5.04 BRIVARACETAM tablets, 25 mg, 50 mg, 75 mg and 100 mg and oral solution, 10 mg/mL Briviact®, UCB Pharma.

1 Purpose of Application

1.1 The submission requested a Section 85, Authority Required (STREAMLINED) listing for brivaracetam for the treatment of intractable partial epileptic seizures.

2 Requested listing

2.1 The submission requested the following listing. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BRIVARACETAM 15 mg, 50 mg, 75 mg, 100 mg tablet, 56	1	5	$[redacted]	BRIVIACT	UCB Pharma

Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Epilepsy
PBS Indication:	*Intractable* partial epileptic seizures
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	~~Intractable partial epileptic seizures~~ 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. OR The condition ~~is~~ *must be* controlled satisfactorily by levetiracetam but the patient ~~is~~ *must be* unable to tolerate continued use due to adverse effects.
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.* *Special Pricing Arrangements apply*

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BRIVARACETAM 10 mg/mL 300 mL bottle	1	12	$[redacted]	BRIVIACT	UCB Pharma

Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Epilepsy
PBS Indication:	*Intractable* partial epileptic seizures
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.
Clinical criteria:	~~Intractable partial epileptic seizures~~ 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. OR The condition ~~is~~ *was* controlled satisfactorily by levetiracetam but the patient ~~is~~ *must be* unable to tolerate continued use due to adverse effects. AND Patient must be unable to take a solid dose form of *this drug* ~~brivaracetam~~.
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.* *Special Pricing Arrangements apply*

2.2 The submission proposed two formulations of brivaracetam to be listed on the PBS: tablets and oral solution. The liquid presentation is intended for use in patients unable to consume and swallow oral tablets. A price premium of [redacted]% for oral liquids over tablets was proposed at an ex-manufacturer price level (per bottle vs per pack).

The submission argued that smaller prescription volumes apply to liquid presentations, relative to oral tablets, resulting in a higher requested price for the liquid due to diseconomies of scale. The submission did not provide further details on how the magnitude of the price premium (■%) was determined.

2.3 The proposed PBS restriction allows for the use of brivaracetam either as monotherapy or in combination with other antiepileptic drugs (AEDs) for partial onset seizures (POS). The Sponsor stated in the Pre Sub-Committee Response (PSCR) that they did not intend for the listing to allow for brivaracetam monotherapy and agreed with wording the restriction so that brivaracetam was available only as an add-on therapy. The ESC suggested wording be added to the clinical criteria section of the restriction to indicate that treatment must be in conjunction with other anti-epileptic drugs.

2.4 The type of prescribers includes nurse practitioners. Prescribing by nurse practitioners only applies for continuing therapy with lacosamide, where the treatment of, and prescribing of the drug has been initiated by a medical practitioner. No initiation or continuation criteria were specified for brivaracetam.

2.5 The European Medicines Association (EMA) assessment report for brivaracetam (EMA/CHMP/822086/2015; p87) stated that subjects with concomitant levetiracetam had no benefit from brivaracetam, and this may be due to competition between the compounds at the synaptic vesicle SV2A binding site. The Committee for Medicinal Products for Human Use (CHMP) also considered that the information on prior and concomitant use of levetiracetam was relevant to prescribers and should be reflected in the product information. The draft Product Information for brivaracetam mentions that in two of the key trials (1252 and 1253), approximately 20% of the patients were on concomitant levetiracetam, and although the number of subjects was limited, there was no observed benefit versus placebo when brivaracetam was added to levetiracetam. The ESC noted that the neuropsychiatric side-effects may also compound when brivaracetam and levetiracetam are used concomitantly, and the listing should exclude concomitant use. The PBAC considered that the listing should preclude concomitant use of brivaracetam and levetiracetam.

2.6 The submission was based on a cost-minimisation analysis of brivaracetam compared with lacosamide.

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

3 Background

3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of the PBAC meeting, brivaracetam had been recommended by the ACPM as add-on therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy.

3.2 This is the first submission for brivaracetam to the PBAC for the treatment of partial onset seizures.

3.3 The PBAC has previously considered several submissions for lacosamide, the comparator in the current submission (November 2009, November 2011, November 2012, and March 2015). Two issues were noted by the PBAC in November 2012 that were relevant for the current submission:

1. Neurologists did not consider treatments to be clearly separated into first-, second- or subsequent-line options; and
2. The PBAC recommended amending the continuing restriction to allow prescribers to introduce lacosamide in combination with two other AEDs and then to remove the concurrent AEDs (*i.e.* allows for lacosamide monotherapy) as a matter of clinical judgement, whilst maintaining the existing risk-share arrangement.

4 Clinical place for the proposed therapy

4.1 Epilepsy is a common neurological condition, characterised by recurrent, unprovoked seizures, and produces significant morbidity in the general community.

4.2 The submission proposed two populations to receive brivaracetam treatment:

1) A refractory population whose POS failed to be controlled by at least one first-line agent and at least two second-line agents; and
2) Patients whose POS are controlled by levetiracetam but the patient is unable to tolerate the drug. The ESC and PBAC noted that there were no robust clinical data provided to support this indication.

4.3 For the first proposed PBS population, brivaracetam would be used as a third or later-line therapy. For the second proposed PBS population, brivaracetam would be used as either a second-line therapy or as later-line therapy (after being intolerant to levetiracetam).

