12.0% Year 6: 15.0%	Assumption	The sponsor did not provide any rationale for this assumption. The PSCR stated that the uptake was estimated based on the uptake and growth of perampanel and brivaracetam when they were recommended for listing, with ESL expected to take a small share of the current market.

Source: Compiled during evaluation from Table 4-2 -4.4, pp120-121 of the submission

6.34 The estimated use and financial implications of listing ESL on the PBS are summarised below. Revised figures were provided during the evaluation to correct a typographical error in the worksheet calculations. The ESC considered that the market share approach applied in the submission is likely to overestimate the ESL uptake rate since the proposed comparator LAC is used as a second-line treatment for the management

Public Summary Document – March 2021 PBAC Meeting

of intractable POS in clinical practice, not only as third-line adjunctive agent, and it is also used in children <16 years, but ESL is not.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	█ ¹	█ ¹	█ ²	█ ²	█ ³	█ ³
Revised	█ ¹	█ ²	█ ²	█ ³	█ ³	█ ³
Estimated financial implications of eslicarbazepine acetate						
Cost to PBS/RPBS less copayments	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Revised	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Estimated financial implications for lacosamide						
Cost to PBS/RPBS less copayments	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Revised	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Net financial implications						
Net cost PBS / RPBS	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Revised	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴

Source: Compiled during evaluation from Tables 4-6 and 4-10, p122/pp125 and Zebinix Section 4 workbook of the submission

^a Assuming █⁵ scripts per year as estimated by the submission

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ \$0 to < \$10 million

⁵ < 500

6.35 The total cost to the PBS/RPBS of listing ESL was estimated to be \$0 to < \$10 million in Year 6, and a total of \$0 to < \$10 million in the first 6 years of listing. Although cost-minimised on AEMP prices, net financial costs to the PBS/RPBS are observed due to the expected increase in the number of prescriptions (and therefore dispensing fees), because when ESL is dosed at 1,200 mg daily a script only lasts 20 days.

6.36 There are significant concerns with the assumptions applied to estimate the cost-minimised price calculation for ESL (including establishing equi-effective doses, the claim of equi-effectiveness being poorly justified, uncertainty around LAC weighted average price calculation given it is based on just the two highly dispensed PBS items, and uncertainties around the ‘scripts per year’ and ‘days lasted per pack’, uptake rate etc). Price and uptake rates are the major components in financial impact estimation, and the ESC agreed with the evaluation that given the considerable uncertainty in both of these, the financial impact of eslicarbazepine acetate is difficult to measure and quantify with the limited evidence available.

Financial Management – Risk Sharing Arrangements

6.37 The submission did not provide details of a risk sharing arrangement (RSA). There is a RSA in place for the nominated comparator, lacosamide, in conjunction with brivaracetam and perampanel for the treatment of intractable partial epileptic seizures. The pre-PBAC response stated that the sponsor would be agreeable to joining the RSA, pending the Department providing the details of the agreement.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of eslicarbazepine acetate (ESL) for the treatment of intractable partial epileptic seizures, with or without secondary generalised seizures. The PBAC considered that the efficacy of ESL compared to placebo in a treatment-resistant population, and the claim of non-inferior effectiveness and safety of ESL compared with lacosamide (LAC), were not supported by the clinical data and indirect treatment comparison (ITC). The PBAC also considered that the economic analysis was problematic with respect to the estimation of equi-effective doses.
- 7.2 Like carbamazepine and oxcarbazepine, the PBAC noted that ESL is a member of the dibenzazepine family (the carboxamides), with similar potential side effects. If ESL were used third-line, the PBAC considered that it may be a less attractive option for clinicians in an adjuvant setting compared to an agent from a novel therapeutic class (e.g. LAC), and that LAC may not be the therapy that is replaced. The PBAC also considered that ESL may be used earlier in the treatment pathway, and could replace the other dibenzazepines in this indication. The PBAC considered the clinical need for an additional medicine with a similar mechanism of action to other listed medicines is moderate. The PBAC indicated that other comparators should have been included in the submission.
- 7.3 The PBAC noted the substantial discontinuation observed in the 1,200 mg arm of the key ESL trial, Study 304, due to adverse events (AEs), as well as the missing data due to the 'Not Evaluable' participants. The PBAC considered that both the submission and the Clinical Study Report were unclear about how these missing data were handled, and that it was difficult to determine the direction of any resulting bias.
- 7.4 The PBAC noted that the primary efficacy analysis of Study 304 (ITT population), reduction in standardised seizure frequency (versus placebo), reached statistical significance in the ESL 1,200 mg group but not in the ESL 800 mg group. With respect to the secondary outcome (proportion of patients with a $\geq 50\%$ reduction in seizures from baseline), again, only the 1,200 mg arm reached statistical significance. The PBAC noted the point estimate for the 1,200 mg arm decreased from 42.6% to 38.0% after accounting for the 'Not Evaluable' patients. Overall, the PBAC considered that Study 304 failed to demonstrate a robust benefit of ESL over placebo as adjunctive therapy in a refractory population.
- 7.5 The PBAC noted that the ITC performed between Study 304 (ESL) and the four LAC studies, using placebo as the common reference, suffered from transitivity concerns in terms of baseline differences across the ESL and LAC populations, suggesting the ESL cohort may have been under-treated at baseline compared to the LAC cohort and therefore more responsive to the addition of another anti-epileptic drug. The PBAC also noted the ITC did not pre-specify a non-inferiority margin, and the lower 95% CIs for both the low dose and high dose comparisons were outside the margin in the brivaracetam submission (November 2017). Overall, the PBAC considered that the

claim of non-inferior comparative effectiveness for ESL (both 800 mg and 1,200 mg doses) compared with LAC in the third-line treatment setting was not adequately supported by the available data.

- 7.6 Due to the high rate of discontinuations observed for the ESL 1,200 mg dose in Study 304 and the upper CIs for withdrawal due to AE and somnolence being very wide, the PBAC also considered that the claim of non-inferior comparative safety versus LAC was not adequately supported by the available data.
- 7.7 The PBAC considered the cost-minimisation analysis of ESL compared to LAC was not appropriate because (i) it did not accept that LAC is the appropriate comparator; and (ii) it did not accept that ESL is non-inferior to LAC, in terms of both efficacy and safety. The PBAC also considered the analysis was problematic given the method used to estimate the equi-effective doses based only on the recommended doses used in the trials and the respective Australian Product Information.
- 7.8 The PBAC did not consider the estimated usage and financial implications in the submission would be an accurate reflection of ESL use, given the proposed clinical place and comparator were not appropriate. The PBAC noted that net financial costs for ESL were observed due to the expected increase in the number of prescriptions (and therefore dispensing fees) for patients on the 1,200 mg daily dose. Given the uncertainty with respect to price and uptake rates, the PBAC considered the estimated financial impact of ESL was highly uncertain.
- 7.9 The PBAC advised that any resubmission for ESL would be required to address the uncertainties with respect to the clinical data and economic analysis. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

STADA is disappointed with the outcome. STADA is committed to work collaboratively with the Department of Health to review our progress. This aligns with STADA's mission to care for people's health and we will still work towards the opportunity to provide patients with refractory epilepsy in Australia to access eslicarbazepine acetate through the PBAC.