7.01 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 resubmission requested a Schedule 85 - General listing for brivaracetam for the treatment of intractable partial epileptic seizures. The first submission was considered in July 2016.

2 Requested listing

2.1 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 Tablets 25 mg, 50 mg, 75 mg and 100 mg, 56	1	5	$[redacted]	Briviact®	UCB Pharma

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ ~~Nurse practitioners~~ ☐ Optometrists ☐ Midwives
Episodicity:	Partial onset
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial onset epileptic seizures
Treatment phase:	Initial treatment
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:	Treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, AND The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents, *AND* *The treatment must not be given concomitantly with levetiracetam*
Population criteria:	Patients must be aged 16 years or older
Administrative Advice	*Special Pricing Arrangements apply*

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Partial onset
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial onset epileptic seizures
Treatment phase:	Continuing treatment
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:	Patient must have previously been treated with PBS-subsidised *treatment with this drug* ~~brivaracetam~~. *AND* *Treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent.* *AND* *The treatment must not be given concomitantly with levetiracetam*
Population criteria:	Patients 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. *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 Oral solution, 10 mg/mL, 300 mL	1	5	$[redacted]	Briviact® UCB Pharma

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ ~~Nurse practitioners~~ ☐ Optometrists ☐ Midwives
Episodicity:	Partial onset
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial onset epileptic seizures
Treatment phase:	Initial treatment
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:	Treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent. AND The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents. AND Patient must be unable to take a solid dose form of *this drug* ~~brivaracetam~~. *AND* *The treatment must not be given concomitantly with levetiracetam*
Population criteria:	Patients must be aged 16 years or older
Administrative Advice	*Special Pricing Arrangements apply*

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Partial onset
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial onset epileptic seizures
Treatment phase:	Continuing treatment

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:	Patient must have previously been treated with PBS-subsidised *treatment with this drug* ~~brivaracetam~~. AND Patient must be unable to take a solid dose form of *this drug* ~~brivaracetam~~ *AND* *Treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent.* *AND* *The treatment must not be given concomitantly with levetiracetam*
Population criteria:	Patients 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. *Special Pricing Arrangements apply*

2.2 The resubmission positioned brivaracetam as a third-line adjunctive therapy for use in the same population who would be eligible for lacosamide and perampanel.

2.3 The treatment criteria were based on the current PBS listings for lacosamide and perampanel. The Economic-Sub-Committee (ESC) considered it may be more appropriate to only require initiation by a neurologist.

2.4 The proposed restriction in the July 2016 submission was for (i) a refractory population who were not adequately controlled on three or more anti-epileptic drugs (at least one first-line agent and at least two second-line agents) and (ii) patients who were controlled on levetiracetam, but who could not tolerate the drug and had to discontinue due to adverse events.

2.5 The key differences between the requested restriction in the original submission and the resubmission were:

- in the revised restriction, treatment must be in combination with two or more anti-epileptic drugs, which included one second-line agent. Although this is in line with the restrictions for lacosamide and perampanel, during the evaluation it was noted it might not be appropriate as, per the original submission, brivaracetam could potentially be used as part of dual therapy in patients who did not need to be treated with triple therapy; and
- removal of the second previously proposed population of patients in whom partial onset seizures are controlled by levetiracetam but the patient is unable to tolerate the drug. This was consistent with the ESC and PBAC comments from July 2016 which noted the lack of robust clinical data provided to support this indication.

2.6 Based on advice from the PBAC at its July 2016 meeting and the ESC, the Secretariat added criteria which precludes concomitant use of brivaracetam and

levetiracetam. This would result in a flow-on change to the levetiracetam restrictions with the following wording added to the clinical criteria 'AND The treatment must not be given concomitantly with brivaracetam'.

2.7 In its pre-PBAC response the sponsor argued the standard of care for switching patients from one AED to another is to cross-titrate. This involves slowly discontinuing levetiracetam, whilst slowly initiating brivaracetam and therefore concomitant use.

2.8 The resubmission 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 25% for oral liquids over tablets was proposed at an ex-manufacturer price level (per bottle versus per pack). The resubmission 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 resubmission did not provide further details on how the magnitude of the price premium (25%) was determined. The ESC noted people with developmental delay and cerebral palsy represent a substantial proportion of people with refractory epilepsy, and difficulty swallowing tablets is common in this group. It was further noted that the options for non-tablet oral antiepileptics are currently limited (valproate oral liquid, levetiracetam oral liquid, and ethosuximide oral liquid) and therefore there may be significant demand for a liquid presentation of brivaracetam.

2.9 In its pre-PBAC response the sponsor argued that the use of the brivaracetam oral solution would be expected to be low and definitely in the lower end of the spectrum of use observed for medicines currently available as an oral solution. It was noted that ethosuximide is indicated specifically for childhood absence epilepsy and both valproate and levetiracetam are indicated for children and adults, whereas brivaracetam is not TGA registered for use in patients under 16 years of age.