4.4 The recommended starting dose of brivaracetam is 100 mg/day. The daily dose is administered in two equally divided doses, once in the morning and once in the evening. Based on individual patient response, the dose may be adjusted between 50 mg/day and 200 mg/day. Initial dose titration to an effective dose is not required to establish tolerability.

5 Comparator

5.1 For the refractory population the submission nominated lacosamide as the main comparator. The ESC and PBAC noted that levetiracetam would also be an appropriate comparator for this indication as it is chemically related to brivaracetam and likely to be replaced by it in clinical practice.

5.2 The ESC noted that there are currently numerous medications listed on the PBS that can be prescribed for partial epileptic seizures which may also be alternative therapies to brivaracetam in clinical practise.

5.3 The ESC recommended that further clinical advice be sought from the Epilepsy Society of Australia regarding current clinical practise. Advice was not received prior to the PBAC meeting.

5.4 The lacosamide PBS restriction requires that, in the initiation phase, the treatment must be in combination with two or more AEDs which includes one second-line adjunctive agent, while the proposed restriction for brivaracetam does not include this requirement. The submission (p2 of the Executive Summary) claimed that "in nominating lacosamide as the main comparator, it is recognised that the proposed clinical place of brivaracetam is not the same as that for lacosamide, but rather in a refractory population which does not need to be treated with triple therapy, unlike lacosamide." For the stated use, the PBAC considered the appropriate comparator would be AEDs other than lacosamide.

5.5 For the population intolerant to levetiracetam, no comparator was nominated and no clinical evidence was provided in the submission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the current treatment options available to patients with epilepsy and how they are used in practice. It was noted that approximately 30% of patients are not well controlled despite having tried all appropriate treatments (likely to be 5-6 different drugs). The treatments are tailored based on tolerability as adverse events have a significant impact on patient quality of life. Brivaracetam was considered to be an additional option for patients, and it was thought that initially it would be used in patients who have exhausted all other treatment options. The PBAC considered that the hearing was informative as it provided a clinical perspective.

Consumer comments

6.2 The PBAC noted and welcomed the input from several organisations (3) via the Consumer Comments facility on the PBS website. The comments described the need for a variety of treatments to be available to patients with epilepsy, particularly those with refractory conditions.

Clinical trials

6.3 The submission was based on an indirect comparison of brivaracetam and lacosamide in patients with refractory or intractable epilepsy. Six double-blinded placebo controlled trials (three for each drug) were used in the indirect comparison which used placebo as the common reference.

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

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Proposed drug brivaracetam *versus* placebo		
1252	Primary clinical study report NCT00490035 - A multi-center, double-blind, parallel-group, placebo-controlled, randomised study: Evaluation of the efficacy and safety of brivaracetam in subjects (≥16 to 70 years old) with partial-onset seizures. UCB Pharma SA <u>Publications</u> Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomised, placebo-controlled trial.	26 July 2010 *Epilepsia* 2013; 55(1):47-56
1253	Primary clinical study report NCT00464269 - An international, double-blind, parallel-group, placebo-controlled, randomised study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with Partial Onset Seizures. UCB Pharma SA <u>Publication</u> Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomised, double-blind, placebo-controlled trial.	3 June 2011. *Epilepsia* 2014; 55(1):57-66
1252 and 1253	<u>Additional publications</u> Werhahn KJ, Biton V, Johnson ME, Merschhemke M, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from two randomised, double-blind, placebo-controlled trials [abstract no: p507].	*Epilepsia* 2010; 51 (Suppl 4):150

	Biton V, AU: Werhahn KJ, Johnson ME, Falter U, Climo K, Schelstraete I, Brodsky AC, Rosenstiel P. Brivaracetam as adjunctive treatment of refractory partial-onset seizures in adults: results from two randomised, double-blind, placebo-controlled trials [abstract no: 1.216]. Epilepsia 50 (Suppl 11):106-7.	*Epilepsia* 2009; 50 (Suppl 11):106-107
1358	Primary clinical study report NCT01261325 - A randomised, double-blind, placebo-controlled, multicentre, parallel-group study to evaluate the efficacy and safety of brivaracetam in subjects (≥16 to 80 Years Old) with partial-onset seizures. UCB Pharma SA.	19 September 2014.
	<u>Publication</u> Klein P, Schiemann J, Sperling MR, Whitesides J, Liang W, Stalvey T, Brandt C, Kwan P. A randomised, double-blind, placebo-controlled, multicentre, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures.	*Epilepsia* 2015; 56(12):1890-1898
	Klein P, Schiemann J, Sperling M, Whitesides J, Liang W, Stalvey T. A randomised, double-blind, placebo-controlled, multicentre, parallel-group study to evaluate the efficacy and safety of brivaracetam in adult patients with partial onset seizures.	*Epilepsy Currents* 2015; (15):379
	<u>Conference abstracts</u> Klein P, Schiemann J, Sperling M, Whitesides J, Liang W, Stalvey T. A randomised, double-blind, placebo-controlled, multicentre, parallel-group study to evaluate the efficacy and safety of brivaracetam in adult patients with partial onset seizures.	68th Annual Meeting of the American Epilepsy Society, AES 2014 Seattle, WA United States. January-February 2015.
	Klein P, Schiemann J, Sperling M, Whitesides J, Liang W, Stalvey T. A randomised, double-blind, placebo-controlled, multicentre, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with partial-onset seizures.	Neurology. Conference: 67th American Academy of Neurology Annual Meeting, AAN 2015 Washington, DC United States. 06 Apr 2015
Proposed comparator lacosamide *versus* placebo		
SP667	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	9 Mar 2005.

