

6.01 BRIVARACETAM, Tablet, 25 mg, 50 mg, 75 mg and 100 mg, Oral solution 10 mg/mL, 300 mL, Briviact®, UCB Pharma

1 Purpose of Application

- 1.1 The purpose of the submission was to request an extension to the existing Authority Required (Streamlined) listing for brivaracetam for treatment of intractable partial onset epileptic seizures, in combination with two or more anti-epileptic drugs (AEDs), to include patients aged 4 - 15 years whose condition has not been satisfactorily controlled by other AEDs. The submission also sought removal of the requirement in the continuation criteria that patients be maintained on two or more other AEDs in combination with brivaracetam.
- 1.2 The requested listing was on the basis of non-inferior effectiveness and safety when compared with lacosamide.

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

Component	Description
Population	Children aged ≥ 4 years (4 - 15 years) with partial onset (focal) epileptic seizures
Intervention	Brivaracetam tablets and oral solution
Comparator	Lacosamide
Outcomes	Frequency of partial onset intractable epileptic seizures with or without secondary generalisation
Clinical claim	When used as add-on therapy following multiple failed lines of AED treatment, brivaracetam is as effective in reducing partial-onset epileptic seizure frequency in paediatric patients aged 4 - 15 years as in patients aged 16 years and above and is non-inferior to lacosamide in paediatric patients aged 4 - 15 years in this setting.

Source: Table 1.1, p14 of the submission

AED = antiepileptic drug

2 Requested listing

- 2.1 Deletions requested by the submission to the current listings are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Max. Qty	Price for	Proprietary Manufacturer	Name and
BRIVARACETAM Tablets 25 mg, 50 mg, 75 mg and 100 mg	56	5		\$160.69 ^a	Briviact®	UCB Pharma

^a Dispensed price updated to reflect updated pharmacy mark-ups

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Initial treatment

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	<p>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, except for cross titration.</p>
Population criteria	Patient must be aged 16 years or older.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	<p>Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition, AND The 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.</p>
Population criteria	Patient must be aged 16 years or older.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
BRIVARACETAM Oral solution, 10 mg/mL, 300 mL	1	5	\$198.21 ^a	Briivact®	UCB Pharma

^a Dispensed price updated to reflect updated pharmacy mark-ups

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Initial treatment

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	<p>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, AND The treatment must not be given concomitantly with levetiracetam, except for cross titration.</p>
Population criteria	Patient must be aged 16 years or older.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	<p>Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition, AND The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent AND Patient must be unable to take a solid dose form of this drug, AND The treatment must not be given concomitantly with levetiracetam.</p>
Population criteria	Patient must be aged 16 years or older.

2.2 The current PBS restriction is narrower than the TGA approved indication because it requires patients to have previously been treated with at least one first-line AED and at least two second-line adjunctive AEDs which have not been effective and to initiate brivaracetam in combination with two or more other AEDs (compared with 'add on therapy' in the TGA approved indication). The submission requested to remove the current requirement under the continuation rule for patients to remain on two other AEDs on the basis that the continuation criterion was erroneously included in the November 2017 resubmission for the population aged 16 years and older. The submission noted that at the November 2012 consideration of lacosamide, the PBAC

noted that it would be reasonable to remove ineffective AEDs from a patient's regimen as early as practicable (see paragraph 3.5).

- 2.3 The submission requested the current age criterion be removed from the restriction on the basis of non-inferior effectiveness and safety in the paediatric population compared with lacosamide. This was broader with respect to age than the TGA approved indication which is for patients aged four years and older but was consistent with the PBS listing for lacosamide for the same indication (see paragraph 3.3).
- 2.4 The current listings for brivaracetam allow nurse practitioner prescribing for continuing therapy.

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

3 Background

Registration status

- 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 The TGA registered indication for brivaracetam was extended in May 2019 to: Briviact tablets and oral solution are indicated as 'add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 4 years of age with epilepsy'.
- 3.3 TGA registration was primarily based on extrapolation from adult efficacy data using pharmacokinetic and dose-response studies in children. This was based on TGA, European Medicines Agency (EMA), and United States Food and Drug Administration (FDA) allowing extrapolation of drug efficacy, but not safety, from partial (focal) epilepsy trials in adults to children aged four years and older. An assessment of safety data in children was performed.