2.10 The requested basis for listing was a cost-minimisation analysis of brivaracetam compared with lacosamide. The requested price in this resubmission is higher than requested in the July 2016 submission ([redacted]% higher for tablets and [redacted]% higher for oral liquid).

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

3 Background

3.1 Brivaracetam was TGA registered on 2 August 2016 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 Brivaracetam was considered by PBAC once previously, in July 2016. A summary of the previous submission and the current resubmission is presented in the table below.

Table 1: Summary of the previous submission and current resubmission

	Brivaracetam July 2016 submission	Current resubmission
Requested PBS listing	The proposed PBS listing included two populations: 1) A refractory population who were not adequately controlled on ≥ 3 anti-epileptic drugs (≥1 first-line agent and ≥2 second-line agents). 2) Patients who were controlled on levetiracetam, but who could not tolerate levetiracetam and had to discontinue due to adverse events. **PBAC Comment:** The PBAC considered that the proposed PBS restriction was not well justified. The PBAC considered that the appropriate place in therapy for brivaracetam was as an alternative to levetiracetam and other similarly listed anti-epileptic drugs (Paragraph 7.3, PBAC PSD). The ESC and PBAC noted that there were no robust clinical data provided to support the proposed listing for the second population of patients not tolerating levetiracetam (Paragraphs 4.2, 6.18, 7.8, PBAC PSD). No initiation or continuation criteria were specified for brivaracetam (Paragraph 2.4, PBAC PSD). The listing should preclude concomitant use of brivaracetam and levetiracetam (Paragraphs 2.5, 7.2, PBAC PSD).	The proposed PBS restriction was for use of brivaracetam in combination with ≥ 2 anti-epileptic drugs which includes one second-line adjunctive agent; AND in patients not adequately controlled on ≥ 3 anti-epileptic drugs (≥1 first-line agent and ≥2 second-line agents). Clinical criteria have been refined to position brivaracetam in the same patient population as for lacosamide and perampanel. No clinical justification was provided for the refined restriction. The second population has been removed from the current requested listing. The revised restriction for brivaracetam was structured as an initial and continuing listing. Not addressed in resubmission.
Requested price	Effective DPMQ: Tablets - $[redacted]/56 tablets (flat price across all strengths) Oral liquid - $[redacted]/300 mL (Published DPMQ: Tablets - $[redacted]/56 tablets Oral liquid - $[redacted]/300 mL)	Effective and published DPMQ: Tablets - $[redacted]/56 tablets (flat price across all strengths) (28% price increase). Oral liquid - $[redacted]/300 mL (16% price increase). No Special Pricing Arrangement proposed.
Main comparator	Lacosamide **PBAC Comment:** The PBAC considered that the submission's nomination of lacosamide as the comparator was not appropriate, and was not consistent with the positioning of brivaracetam earlier in the treatment pathway. The PBAC considered that a comparison with levetiracetam and other similar listed anti-epileptic drugs (e.g. lamotrigine and topiramate) would be more appropriate (Paragraph 7.4, PBAC PSD).	No change. The resubmission stated that as the revised restriction positioned brivaracetam in the same selective PBS patient populations as lacosamide and perampanel, lacosamide was now an appropriate comparator.

	Brivaracetam July 2016 submission	Current resubmission
Clinical evidence	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 were presented. Placebo was the common reference. **PBAC Comment:** 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 anti-epileptic drugs. The lacosamide trial populations appeared to be more refractory to treatment with other anti-epileptic drugs, compared with the brivaracetam populations. Data for equivalently pre-treated patients were not presented for brivaracetam (Paragraph 6.6, PBAC PSD).	No new trials were presented. The transitivity concerns were not addressed within the resubmission.
Key effectiveness data	Based on the indirect comparisons, there were no statistically significant differences between brivaracetam and lacosamide in terms of: i) The proportion of patients achieving ≥ 50% reduction from baseline in partial onset frequency per 28 days (RR = 1.06; 95% CI: 0.79, 1.43); ii) The reduction from baseline in seizure frequency per 28 days (ratio of medians = 1.00; 95% CI: 0.89, 1.14); and iii) The proportion of patients who experienced seizure free status during the treatment phase of the trials (RR = 2.73; 95% CI: 0.54, 13.70). **PBAC Comment:** The PBAC considered the efficacy claim was not adequately supported as the brivaracetam trials included a less resistant patient population compared with the lacosamide trials (Paragraphs 6.17, 7.5, PBAC PSD). The PBAC noted that the submission provided a non-inferiority margin for the comparison of brivaracetam and placebo, but not for the comparison with lacosamide (Paragraph 6.17, PBAC PSD).	The clinical data sets for brivaracetam and lacosamide (for selected daily doses) were stratified post hoc according to concomitant medications and prior anti-epileptic drug history. Based on an indirect comparison of these subgroups the resubmission claimed that there were no significant differences between brivaracetam and lacosamide in terms of the proportion of patients achieving a 50% responder rate (RR = 0.97; 95% CI: 0.66, 1.44) in the proposed PBS population. A lower non-inferiority margin within the range of 0.62 and 0.68 was nominated based on the lower 95% confidence limits of perampanel (July 2014) and zonisamide (November 2007).