	Publication 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	*Epilepsia* 2007; 48(7): 1308-17.
SP754	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 600mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization. Schwartz Biosciences, Inc Publication 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.	13 March 2007. *Epilepsia*. 2010; 51(6):958-67
SP755	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 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization. Schwartz Biosciences GmbH. Publication 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.	8 September 2006. *Epilepsia* 2009; 50 (3):443-453

SPM927 = lacosamide.
Source: Table B.5, pp49-52 of the main body of the submission.

6.5 The key features of the evidence included in the indirect comparison are summarised in Table 2.

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome
brivaracetam vs. placebo					
1252	399	R, DB Up to 14 weeks of treatment	Low	Adult patients with intractable POS	1) POS frequency per week over the treatment period 2) ≥50% response rate for POS (≥50% reduction from baseline in seizure frequency/week) 3) POS freedom rate over the treatment period
1253	400	R, DB Up to 13 weeks of treatment	Low	Adult patients with intractable POS	Same as Trial 1252
1358	768	R, DB Up to 16 weeks of treatment	Low	Adult patients with intractable POS	1) POS frequency per 28 days over the treatment period; 2) 50% responder rate and seizure freedom rate (same as that presented for Trials 1252 and 1253)
lacosamide vs. placebo					
SP667	497	R, DB 12 weeks of maintenance treatment	Low	Adult patients with intractable POS	1) ≥50% response rate for POS 2) Change in % seizure-free days from baseline to maintenance 3) Seizure freedom
SP754	489	R, DB 12 weeks of treatment	Low	Adult patients with intractable POS	Same as SP667
SP755	546	R, DB 12 weeks of treatment	Low	Adult patients with intractable POS	Same as SP667
Brivaracetam vs. lacosamide					
Indirect comparison		Non-randomised observational study (12-16 weeks)	High	Adult patients with intractable POS	≥50% response rate and changes in POS frequency

DB = double blind; POS = partial onset seizures; R = randomised.

Note: POS assessed in the brivaracetam and lacosamide trials were primarily Type 1 partial seizures which included simple partial seizures (no alteration of consciousness), complex partial seizures (alteration or impairment of awareness) and partial seizures evolving to secondarily generalised seizures (partial seizure with secondary generalisation; evolvement into loss of consciousness and onset of convulsions).

Source: Compiled during the evaluation

6.6 There were transitivity concerns between the brivaracetam and lacosamide trials due to differences across the trials in the common reference (placebo) arms in terms of seizure types, and the number and types of concomitant AEDs. The ESC noted the trial populations in the indirect comparison were not well matched. It was noted that the lacosamide trial populations appeared to be more refractory to treatment with other AEDs, compared with the brivaracetam trial populations. The PBAC further noted that the lacosamide trials in the current submission were the same as included in the November 2009 lacosamide PBAC submission, and the PBS listing for lacosamide in refractory patients reflects, at least in part, that lacosamide appears to be effective in heavily pre-treated patients (Public Summary Document, lacosamide

November 2009). Data for equivalently pre-treated patients were not presented for brivaracetam.

Comparative effectiveness

6.7 The submission presented meta-analyses of the brivaracetam versus placebo trials and of the lacosamide versus placebo trials. An indirect comparison of the meta-analysed results was undertaken using placebo as the common reference. These analyses were based on the intention-to-treat (ITT) or modified ITT populations of the key trials. The three outcomes of interest were: ≥50% responder rate (Table 3), change in seizure frequency (Table 4) and seizure freedom (Table 5).

Table 3: Indirect comparison between brivaracetam and lacosamide to achieve ≥50% reduction in POS frequency per 28 days

Brivaracetam dose	Lacosamide dose	Difference in percentages Brivaracetam - Lacosamide	
		Estimate	95% confidence interval
By individual dose			
50 mg per day	200/400 mg per day	-3.67	-13.87, 6.53
100 mg per day	200/400 mg per day	1.60	-7.03, 10.23
200 mg per day	200/400 mg per day	0.83	-8.74, 10.40
All doses			
50-200 mg per day	200/400 mg per day	0.06	-7.41, 7.53
Brivaracetam dose	**Lacosamide dose**	**Risk ratio Brivaracetam / Lacosamide**	
		Estimate	**95% confidence interval**
By individual dose			
50 mg per day	200/400 mg per day	0.98	0.64, 1.50
100 mg per day	200/400 mg per day	1.09	0.79, 1.50
200 mg per day	200/400 mg per day	1.06	0.74, 1.51
All doses			
50-200 mg per day	200/400 mg per day	1.06	0.79, 1.43

POS=partial onset seizures
Source: Table B.32, p100 of the main body of the submission

Table 4: Indirect comparison between brivaracetam and lacosamide for reduction in POS frequency

Brivaracetam dose	Lacosamide dose	Ratio of medians (seizure frequency + 1)[a] Brivaracetam/Lacosamide	
		Estimate	95% confidence interval
By individual dose			
50 mg per day	200/400 mg per day	1.08	0.94, 1.24
100 mg per day	200/400 mg per day	0.98	0.86, 1.11
200 mg per day	200/400 mg per day	0.94	0.81, 1.09
All doses			
50-200 mg per day	200/400 mg per day	1.00	0.89, 1.14