Previous PBAC consideration

- 3.4 The PBAC recommended listing of brivaracetam for the treatment of intractable partial epileptic seizures in patients aged 16 years and older at its November 2017 meeting. Based on an indirect comparison of brivaracetam and lacosamide, the PBAC recommended listing brivaracetam considering, among other matters, that the cost-effectiveness of brivaracetam would be acceptable if it were cost-minimised against lacosamide (paragraph 7.1, brivaracetam Public Summary Document (PSD), November 2017 PBAC Meeting).
- 3.5 At the November 2012 consideration of lacosamide, the PBAC recommended removing the requirement under the continuation rule for patients to remain on two other AEDs. The PBAC considered that this would allow patients to use lacosamide as eventual dual or monotherapy. The PBAC noted the advice of the sponsor's clinical

expert that given the substantial burden of treatment-related toxicity from AEDs, it was considered clinically appropriate to remove ineffective AEDs from a patient's regimen as early as practicable. The PBAC considered this reasonable. The PBAC also recommended a streamlined authority listing while maintaining the existing risk-share arrangement (paragraph 12, lacosamide PSD, November 2012 PBAC Meeting).

- 3.6 At its November 2018 meeting, the PBAC recommended an extension to the listing for lacosamide to include patients aged 4 - 15 years, with the recommended restriction being silent on age. The PBAC were satisfied that lacosamide provides, for some patients, a significant improvement in efficacy over placebo (paragraph 7.1, lacosamide PSD, November 2018 PBAC Meeting). Among the different types of evidence presented, the PBAC considered the head-to-head randomised trial comparing lacosamide to placebo in patients aged 4 years to less than 17 years provided more robust evidence on the effectiveness and safety of lacosamide in the proposed population than the observational studies and pharmacokinetic studies (paragraph 6.3, lacosamide PSD, November 2018 PBAC Meeting).

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

4 Population and disease

- 4.1 Epilepsy is a neurological condition characterised by recurrent seizures. Partial onset seizures start in one region of the brain but may spread to other regions of the brain. Partial onset seizures are referred to as focal onset seizures using the 2017 International League Against Epilepsy classification of seizure types. However, the term 'partial onset seizures' has been used in the PBAC minutes for consistency with the TGA indication and existing PBS restrictions.
- 4.2 People with epilepsy are at a higher risk of accidents and life-threatening events due to loss of consciousness and falls during seizures, irreversible brain damage, and status epilepticus (prolonged seizures). Children with epilepsy also have a higher risk of death. The prevalence of epilepsy increases with age as children develop epilepsy over the course of childhood (Hollingsworth and Eadie, 2010).
- 4.3 AEDs are used to control seizures in patients with epilepsy. Patients typically start treatment with one AED (monotherapy). Patients may switch to another AED if the first AED does not provide adequate seizure control. If patients have tried several AEDs as monotherapy without good seizure control, two AEDs may be used together as adjunctive treatment. The stepwise approach to treatment in order to obtain seizure control is the same for adults and for children.

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

5 Comparator

- 5.1 The submission nominated lacosamide as the main comparator. This was appropriate. At its November 2017 consideration of brivaracetam for patients aged 16 years and older, the PBAC 'accepted lacosamide as the appropriate comparator' (paragraph 7.5, brivaracetam PSD, November 2017 PBAC Meeting).
- 5.2 The submission considered that perampanel is not a comparator given it is TGA registered for use in patients 12 years and older. The evaluation noted perampanel has a similar restriction to the proposed brivaracetam restriction, i.e. it is silent on age and does not require continuing therapy to be in combination with two or more anti-epileptic drugs. At its November 2018 consideration of lacosamide for the same population, the ESC agreed that perampanel may be an appropriate comparator for the proposed population aged 12 years and older despite the lack of comparative data (paragraph 5.2, lacosamide PSD, November 2018 PBAC Meeting). The evaluation considered perampanel may also be a comparator for the sub-population aged 12 - 15 years.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from the National Paediatric Medicines Forum (NPMF) via the Consumer Comments facility on the PBS website. The comments highlighted the benefits that further treatment options would bring to paediatric patients with epilepsy, including improved seizure control and compliance leading to improved school and social activities, reduced burden on carers, and reduced presentations to hospital and GPs.

Clinical trials

- 6.3 The submission presented a clinical evaluation based on an approach accepted by regulatory agencies that:
- the effectiveness of brivaracetam as an adjunctive treatment for partial onset seizures in adults has been demonstrated;
 - the results of efficacy trials performed in adults with partial onset epilepsy can be extrapolated to paediatric patients aged 4 years and older; and
 - safety studies of brivaracetam demonstrate that the safety of brivaracetam in paediatric patients was consistent with studies in adults.