	Brivaracetam July 2016 submission	Current resubmission
Key safety data	The most commonly reported adverse events in the brivaracetam trials were somnolence (14%), dizziness (11%) and fatigue (8%). The most commonly reported adverse events due to lacosamide were dizziness (31%), headache (13%) and nausea (11%). An indirect comparison showed there were no significant differences in TEAEs between brivaracetam and lacosamide. There were no long term safety data for brivaracetam. **PBAC Comment:** The PBAC considered that the safety claim was not adequately supported given the short-term trials used as evidence and known psychological issues (suicidal thoughts) with brivaracetam and other anti-epileptic drugs (Paragraph 6.17, 7.7, PBAC PSD).	No new information was presented. The resubmission noted that the length of trials presented in the submission were standard for add-on therapies in epilepsy and that the PBAC has previously drawn conclusions based on trials of the same length between perampanel and lacosamide.
Clinical claim	The submission described brivaracetam as non-inferior to lacosamide in terms of both comparative effectiveness and comparative safety. **PBAC Comment:** The PBAC considered the claim was not adequately supported given concerns regarding transitivity of the populations included in the indirect comparisons and the short duration of trials, particularly as the proposed treatment is a life-long therapy (Paragraph 6.16, PBAC PSD). There was no clinical claim, nor data provided, for the second requested listing for patients responding to levetiracetam but not tolerating it (Paragraphs 6.18, 7.8, PBAC PSD).	When results were stratified post hoc by prior anti-epileptic drug use, the resubmission claimed that brivaracetam was shown to be non-inferior to lacosamide in the subgroups with ≥ 2 concomitant anti-epileptic drugs and ≥ 3 prior anti-epileptic drugs. Clinical criteria have been refined to remove the second requested population and to position brivaracetam in the same patient population as for lacosamide and perampanel.
Economic evaluation	Cost-minimisation with equi-effective doses of: Brivaracetam 124.55 mg daily = Lacosamide 291.35 mg daily **PBAC Comment:** The PBAC considered the cost minimisation versus lacosamide was not appropriate, given the lack of evidence comparing the two treatments in patients of similar 'resistant' epilepsy (Paragraphs 6.19, 7.9, PBAC PSD). The PBAC noted that the equi-effective 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 (Paragraph 7.10, PBAC PSD).	Cost-minimisation with equi-effective doses of: Brivaracetam 117.6 mg daily = Lacosamide 316.2 mg daily Mean daily doses were calculated for the pivotal brivaracetam and lacosamide studies for selected doses within the trial populations. Mean daily doses for brivaracetam were also calculated for the post hoc subgroup of patients who matched the proposed PBS patient population.
Number of patients	Less than 10,000 patients in Year 1 increasing to less than 10,000 in Year 5.	Less than 10,000 patients in Year 1 increasing to less than 10,000 in Year 5.
Estimated cost to PBS/RPBS	Less than $10 million in Year 1 decreasing to less than $10 million in Year 5 for a total of $10 – 20 million over the first 5 years of listing.	A cost saving of less than $10 million in Year 1 increasing to a cost saving of less than $10 million in Year 5 for a total of cost saving of less than $10 million over the first 5 years of listing.

	Brivaracetam July 2016 submission	Current resubmission
PBAC decision	Reject **PBAC Comment:** The PBAC did not recommend the listing on the basis of a lack of clinical data in the requested patient population and a lack of comparison with levetiracetam, or other similarly listed anti-epileptic drugs, which the PBAC considered would be replaced by brivaracetam (Paragraph 7.1, PBAC PSD).	-

Source: Compiled during the evaluation

CI = confidence interval; DPMQ = dispensed price for maximum quantity; ESC = Economics Sub-Committee; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RR = risk ratio; TEAE = treatment-emergent adverse event

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

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. Partial onset seizures originate within specific neuronal networks in one cerebral hemisphere. Partial onset seizures with secondary generalisation are initially localised to a particular area of the brain but then spread to both hemispheres after the initial event.

4.2 Brivaracetam, the 4-n-propyl analogue of levetiracetam, is an antiepileptic drug which displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is considered to be the primary mechanism for brivaracetam anticonvulsant activity. However, the resubmission noted that the precise mechanism by which brivaracetam exerts its anticonvulsant activity has not been fully elucidated.

4.3 The resubmission's proposed place in therapy for brivaracetam was as a third-line adjunctive therapy in the same population who are eligible for lacosamide and perampanel i.e. patients on two or more anti-epileptic drugs (which includes one second-line adjunctive agent) and not adequately controlled on three or more anti-epileptic drugs (at least one first line and two second line agents).