[a] In each study, statistical analysis was performed on the log-transformed scale; if x is the average number of seizures per measurement period, the log transformation used was log(4x + 1) for studies 1252 and 1253 and log(x + 1) for study 1358. The addition of 1 before taking logarithms was the approach taken in the submission to address zero seizure frequencies in some cases.
POS = partial onset seizures
Source: Table B.35, p102 of the main body of the submission

Table 5: Indirect comparison between brivaracetam and lacosamide for proportion of patients achieving seizure free status (all seizure types[a]) in the treatment phase

Brivaracetam dose	Lacosamide dose	Difference in percentages Brivaracetam - Lacosamide	
		Estimate	95% confidence interval
50-200 mg per day	200/400 mg per day	0.92	-1.46, 3.30
Brivaracetam dose	**Lacosamide dose**	**Risk ratio Brivaracetam / Lacosamide**	
		Estimate	**95% confidence interval**
50-200 mg per day	200/400 mg per day	2.73	0.54, 13.70

[a] The majority of seizures in the assessed in the brivaracetam and lacosamide trials constituted of partial onset seizures.
Source: Table B.37, p103 of the main body of the submission.

6.8 Based on the indirect comparisons there were no statistically significant differences between brivaracetam and lacosamide in terms of 1) the proportion of patients achieving ≥50% reduction from baseline in POS frequency per 28 days, 2) the reduction from baseline in seizure frequency per 28 days, and 3) the proportion of patients who experienced all seizure free status during the treatment phase of the trials. The evaluation considered the results of the indirect comparisons should be viewed with caution given transitivity concerns across the brivaracetam and lacosamide trials in terms of patient baseline characteristics for seizure type (simple partial and partial secondary generalised), and the number and type of concomitant AEDs, which are potential treatment effect modifiers.

6.9 The inclusion criteria for the brivaracetam trials did not match the proposed PBS restrictions. The first proposed restriction was for refractory patients i.e. those who were not adequately controlled on three or more AEDs (at least one first-line AED and at least two second-line adjunctive AEDs). However, the brivaracetam trials enrolled some patients who were not adequately controlled on less than three AEDs. The second proposed restriction was for patients who were adequately controlled on levetiracetam but intolerant to it. The proportion of patients who discontinued levetiracetam due to adverse events (AEs) in the key trials was too small for any meaningful analyses (10% in Trial 1358). The submission attempted to address these applicability issues by analysing subgroups from the brivaracetam placebo-controlled trials and comparing the results with the findings in the ITT trial population. The submission claimed that the patient baseline characteristics and the efficacy of brivaracetam in the subgroups were similar to those in the ITT populations for Trials 1252, 1253 and 1358. These analyses were post hoc in nature and there were differences in baseline disease characteristics across treatment arms that could potentially confound the results. The submission did not consider any applicability issues relating to the lacosamide trials.

6.10 The submission noted the indirect comparisons were based on the broader brivaracetam trial populations which included patients receiving concomitant treatment with levetiracetam and since levetiracetam has the potential to mitigate the efficacy of brivaracetam (given that they both compete at synaptic vesicle (SV2A) binding site), and thus the submission considered the findings of the indirect comparisons to be “conservative”.

6.11 The submission presented pooled efficacy data from the key brivaracetam trials excluding patients who were on concomitant levetiracetam (defined as Pool E1

analysis in the submission). Trials 1252 and 1253 restricted the enrolment of patients on concomitant levetiracetam to approximately 20% whilst Trial 1358 did not enrol such patients. The Pool E1 results were not substantially different to the broader ITT results of the individual trials which included concomitant levetiracetam use. This probably reflects that the subgroup of patients who were not on concomitant levetiracetam made up the majority of the trial ITT populations. Additional informative analyses, not presented in the submission, would be based on the complement sub-group of patients on concomitant levetiracetam from Trials 1252 and 1253 and subsequent statistical interaction tests between the concomitant use and non-concomitant use of levetiracetam subgroups.

Comparative harms

6.12 An indirect comparison of any treatment-emergent adverse events (TEAEs), serious AEs (SAEs) and common TEAEs for brivaracetam and lacosamide for the recommended doses is presented in Table 6.

Table 6: Indirect comparison of Pool S1[a] TEAE data between brivaracetam and lacosamide (recommended doses)