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The submission did not consider comparative effectiveness and safety with lacosamide in paediatric patients.

6.4 Table 2 presents an overview of the evidence presented in the submission, including:

- three single-arm studies (N01266, N01263, Schubert-Bast (2018)) of brivaracetam in paediatric patients to support the safety of brivaracetam in the paediatric population. Two of these studies (N01263 and Schubert-Bast 2018) also included effectiveness outcomes;
- indirect treatment comparisons that compared three brivaracetam RCTs with three lacosamide RCTs in adults (using placebo as the common arm) which the submission considered could be extrapolated to the paediatric population aged 4 - 15 years. These were considered by the PBAC at its previous considerations of brivaracetam for the population aged 16 years and older (July 2016, March 2017, November 2017 PBAC Meeting); and
- two pharmacokinetic studies (CL0187 and CL0258) to support the extrapolation of adult effectiveness outcomes to the paediatric population. These were assessed by the TGA in its consideration to extend the brivaracetam indication to include children aged 4 years and older.

Table 2: Overview of evidence

Study	Design/ duration	Patient population	Previously seen by PBAC	Evaluated by TGA	Presented in commentary
Paediatric brivaracetam studies					
N01266	Single-arm, OL, MC 23 days (mean duration)	Children with intractable POS/generalised epileptic seizures	No	Yes	Yes
N01263	Single-arm, OL, MC 23 months (mean duration)	Children with intractable POS/generalised epileptic syndrome	No	Yes	Yes
Schubert-Bast (2018)	Single-arm, retro, OL, MC	Children with BRV treatment for POS	No	No	Yes
Pharmacokinetic studies					
CL0187	Population PK model	From N01263	No	Yes	Yes
CL0258	Paediatric exposure response model	LEV trial patients BRV trial patients	No	Yes	Yes
Brivaracetam vs. lacosamide in adults					
Indirect comparison	3 BRV RCTs (1252, 1253, 1258) 3 LCM RCTs (SP667, SP754, SP755) 12-16 weeks	Adults with intractable POS	Yes	No	Yes
Lacosamide indirect treatment comparison (children vs. adults)					
Indirect comparison	1 paediatric LCM RCT 3 adults LCM RCTs	Adults and children with intractable POS	Yes	No	No

Source: Compiled during the evaluation from Section 2.2 – Section 2.4, pp40-53; Section 2.5.2, pp59-62; Section 2.5.5, p77; Section 2.6.1, pp78-80; Table 2.12, p54; of the submission; Study N01263 CSR, Study N01266 CSR; Table 2, p9 July 2016 brivaracetam PBAC PSD; and assessed during the evaluation

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AED = antiepileptic drug; BRV = brivaracetam; DB = double-blind; LCM = lacosamide; LEV = levetiracetam; MC = multicentre; N = number of patients; OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee; PK = pharmacokinetic; POS = partial onset seizures; PSD = public summary document; R = randomised; RCT = randomised controlled trial; retro = retrospective; TGA = Therapeutic Goods Administration; yr = year

6.5 The details of the three new single-arm studies of brivaracetam in paediatric patients presented in the submission are provided in the table below. The details of the studies which have previously been seen by PBAC and/or TGA are not included. Instead, the relevant considerations from the PBAC or TGA are summarised herein.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NO1266	Open-label Long-term Study of Adjunctive brivaracetam in Paediatric Subjects With Epilepsy	CSR March 2017
	Badalamenti V, Gasalla T, Dilley D, et al. Interim safety and tolerability analysis from an open-label, long-term study of adjunctive brivaracetam in paediatric patients with epilepsy.	46th Annual Meeting of the Child Neurology Society. 2017; 82 (Supplement 21): S278-S279.
	Liu E, Hepner A, Dilley D, et al. Safety and tolerability of adjunctive brivaracetam administered as oral solution in paediatric patients aged >1 month to 16 years with epilepsy.	2013 Annual Meeting of the American Epilepsy Society
NO1263	Open-label, Pharmacokinetic, Safety and Efficacy Study of Adjunctive brivaracetam in Children With Epilepsy	CSR August 2013
	Schoemaker R, Wade JR, Stockis A. Brivaracetam population pharmacokinetics in children with epilepsy aged 1 month to 16 years.	Eur J Clin Pharmacol 2017 73:727–733
	Schoemaker R, Wade JR, Stockis A, Extrapolation of a brivaracetam Exposure-Response Model from Adults to Children with Focal Seizures.	Clinical Pharmacokinetics 2018; 57 (7):843-854.
Schubert-Bast, 2018	Schubert-Bast S, Willems LM, Kurlmann G., et al. Postmarketing experience with brivaracetam in the treatment of focal epilepsy in children and adolescents.	Epilepsy and Behavior 2018; 89:89-93.
	Steinig I, von Podewils F, Möddel G, et al. Postmarketing experience with brivaracetam in the treatment of epilepsies: A multicentre cohort study from Germany.	Epilepsia 2017; 58(7):1208-1216.
	Strzelczyk A, Steinig I, Von Podewils F, et al. Postmarketing experience with brivaracetam in the treatment of epilepsies: A multicentre cohort study from Germany.	32nd International Epilepsy Congress. Epilepsia 2017; (Supplement 5):S160