4.4 At its July 2016 PBAC meeting, the PBAC considered that the appropriate place in therapy for brivaracetam was as an alternative to levetiracetam and other similarly listed anti-epileptic drugs (AEDs) (PSD, July 2016).

4.5 The Pre-Sub-Committee Response (PSCR) argued that based on the proposed restriction, only very refractory patients who require at least 3 concomitant AEDs would be eligible for brivaracetam. The PSCR referred to the PBAC hearing for the July 2016 submission at which it was stated neurologists are highly conservative in treating their patients, and take years or even decades to generate comfort to take on newer AEDs and use them earlier in the treatment algorithm. The PSCR referred specifically to levetiracetam which after 20 years of listing is now being used as a first add-on AED in partial onset epilepsy.

4.6 The ESC noted it is possible that brivaracetam will be used more as an alternative to levetiracetam than purely a third-line add-on. In its pre-PBAC response the sponsor

stated there is good evidence to show that PBS use of lacosamide and perampanel is constrained by the Authority required listing, and based on this the sponsor considered the use of brivaracetam would be similarly constrained to the same target patient population.

4.7 The PBAC requested advice from the Epilepsy Society of Australia (ESA). The PBAC noted the advice from the ESA positioned lacosamide and perampanel as second line treatments for the management of intractable partial onset seizures, which was inconsistent with the advice from the sponsor that lacosamide is used as a third line therapy in practice. The PBAC noted the advice from the ESA also stated the choice of second line or third line treatments will be affected by the first line therapy used, as clinicians will consider potential drug-drug interactions and mechanisms of action. The ESA positioned levetiracetam as a first line therapy.

4.8 The ESC noted it is possible that IV brivaracetam will be used by neurosurgeons and in emergency departments, and this will result in use as a first or second line drug as patients would likely remain on brivaracetam to avoid switching to an alternative antiepileptic. In its pre-PBAC response the sponsor argued neurosurgeons will not initiate use of brivaracetam to any significant degree, as choice of AEDs in emergency departments is dictated by protocol and cost.

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

5 Comparator

5.1 The resubmission nominated lacosamide as the main comparator. This was the same comparator as in the original submission. Although the revised PBS restriction requested for brivaracetam was the same as that for lacosamide, in clinical practice brivaracetam could potentially be used in refractory patients who do not need to be treated with triple therapy. As per the PBAC's previous consideration, second-line anti-epileptic drugs, such as levetiracetam, lamotrigine or topiramate, might have been more appropriate comparators.

5.2 The ESC noted the appropriate comparator will depend on where brivaracetam is positioned in the treatment algorithm in clinical practice. The ESC noted that in clinical practice brivaracetam may be considered as an alternative to levetiracetam.

5.3 Perampanel was recommended for listing on a cost-minimisation basis compared with lacosamide. Both drugs are listed in the F1 formulary, however, a 5% statutory price reduction has been applied to lacosamide but not perampanel. Therefore, the price of lacosamide is lower than that of perampanel.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (7) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with brivaracetam including broadening the therapeutic options in the care of people with epilepsy, and a desirable reported efficacy and tolerability profile.

6.3 The PBAC noted the advice received from Epilepsy Action Australia and Epilepsy Foundation clarifying the likely use of brivaracetam in clinical practice. The PBAC specifically noted the advice that the use of brivaracetam may reduce or control seizures for patients who have not gained seizure control from currently listed PBS medications.

6.4 The PBAC noted the advice received from the ESA stated that brivaracetam may have a role in the treatment of patients with intractable partial onset seizures and there is a clinical need for brivaracetam as an alternative to lacosamide and perampanel given its different mechanism of action and that it may have a different efficacy and tolerability profile for individual patients.

Clinical trials

6.5 The resubmission was based on the same trials as the original submission.

6.6 Details of the trials presented in the resubmission are provided in the table below.

Table 2: Trials and associated reports presented in the original 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. Publication 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. Publication 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

Trial ID	Protocol title Publication title	Publication citation
1358	Primary clinical study report NCT01261325 - A randomised, double-blind, placebo-controlled, multi-centre, 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. Publications Klein P, Schiemann J, Sperling MR, Whitesides J, Liang W, Stalvey T, Brandt C, Kwan P. A randomised, double-blind, placebo-controlled, multi-centre, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial onset seizures. Klein P, Schiemann J, Sperling M, Whitesides J, Liang W, Stalvey T. A randomised, double-blind, placebo-controlled, multi-centre, parallel-group study to evaluate the efficacy and safety of brivaracetam in adult patients with partial onset seizures.	19 September 2014 *Epilepsia* 2015; 56(12):1890-1898 *Epilepsy Currents* 2015; (15):379
Proposed comparator lacosamide versus placebo		
SP667	Primary clinical study report - A multi-centre, 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. 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	9 Mar 2005 *Epilepsia* 2007; 48(7):1308-1317.
SP754	Primary clinical study report NCT00136019 - A multi-centre, 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 multi-centre, 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

Source: Table 1, p6 of the July 2016 PBAC Minutes
SPM 927 = lacosamide

6.7 The same indirect comparison of brivaracetam and lacosamide in patients with refractory or intractable epilepsy was presented. Six double-blinded placebo controlled trials (three for each drug) were used in the indirect comparison, with placebo as the common reference (see Table 1 in the Background above).