	Brivaracetam			Lacosamide			ITC BRV vs. LAC
	BRV 50-200 mg/day	**PBO**	**RR, 95% CI**	**LAC 200 & 400 mg/day**	**PBO**	**RR, 95% CI**	**RR, 95% CI**
N	803	459		741	364		
Any TEAE	546 (68%)	285 (62.1%)	1.10 [1.01, 1.19]	576 (77.7%)	234 (64.3%)	1.21 [1.11, 1.32]	0.91 [0.81, 1.02]
Discontinuation due to TEAE	54 (6.7%)	18 (3.9%)	1.71 [1.02, 2.89]	102 (13.8%)	18 (4.9%)	2.78 [1.71, 4.52]	0.62 [0.30, 1.25]
SAE	24 (3.0%)	13 (2.8%)	1.06 [0.54, 2.05]	57 (7.7%)	14 (3.8%)	2.00 [1.13, 3.54]	0.53 [0.22, 1.28]
Common TEAEs[b]							
Fatigue	70 (8.7%)	17 (3.7%)	2.35 [1.40, 3.95]	52 (7.0%)	20 (5.5%)	1.28 [0.77, 2.11]	1.84 [0.89, 3.78]
Somnolence	122 (15.2%)	39 (8.5%)	1.79 [1.27, 2.52]	52 (7.0%)	17 (4.7%)	1.50 [0.88, 2.56]	1.19 [0.63, 2.25]
Dizziness	90 (11.2%)	33 (7.2%)	1.56 [1.06, 2.28]	182 (24.6%)	29 (8.0%)	3.08 [2.13, 4.47]	**0.51 [0.30, 0.86]**
Headache	77 (9.6%)	47 (10.2%)	0.94 [0.66, 1.32]	95 (12.8%)	32 (8.8%)	1.46 [1.00, 2.13]	0.64 [0.39, 1.08]
Nausea	32 (4.0%)	11 (2.4%)	1.66 [0.85, 3.27]	73 (9.9%)	16 (4.4%)	2.24 [1.32, 3.79]	0.74 [0.32, 1.74]
Diplopia	7 (0.9%)	4 (0.9%)	1.00 [0.29, 3.40]	66 (8.9%)	7 (1.9%)	4.63 [2.15, 9.99]	**0.22 [0.05, 0.92]**
Vomiting	17 (2.1%)	4 (0.9%)	2.43 [0.82, 7.18]	56 (7.6%)	9 (2.5%)	3.06 [1.53, 6.11]	0.79 [0.22, 2.88]
Vision blurred	11 (1.4%)	3 (0.7%)	2.10 [0.59, 7.47]	46 (6.2%)	8 (2.2%)	2.82 [1.35, 5.92]	0.75 [0.17, 3.24]
Coordination abnormal	3 (0.3%)	0	4.00 [0.21, 77.36]	45 (6.1%)	6 (1.6%)	3.68 [1.59, 8.56]	1.09 [0.05, 23.47]
Tremor	9 (1.1%)	6 (1.3%)	0.86 [0.31, 2.39]	39 (5.3%)	15 (4.1%)	1.28 [0.71, 2.29]	0.67 [0.21, 2.18]
Nasopharyngitis	27 (3.4%)	14 (3.1%)	1.10 [0.58, 2.08]	53 (7.2%)	21 (5.8%)	1.24 [0.76, 2.02]	0.89 [0.40, 1.98]
Nystagmus	4 (0.5%)	1 (0.2%)	2.29 [0.26, 20.40]	27 (3.6%)	14 (3.8%)	0.95 [0.50, 1.78]	2.41 [0.25, 23.38]

Statistically significant results bolded.

BRV = brivaracetam; ITC = indirect treatment comparison; LAC = lacosamide; PBO = placebo; RR = risk ratio; SAE = serious adverse event; TEAE = treatment emergent adverse event

[a] Pool S1 is pooled safety data for brivaracetam (Trials 1252, 1253 and 1358 which included 5-200 mg/day doses) and lacosamide (Trials SP667, SP754 and SP755 which included 200 – 400 mg/day doses).

[b] Common TEAEs are those reported by ≥5% subjects in Pool S1 (brivaracetam: Trials 1252, 1253 and 1358 which included 5-200 mg/day doses and lacosamide: Trials SP667, SP754 and SP755 which included 200 – 400 mg/day doses). Safety data were sourced from the Treatment Phase (i.e. both titration and maintenance phases).

Source: Table B.66, p141 of the main body of the submission.

6.13 Brivaracetam related TEAEs (as determined by the investigator) were substantially higher in the overall brivaracetam group compared with placebo (42% vs. 30%) although the majority of these were mild to moderate AEs. The most common TEAEs reported were somnolence (14% vs 9%), dizziness (11% vs 7%), and fatigue (8% vs

4%). No dose relationship was seen for TEAEs with the exception of non-serious somnolence and fatigue, the incidence of which increased as the dose of brivaracetam increased from 50 mg/day to 200 mg/day.

6.14 Lacosamide related TEAEs during the Treatment Phase (both titration and maintenance) were reported by 81.0% of subjects in the total lacosamide group and 64.3% of subjects in the placebo group. The overall incidence of subjects reporting any TEAE increased with increasing doses of lacosamide (69.6%, 82.2%, and 93.6% for lacosamide 200 mg/day, 400 mg/day, and 600 mg/day, respectively). The most frequent AEs occurring in ≥5% of lacosamide-treated subjects compared with placebo were dizziness (31% vs. 8%), headache (13% vs. 9%), and nausea (11% vs. 4%).

6.15 There were no significant differences in TEAEs between brivaracetam and lacosamide from pooled safety data for the key trials. There are no long term safety data for brivaracetam.

Clinical claim

6.16 The submission described brivaracetam as non-inferior to lacosamide in terms of comparative effectiveness and comparative safety. The evaluation considered the claim was not adequately supported given that:

- There were concerns regarding the transitivity of the populations in the brivaracetam and lacosamide trials included in the indirect comparison. There were differences across the trials with respect to potential effect modifiers such as seizure type, the number and type of concomitant AEDs and the number of prior AEDs.
- The trials were of short duration, therefore the efficacy and safety of long-term use of brivaracetam are unknown. This is particular relevant given that the proposed treatment is a life-long therapy.