6.8 Brivaracetam trials:

- 1252: randomised; double-blind; 14 weeks; versus placebo; N = 399;
- 1253: randomised; double-blind; 13 weeks; versus placebo; N = 400; and
- 1358: randomised; double-blind; 16 weeks; versus placebo; N = 768.

6.9 Lacosamide trials:

- SP667: randomised; double-blind; 12 weeks; versus placebo; N = 497;
- SP754: randomised; double-blind; 12 weeks; versus placebo; N = 489; and
- SP755: randomised; double-blind; 12 weeks; versus placebo; N = 546.

6.10 The resubmission presented a new indirect comparison based on a post hoc subgroup analysis of patients who were more similar to the target PBS population. This new post hoc subgroup analysis included patients with three or more previous anti-epileptic drugs, at least two concomitant anti-epileptic drugs and no concomitant levetiracetam (and brivaracetam doses of 50 mg to 200 mg per day and lacosamide doses of 200 mg to 400 mg per day, as per the respective recommended daily doses). The PSCR states that this analysis was conducted to address the PBAC's concerns about transitivity of the patient populations. The ESC noted that the transitivity concerns remained.

Comparative effectiveness

6.11 The key efficacy results from the original indirect comparison were unchanged. The PBAC noted at its July 2016 meeting 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 (PSD, July 2016). The PSCR argued the brivaracetam and lacosamide trials were generally very similar. It was noted in the brivaracetam trials the average time since diagnosis was 20 years, 20% of the patients in the 1252 and 1253 trials had a concomitant history of 4 or more AEDs and 50% of the patients in the 1358 trial had previously tried 5 or more AEDs. In the lacosamide trials mean time since diagnosis was 22-24 years and across the three trials 32.2% of patients had previously been treated with 4 to 6 AEDs. The PCSR stated that in the post hoc analysis, the subgroups in the brivaracetam and lacosamide trials were matched with respect to the important parameters of number of prior AEDs and number of concomitant AEDs.

6.12 In its pre-PBAC response , the sponsor reiterated the subjects in the brivaracetam and lacosamide trials were sufficiently similar to allow comparison in the post hoc analysis of patients who matched the PBS eligibility criteria. It was specifically noted that the pooled proportion of 50% responders in the placebo groups for the post-hoc analysis were similar (brivaracetam trials: 18.4%; lacosamide trials: 20.3%), and this supported that the patient populations of the brivaracetam and lacosamide subgroups were well matched.

6.13 Results from the post hoc subgroup indirect comparison are presented in Table 3. The primary outcome for the post hoc analysis was 50% responder rate. This has been previously considered clinically meaningful by the PBAC.

6.14 The July 2016 submission did not provide a non-inferiority margin for the comparison between brivaracetam and lacosamide. The resubmission nominated a lower relative

risk margin within the range of 0.62 and 0.68 to support a claim of non-inferiority over the active comparator, lacosamide. This was based on the lower 95% confidence limits of perampanel (July 2014) and zonisamide (November 2007). The resubmission again used the same non-inferiority margin to reflect a clinically relevant effect (a 15% absolute difference in response rates) in the comparison of brivaracetam and placebo. The nominated non-inferiority margins were considered reasonable.

Table 3: 50% responder rate for partial onset seizure frequency in patients with ≥ 3 previous anti-epileptic drugs, ≥ 2 concomitant anti-epileptic drugs and no concomitant levetiracetam – a *post hoc* subgroup analysis of the Pool E1 population [a]

	Brivaracetam, n/N (%)	Placebo, n/N (%)	Lacosamide, n/N (%)	RR (95% CI)	p-value
Brivaracetam trials [b]	117/362 (32.3%)	38/206 (18.4%)	-	**1.75 (1.3, 2.4)**	0.00059
Lacosamide trials [c]	-	55/271 (20.3%)	198/540 (36.7%)	**1.80 (1.4, 2.3)**	< 0.00001
Indirect comparison	-	-	-	0.97 (0.66, 1.44)	-
Indirect comparison July 2016 - Pool E1 population [a,d]	-	-	-	1.06 (0.79, 1.43)	-

Source: Table 44, p96 and Tables 87-89, pp153-154 of the resubmission

CI = confidence interval; RR = relative risk; **Bold** = statistically significant

[a] Pool E1 population consisted of patients included in the primary efficacy analyses for Trials 1252, 1253 and 1358, but excluded patients receiving levetiracetam at the time of study entry for Trials 1252 and 1253.

[b] *Post hoc* subgroup analysis included patients from Trials 1252, 1253 (data for 50 mg to 200 mg per day doses only) and Trial 1358 (data for 100 mg to 200 mg per day doses only).

[c] *Post hoc* subgroup analysis included patients from Trials SP667, SP754 and SP755 (data for 200 mg and 400 mg per day doses only).

[d] E1 population patients receiving brivaracetam 50 mg to 200 mg per day or lacosamide 200 mg to 400 mg per day.

6.15 The post hoc subgroups were not well balanced in terms of baseline characteristics and the resubmission grouped data from the individual trials together without sufficient justification.

Comparative harms

6.16 The resubmission provided no new comparative safety data.

Clinical claim

6.17 The resubmission stated that the post hoc subgroup analysis and subsequent indirect comparison demonstrated that brivaracetam was non-inferior in relation to lacosamide in the proposed PBS population.

6.18 The resubmission claimed that this supported the original conclusion of non-inferiority for brivaracetam compared with lacosamide based on the total trial population. Therefore, the resubmission again described brivaracetam as non-inferior in terms of comparative effectiveness, and non-inferior in terms of comparative safety compared with lacosamide.

6.19 During the evaluation it was considered this claim was not adequately supported given that:

(i) the resubmission did not address the following issues, which were highlighted by the PBAC in July 2016 –
- the transitivity concerns between the brivaracetam and lacosamide trials as

highlighted by the differences across the trials in the results for the common reference (placebo) arms.
- the efficacy claim of non-inferiority in the total trial population was not adequately supported as the brivaracetam trials included a less resistant patient population compared with the lacosamide trials; and
- the safety claim was not adequately supported given the short-term trials used as evidence. In addition, the original submission did not address the increased risk of known psychological issues (suicidal thoughts) associated with brivaracetam and other anti-epileptic drugs. The PSCR states the trial durations represent the standard for add-on therapies in epilepsy. It further states that the resubmission presented long-term safety data which included use of brivaracetam for up to 8 years, and surveillance has yet to identify further safety concerns (such as suicidal thoughts) beyond what was identified in the short-terms trials.

(ii) concern remained over how brivaracetam would be used in clinical practice and whether the nominated comparator, lacosamide, and the nominated place in the treatment algorithm as a third-line adjunctive option, were appropriate –
- although the PBAC considered in July 2016 that the appropriate place in therapy for brivaracetam was as an alternative to levetiracetam and other similarly listed anti-epileptic drugs, the resubmission positioned brivaracetam as an alternative to lacosamide and perampanel in patients with intractable partial onset seizures. There would be potential for leakage, with brivaracetam used in refractory patients who did not need to be treated with triple therapy.

(iii) the results of the post hoc subgroup analysis presented in the resubmission were unreliable as –
- the imbalanced baseline characteristics between patients receiving differing daily doses of brivaracetam and lacosamide and their respective placebo arms suggested that there was considerable potential for both bias and confounding due to the non-randomised assignment of patients;
- differences in the number of concomitant anti-epileptic drugs between the brivaracetam and lacosamide subgroups suggested that there was a difference between these populations in terms of resistant epilepsy; and
- it was unclear whether the meta-analysis of the individual trials included in the indirect comparison was appropriate as the heterogeneity across the individual trials was not assessed.

6.20 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.21 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.22 Similar to the original submission, a cost-minimisation analysis of brivaracetam versus lacosamide in patients with refractory partial epileptic seizures was conducted. This approach relies on the acceptance of the non-inferiority claim of brivaracetam versus lacosamide in terms of comparative effectiveness and safety.

6.23 The trial based equi-effective daily doses in the resubmission were estimated as 117.6 mg for brivaracetam and 316.2 mg for lacosamide, in comparison with 124.6 mg for brivaracetam and 291.4 mg for lacosamide in the original submission. The weighted mean daily dose of brivaracetam for the subgroup of PBS-eligible patients was estimated as 125.4 mg. A mean daily dose specific to the PBS-eligible patients was not available for the lacosamide trials.

6.24 The sponsor argued in its pre-PBAC response that the current listing for lacosamide was on the basis of a mean daily dose of 316.2 mg (lacosamide PSD, July 2009) and therefore on the total trial populations from the same trials used in this resubmission.

6.25 The equi-effective doses calculated in the resubmission were trial based (this was consistent with the ESC recommendation for the original submission that trial doses of lacosamide should be used to inform the dose relativity with brivaracetam). Doses outside those recommended in the respective Product Information were excluded from the calculations (i.e. brivaracetam equi-effective dose did not include patients who received daily doses of 5 mg and 20 mg; and the lacosamide equi-effective dose did not include patients who received a daily dose of 600 mg).

6.26 The resubmission calculated the brivaracetam price based on the PBS approved ex-manufacturer price (AEMP) for lacosamide (as of 1 October 2016). The resubmission again proposed a flat pricing structure for all strengths of brivaracetam. Lacosamide has a linear price, with all strengths reimbursed at the same AEMP per milligram ($0.0261).