6.17 The PBAC considered the efficacy claim was not adequately supported given the brivaracetam trials included a less resistant patient population compared with the lacosamide trials. The PBAC further noted that the submission provided a non-inferiority margin for the comparison of brivaracetam and placebo, but not for the comparison with lacosamide. The PBAC considered the safety claim was not adequately supported given the short-term trials used as evidence and that there is known psychological issues (suicidal thoughts) with brivaracetam and other AEDs.

6.18 The PBAC noted that there was no clinical claim, nor any data provided, for the second requested listing for patients responding to levetiracetam but not tolerating it.

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

Economic analysis

6.19 The submission presented a cost minimisation analysis of brivaracetam and lacosamide. The PBAC considered the cost minimisation analysis versus lacosamide was not appropriate given the lack of evidence comparing the two treatments in patients of similar 'resistant' epilepsy. The ESC and PBAC noted the potential for

other PBS listed AEDs to be alternative therapies for brivaracetam, and therefore a different economic analysis may be appropriate.

6.20 The equi-effective doses were estimated in the submission as brivaracetam 124.55 mg daily and lacosamide 291.35 mg daily. The steady-state dose of brivaracetam was derived from Pool S4 where patients from Phase 2 or 3 studies, and the long-term follow-up studies, were allowed individualised dosing up to brivaracetam 200 mg/day. The dose distribution at Month 24 in Pool S4 was used in the base case analysis. The dose distribution for lacosamide was obtained from the number of lacosamide PBS items processed in the 2014-2015 financial year for the continuing treatment phase listing.

6.21 The submission's approach to determining the dose relativity between brivaracetam and lacosamide in the refractory population was not considered reliable during the evaluation given that:

- All brivaracetam studies included in Pool S4 enrolled patients with a prior treatment history less intensive than the proposed PBS population. Therefore, the brivaracetam dosage in the target population could have been underestimated; and
- The equi-effective doses of brivaracetam and lacosamide were not determined by considering the health outcomes presented in Section B of the submission. Instead, the submission has used long-term brivaracetam exposure data and PBS statistics for lacosamide to inform the dose relativity between these two drugs. The PBAC Guidelines (version 4.5) consider this approach "the least preferred" (p209). The ESC noted that the trial doses should have been used for lacosamide for the purposes of informing the dose relativity between it and brivaracetam. Doses from the trials were presented in the pre-PBAC response, however, it was noted that doses were titrated to a specified doses and hence doses were not representative of those in clinical practice.

6.22 In the cost-minimisation analysis for the proposed levetiracetam-intolerant PBS population, the submission selected levetiracetam as a proxy for all other second-line adjunctive agents and estimated equi-effective doses of 124.55 mg brivaracetam and 1,456.77 mg levetiracetam. The evaluation considered the submission's approach to cost-minimising brivaracetam against levetiracetam in the levetiracetam-intolerant population was neither justified nor conservative, as:

- Levetiracetam is not a reasonable comparator for patients with partial epileptic seizures who cannot tolerate levetiracetam therapy due to AEs; and
- The submission did not provide clinical evidence to support a non-inferiority claim for brivaracetam compared with any other second-line adjunctive AEDs.

6.23 The submission calculated the brivaracetam price for treatment of refractory patients based on the PBS ex-manufacturer price for lacosamide prior to 1 April 2016. The submission proposed flat pricing for all strengths of brivaracetam; whilst lacosamide is linear priced, with all strengths reimbursed at the same approved ex-manufacturer price (AEMP) per milligram ($[redacted] per mg). The cost-minimised price derived for the refractory population (DPMQ of $[redacted]) is the proposed published price for brivaracetam.

6.24 The submission argued that the non-refractory, levetiracetam-intolerant population is much smaller than the requested refractory population; this proportion, however, cannot be reliably estimated. The proportion of non-refractory, levetiracetam-intolerant patients would impact on the cost-minimised price of brivaracetam versus a combination of lacosamide and levetiracetam. To address this uncertainty, the submission proposed a special pricing arrangement that includes a [redacted]% discount off the published ex-manufacturer price ($[redacted] per tablet versus $[redacted] per tablet). This is similar to a cost-minimised price of brivaracetam versus a mixed comparator of lacosamide ([redacted]%) and levetiracetam ([redacted]%) (Table 7). These prices do not include the 1 April 2016 price reductions.

Table 7: Illustrative price scenarios (1 April 2016 price reductions not included)

Daily relativity and component pricing						
Drug		**Daily dose (mg)**		**Relativity to brivaracetam**		**AEMP/mg**
Brivaracetam		124.55				
Lacosamide (refractory)		291.35		2.34		$[redacted]
Levetiracetam (non-refractory, levetiracetam-intolerant)		1456.77		11.70		$[redacted]
Illustrative brivaracetam pricing						
Strength (mg)	**Maximum Quantity**	**Flat price AEMP /tablet**	**AEMP**	**DPMQ**	**Reduction in AEMP *vs.* the proposed published price[a]**	**Reduction in DPMQ *vs.* the proposed published price[a]**
75% refractory and 25% non-refractory, levetiracetam-intolerant						
25, 50, 75, 100	56	$[redacted]	$[redacted]	$[redacted]	-[redacted]%	-[redacted]%
Proposed effective price						
25, 50, 75, 100	**56**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**-[redacted]%**	**-[redacted]%**

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

[a] The cost-minimised price for brivaracetam in the refractory population is the published price proposed for brivaracetam

Source: Table D-15, p175 of the submission.