Table 4: Brivaracetam cost per pack calculations

	Equi-effective dose	Cost per day (AEMP)	Days of therapy per pack	AEMP	DPMQ
Lacosamide tablets	316.2 mg	$[redacted]	28	-	-
Brivaracetam tablets: 25 mg, 50 mg, 75 mg, 100 mg, x 56	117.6 mg [a]	$[redacted]	28	$[redacted]	$[redacted]
Brivaracetam liquid: 10 mg/mL, 300 mL	-	-	-	$[redacted]	$[redacted]

Source: Tables 101-102, pp162-163 of the resubmission
AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity
[a] Table 101 of the resubmission incorrectly listed this figure as 114.0 mg, this table presents the correct equi-effective dose (117.6 mg) that was calculated and presented in the body of the resubmission.

The monthly costs of brivaracetam tablets (25 mg, 50 mg, 75 mg and 100 mg) proposed by the resubmission were: AEMP = $[redacted]; and dispensed price for maximum quantity (DPMQ) = $[redacted]. The costs of the oral solution were calculated by adding a [redacted]% price premium to the tablet cost and were: AEMP = $[redacted]; and DPMQ = $[redacted].

6.27 Although the proposal of a flat pricing structure across dose strengths for brivaracetam tablets ameliorated the economic uncertainty surrounding the mean daily dose of brivaracetam, uncertainty surrounding the equi-effective dose of lacosamide remained.

Drug cost/patient/year: $[redacted]

6.28 The resubmission estimated that the cost of brivaracetam tablets per year would be $[redacted], assuming 100% compliance. The original submission estimated a yearly cost of $[redacted], based on a proposed effective price of $[redacted].

6.29 The yearly cost of lacosamide, was calculated to be $2,187.39 based on a daily dose of 200 mg, and $4,297.48 based on a daily dose of 400 mg.

Estimated PBS usage & financial implications

6.30 This resubmission was not considered by DUSC. The resubmission used a market share approach to estimate the use and financial implications for the requested listing of brivaracetam on the PBS. The original submission used a different approach (an epidemiological and a market share) and considered a different patient population.

Table 5: Estimated use and financial implications of listing brivaracetam on the PBS/RPBS/MBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of brivaracetam use					
Eligible refractory population [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam prescriptions [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS					
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost offsets to PBS/RPBS due to reduced lacosamide use [c]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**
Estimated total net cost					
Cost offsets to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS/MBS	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**

Source: Compiled during the evaluation

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] A corrected average annual growth rate of 24.66% for 2011 to 2016 (calculations in the resubmission incorrectly used a growth rate of 26.05% for 2011 to 2015) was used.

[b] Annual number of PBS prescriptions per patient = 12.16, based on a script analysis conducted by IMS Health.

[c] A corrected dose relativity of 2.69 (the resubmission incorrectly used a dose relativity of 2.77) and corrected patient numbers for patients receiving lacosamide 300 mg/day were used.

6.31 The resubmission estimated that the net cost saving to the PBS/RPBS and MBS would be less than $10 million in the first five years of listing; this compared with an estimated net cost to the government of $10-20 million in the original submission. The change in cost was due to the change in proposed PBS restriction which resulted in an increase in the number of patients likely to be treated with brivaracetam third-line as compared to second-line and the removal of the levetiracetam intolerant population.

6.32 The net cost savings were due to the flat pricing structure of brivaracetam and the price per milligram structure for lacosamide.

6.33 The cost savings presented above in Table 5 may have been under or overestimated as:

- brivaracetam could potentially be used outside the requested PBS restriction as a second-line anti-epileptic drug (overestimate);

- the daily dosage distribution of brivaracetam was uncertain as it was based on a trial population that included non-refractory patients. The proportion of patients receiving higher brivaracetam doses, and therefore higher corresponding lacosamide doses, was likely to be higher than estimated in the resubmission (likely underestimate);
- the resubmission assumed complete replacement of lacosamide for brivaracetam (overestimate);
- the financial estimates are highly sensitive to patients receiving concomitant brivaracetam and lacosamide (overestimate);
- the dose relativity between brivaracetam and lacosamide remained uncertain (over or underestimate); and
- the resubmission did not consider use of the oral solution, which had a higher proposed price than the tablets (overestimate).
    - The PSCR argues levetiracetam is available in an oral liquid and in the 2015/16 financial year, the oral liquid accounted for less than 5% of total PBS services for levetiracetam.

6.34 There was potential for brivaracetam to be used outside of the requested PBS listing in patients who had not fulfilled the requirements for previous treatment failures, i.e. there was potential for leakage into second line use. It is unknown to what extent this would occur; however it would increase the cost of brivaracetam to the PBS/RPBS as the proposed price of brivaracetam is significantly higher than the PBS-listed prices of second-line anti-epileptic drugs.

6.35 Results of the key sensitivity analyses to the PBS/RPBS are summarised in Table 6 below.

Table 6: Results of the key sensitivity analyses to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated net cost to PBS/RPBS					
Base case	-$	-$	-$	-$	-$
Equal daily dose distribution (50 mg: 25%; 100 mg: 25%; 150 mg: 25%; 200 mg: 25%)	$	$	$	$	$
Tendency to higher doses (50 mg: 15%; 100 mg: 20%; 150 mg: 30%; 200 mg: 35%)	-$	-$	-$	-$	-$
10% concomitant use of lacosamide and brivaracetam	$	$	$	$	$
30% concomitant use of lacosamide and brivaracetam	$	$	$	$	$

Source: Compiled during the evaluation
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted table shows that, for each of the sensitivity analyses, the estimated net cost to the PBS/RPBS was less than $10 million per year.

6.36 The estimated cost saving is uncertain. The main areas of uncertainty included:

- concomitant use of lacosamide and brivaracetam (increased costs); and
- the daily dose distribution of brivaracetam (increased cost savings if, as suggested in the resubmission, in practice there was a tendency towards higher brivaracetam doses (and corresponding lacosamide doses) as the trial population included non-refractory patients).

Financial Management – Risk Sharing Arrangements

6.37 There is a Subsidisation Cap which is shared between lacosamide and perampanel, with a rebate that applies on any expenditure above these caps. The ESC noted that the sponsor was requesting PBS listing in the same patient population as lacosamide and that the sponsor was cognisant of the risk share agreement in place (PSCR p4). The pre-PBAC response noted the cost to government for lacosamide and perampanel is contained by a market cap, and the sponsor is aware that brivaracetam would be added to the market cap.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of brivaracetam for intractable partial epileptic seizures on the basis of a lack of a comparison with levetiracetam, or other similarly listed AEDs, which the PBAC considered would be replaced by brivaracetam. The PBAC noted the resubmission proposed listing brivaracetam as third-line adjunctive therapy for use in the same population eligible for lacosamide and perampanel, however considered this was not well justified and that earlier use of brivaracetam was clinically appropriate.

7.2 The PBAC noted uncertainty remained around the compounding of neuropathic side-effects when brivaracetam is used concomitantly with levetiracetam. The PBAC also noted the initial and continuing treatment criteria nominated in the resubmission may not be necessary as unlike lacosamide, brivaracetam does not require dose titration initiation.

7.3 The PBAC considered their concern noted in July 2016 regarding the proposed place in therapy for brivaracetam remained. The PBAC noted the resubmission positioned brivaracetam as a third-line adjunctive agent, however, the PBAC considered it clinically appropriate for brivaracetam to be used earlier in the treatment algorithm, and specifically for brivaracetam to be used in a similar way to levetiracetam given it is an analogue of levetiracetam. In relation to this, the PBAC noted the advice received from the Epilepsy Society of Australia (ESA) which positioned levetiracetam as a first-line therapy and lacosamide as second-line therapy.

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. The PBAC reiterated its view from July 2016 that a comparison versus second-line anti-epileptic medicines, such as levetiracetam, lamotrigine or topiramate would be more appropriate.

7.5 The PBAC noted the resubmission presented a new indirect analysis for brivaracetam and lacosamide based on a post-hoc subgroup analysis that included patients with three or more previous anti-epileptic drugs, at least two concomitant anti-epileptic drugs, no concomitant levetiracetam and TGA recommended doses for brivaracetam and lacosamide. This subgroup was considered in the resubmission to more closely reflect the target PBS population. The PBAC considered the post-hoc analysis to be unreliable for the reasons noted in paragraph 6.19 above, and the

transitivity concerns between the brivaracetam and lacosamide trials noted in July 2016 remained.

7.6 The PBAC recalled in July 2016 it 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 considered the post-hoc subgroup analysis presented in the resubmission did not adequately address this issue.

7.7 The PBAC recalled in July 2016 it considered the claim of non-inferior comparative 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. The PBAC noted no additional comparative evidence for safety was presented in the resubmission and hence did not change its view.

7.8 The PBAC considered that although the proposal of a flat pricing structure across dose strengths for brivaracetam tablets ameliorated the economic uncertainty surrounding the mean daily dose of brivaracetam, uncertainty surrounding the equi-effective dose of lacosamide remained.

7.9 The PBAC considered the estimated net cost to the PBS/RPBS is uncertain and there is a high likelihood that financial implications could vary substantially from that presented in the resubmission. However, the PBAC did note that brivaracetam joining the current market subsidisation cap for lacosamide and perampanel would potentially mitigate against a substantial increase in costs.

7.10 The PBAC reiterated its advice from July 2016 that any resubmission would need to be a major submission, and should compare brivaracetam with second-line AEDs.

7.11 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

UCB will continue to work with the Department to explore all feasible options with the PBAC and Department to make Briviact available to Australian patients.