6.25 As at 1 April 2016, the price for lacosamide was reduced by 5.0%; and levetiracetam moved from the F1 formulary to the F2 formulary with a [redacted]% price reduction. The cost minimised price for brivaracetam in a scenario where 100% of patients would otherwise receive lacosamide would be $[redacted]/tablet. Assuming [redacted]% of the target population would otherwise be treated with lacosamide and [redacted]% with levetiracetam, the cost minimised price was estimated to be $[redacted]/tablet.

6.26 The proposal of a flat pricing structure across dose strengths for brivaracetam ameliorates, to some extent, the economic uncertainty surrounding the dose relativity between brivaracetam and lacosamide as both drugs usually require one tablet per administration during the maintenance therapy period. The appropriateness of a cost-minimisation approach depends on whether the non-inferior effectiveness and safety of brivaracetam versus lacosamide in the proposed refractory PBS population is adequately justified. The cost-effectiveness of brivaracetam versus second-line adjunctive AEDs, including levetiracetam, in the PBS target population cannot be reliably assessed primarily due to the lack of comparative evidence presented.

6.27 The effective price proposed in the submission for brivaracetam is similar to the weighted price assuming that, in the comparator arm, [redacted]% of patients would receive

lacosamide and the remaining [redacted]% would receive levetiracetam. This estimate is not consistent with that used for the financial analysis in the submission, in which it was assumed a higher proportion of patients ([redacted]%-[redacted]%) would otherwise be treated with levetiracetam over the first 5 years of listing. The cost-minimised price of brivaracetam will be lower than the submission's estimate if brivaracetam substitutes for levetiracetam and other second-line AEDs at a higher rate. The PSCR stated levetiracetam is not a comparator and the proposed price is not the result of weighting between comparators. The price is stated to be based on a cost-minimisation analysis with lacosamide and the [redacted]% price reduction represents a practical recognition of use of brivaracetam in patients who are not refractory as defined in the requested listing.

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

Drug cost/patient/day: $[redacted] (effective price).

6.28 $[redacted]/patient/day (published price) or $[redacted]/patient/day (effective price) for brivaracetam (two tablets/patient/day). This is compared with the cost of lacosamide being from $[redacted]/patient/day to $[redacted]/patient/day (200 mg-400 mg/patient/day) and the cost of levetiracetam from being $[redacted]/patient/day to $[redacted]/patient/day (1,000 mg-3,000 mg/patient/day) (1st April 2016 price reductions not included).

Estimated PBS usage & financial implications

6.29 This submission was not considered by DUSC.

6.30 The submission used both an epidemiological approach and a market share approach to estimate the financial implications of listing brivaracetam. The extent of use of brivaracetam has been estimated using a number of published and unpublished data sources, including the Australian Bureau of Statistics, Epilepsy Action Australia, the clinical literature, the AED treatment analyses conducted by IMS Health and the PBS prescription data for AEDs. The submission assumed that patients eligible for brivaracetam would otherwise receive lacosamide or levetiracetam in the refractory population and otherwise receive levetiracetam in the levetiracetam-intolerant non-refractory population. The extent of use and financial implications associated with the proposed listing of brivaracetam are summarised in Table 8.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prescriptions[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

[a] Number of prescriptions = number of patients x (365 ÷ 28) x 93.25%, where 28 is the number of days of treatment supplied per prescription and 93.25% is the adherence rate.
Source: E-18, p194 and Table E-28, p200 of the submission

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than $10 million per year.

6.31 The financial implications to the Government health budget could vary greatly, if the submission's assumptions are not as predicted. The main areas of uncertainty include:

- The response rate following previous AED treatments - the number of monotherapy AEDs trialled as first-line treatment is at the clinician's discretion; thus, the proportion of patients with POS not satisfactorily controlled with monotherapy AEDs and eligible for second-line adjunctive AEDs could vary from study to study. The submission's estimate of the response rate (after one second-line AED) was sourced from a study conducted in Israel more than 10 years ago. The applicability of the findings to the PBS target population is unclear as the epilepsy treatment algorithm and available second-line AEDs have changed since the study was conducted;
- Brivaracetam uptake - the uptake rates were arbitrary;
- The representativeness of levetiracetam for all second-line AEDs - there are a number of AEDs listed on the PBS as second-line adjunctive therapies which are likely to be replaced by brivaracetam. The use of levetiracetam as a proxy for all second-line adjunctive AEDs overestimated the cost offsets because it is more expensive than other AEDs commonly used in clinical practice, eg lamotrigine;
- The costs associated with specialist visits for AED dose titration - the MBS cost offsets are likely to be lower than the submission's estimates, as lacosamide and levetiracetam dose titration only occurs during the initial treatment period, not, as assumed in the submission, once every year.

Quality Use of Medicines

6.32 The submission stated that there are quality use of medicines (QUM) issues associated with treating patients with POS. It was proposed that brivaracetam addresses the following QUM issues:

- Brivaracetam provides a treatment option for patients with partial epilepsy that

is not satisfactorily controlled and who are not yet candidates for lacosamide. In this scenario, the appropriate comparator would likely be earlier-line AEDs rather than lacosamide. However, the submission did not provide any comparative evidence comparing the efficacy and safety of brivaracetam with second-line adjunctive AEDs;

- Most AEDs require titration to reach optimal therapeutic levels. The submission argued that, as brivaracetam does not need initial dose titration, it is possible that patients receiving brivaracetam could avoid breakthrough seizures which might occur during the dose titration period for other AEDs. This, although plausible, has not been well supported by the clinical evidence presented in the submission;
- There is a clinical need for treatment of patients having POS controlled by levetiracetam, but unable to tolerate continued use due to AEs. Results from the Yates 2015[a] study indicated that patients who had predominantly behavioural AEs associated with levetiracetam use benefited from switching to brivaracetam. The ESC noted that this was a single-arm open label study with a subjective outcome measure and included 22 patients. No clinical evidence has been presented in the submission comparing the comparative effectiveness and safety of brivaracetam with second-line adjunctive AEDs in levetiracetam-intolerant patients.

Financial Management – Risk Sharing Arrangements

6.33 In the submission, the sponsor has proposed a Special Pricing Arrangement (SPA) for brivaracetam. The SPA proposed is a [redacted]% discount, applied at the AEMP level. The proposed effective price for brivaracetam is consistent with a weighted cost-minimised price assuming [redacted]% refractory patients would otherwise receive lacosamide and [redacted]% non-refractory, levetiracetam-intolerant patients would otherwise receive levetiracetam.

6.34 It is noted that a Risk Share Agreement (RSA) currently applies to lacosamide. The RSA, which contains a rebate for lacosamide expenditure beyond the cap, is to ensure use of lacosamide remained within the cost-effective population.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing brivaracetam for intractable partial epileptic seizures on the basis of a lack of clinical data in the requested PBS population, and lack of a comparison with levetiracetam, or other similarly listed AEDs, which the PBAC considered would be replaced by brivaracetam. The PBAC noted the submission considered that brivaracetam should be used before lacosamide and considered this was inconsistent with selecting lacosamide as the comparator.

7.2 The PBAC noted that there may be no benefit from brivaracetam when it is added to levetiracetam, and neuropsychiatric side-effects may also compound when these

[a] Yates SL, Fakhoury T, *et al*. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. Epilepsy Behav. 2015;52(Pt A):165-8.

treatments are used concomitantly. The PBAC considered that the restriction for brivaracetam should preclude concomitant use of brivaracetam and levetiracetam.

7.3 The PBAC considered that the submission's proposal to restrict PBS subsidy of brivaracetam to refractory patients who failed to be controlled by at least one first-line agent and at least two second-line agents, and to patients who are unable to tolerate levetiracetam, was not well justified. The submission considered that brivaracetam would be used in refractory patients who do not need to be treated with triple therapy, whereas lacosamide is PBS listed for patients requiring triple therapy. The PBAC considered that the appropriate place in therapy for brivaracetam was as an alternative to levetiracetam and other similarly listed AEDs.

7.4 Given their view on the appropriate clinical place for brivaracetam, the PBAC considered that the submission's nomination of lacosamide as the comparator was not appropriate, and was not consistent with the submission's proposed earlier positioning in the treatment pathway. The Committee considered that a comparison with levetiracetam and other similar listed AEDs (eg. lamotrigine and topiramate) would be more appropriate.

7.5 The PBAC noted that the patient populations in the brivaracetam clinical trials did not match the requested PBS population, and that the patients in the brivaracetam trials had received fewer prior AEDs compared with those in the lacosamide trials. Specifically, fewer patients in brivaracetam trials were treated with 3 or more concomitant AEDs (1-6% versus 31-35%) and patients had received fewer prior AEDs (in the brivaracetam trials 13-46% of patients had received ≥5 AEDs whereas in the lacosamide trials 35-53% of patients had received ≥7 AEDs). The PBAC further noted that the lacosamide trials in the current submission were the same as included in the November 2009 lacosamide PBAC submission, and the PBS listing for lacosamide in refractory patients reflects, at least in part, that lacosamide appears to be effective in heavily pre-treated patients (Public Summary Document, lacosamide November 2009). Data for equivalently pre-treated patients were not presented for brivaracetam.

7.6 The PBAC considered the claim of non-inferior efficacy versus lacosamide was not adequately supported as the brivaracetam trials included a less resistant patient population compared with the lacosamide trials. The PBAC further noted that the submission provided a non-inferiority margin for the comparison of brivaracetam and placebo, but not for the comparison with lacosamide.

7.7 The PBAC considered the claim of non-inferior safety was not adequately supported given the short-term trials used as evidence and that there is known psychological issues (suicidal thoughts) with brivaracetam and other AEDs.

7.8 The PBAC noted that there was no clinical claim, nor any data provided, for the proposed listing for patients not tolerating levetiracetam.

7.9 The PBAC considered the cost minimisation analysis versus lacosamide was not appropriate given the lack of evidence comparing the two treatments in patients of similar 'resistant' epilepsy.

7.10 The equi-effective doses were estimated in the submission as brivaracetam 124.55 mg daily and lacosamide 291.35 mg daily. The PBAC noted that the brivaracetam dose was derived from clinical trial data whereas the lacosamide dose was derived from PBS data, and hence considered the equi-effective doses to not be reliable.

7.11 The PBAC noted the proposed SPA with an effective price [redacted]% lower than the proposed published price (which was based on the cost-minimisation analysis versus lacosamide). The PBAC noted the effective price was similar to a cost-minimised price of brivaracetam versus a mixed comparator of lacosamide ([redacted]%) and levetiracetam ([redacted]%). The PBAC did not consider this to be an appropriate comparison.

7.12 The PBAC considered that any resubmission would need to be a major submission, and should compare brivaracetam with second-line AEDs.

7.13 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 in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.