Source: Table 2.4, pp42-43 of the submission
CSR = clinical study report

6.6 The key features of the new paediatric brivaracetam studies presented in the submission are summarised in the Table 4.

Table 4: Key features of new paediatric brivaracetam studies presented in the submission

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in economic evaluation
N01266	206	Single-arm, OL, MC 23 days (mean duration)	High	≤ 1 yrs to < 17 yrs ^a Intractable POS ^b or generalized seizures Using ≥ 1 AED	Safety	No
N01263	100	Single-arm, OL, MC 23 months (mean duration)	High	≥ 1 month to < 16 yrs partial or generalized epileptic syndrome 1-2 AEDs	Seizure freedom Δ seizure days (per 28-day period) Safety	No
Schubert-Bast (2018)	34	Single-arm, retro, OL, MC	High	≤ 17 yrs BRV treatment for POS	Seizure reduction, Seizure freedom Treatment retention, Safety	No

Source: Compiled during the evaluation from Section 2.2 – Section 2.4, pp40-53; Section 2.5.2, pp59-62; Section 2.5.5, p77; Section 2.6.1, pp78-80; Table 2.12, p54; of the submission; Study N01263 CSR, Study N01266 CSR

AED = antiepileptic drug; BRV = brivaracetam; CSR = clinical study report; MC = multicentre; OL = open label; POS = partial onset seizures; retro = retrospective; yr = year; Δ = change in

^a Study N01266 enrolled patients from N01263. Study N01266 only recruited patients with POS aged ≥ 4 yrs < 17 years. Study N01263 included participants with generalised seizures and those less than 4 yrs. 85% of study N01266 participants had POS and 23% had generalized seizures.

^b After treatment with at least one AED

6.7 The three studies were considered to have a high risk of bias because the studies were single-arm studies (mostly before-and-after study design) that assessed safety and seizure frequency outcomes compared with baseline. There was potential for placebo responses (response due to expectation the drug may be beneficial), selection bias, and detection biases.

6.8 The evaluation presented a naïve comparison of brivaracetam with lacosamide in the paediatric population using data from SP0969, the lacosamide randomised trial considered by the PBAC at its November 2018 consideration.

Comparative effectiveness

6.9 Table 5 presents the results of the seizure reduction outcomes from the paediatric brivaracetam studies and a naïve comparison with lacosamide using study SP0969. A 50% or greater reduction in seizure frequency (response rate) was the key effectiveness outcome considered by the PBAC in its previous considerations of AEDs. At the November 2009 lacosamide consideration, the PBAC considered ‘the outcome of 50% responder rate is dependent on a patient’s baseline seizure frequency and in a less severe population is of doubtful clinical relevance. However, although an outcome in epilepsy trials that is potentially more patient-relevant is the proportion of patients achieving a particular threshold such as the proportion of seizure-free patients, the PBAC recognised that in patients with intractable epilepsy, a 50% reduction in seizures was likely to be clinically important. Further, it would be unlikely for such patients to be seizure-free’ (paragraph 12, lacosamide PSD, November 2009 PBAC Meeting).

Table 5: Results of seizure response across the paediatric studies

Study	Brivaracetam	Placebo	Lacosamide	Relative risk (95% CI)
≥ 50% reduction in seizure-days^a				
N01263 (all patients)	17/80 (21%)	-	-	-
partial onset seizures	11/35 (31%)	-	-	-
other seizure types	6/45 (13%)	-	-	-
≥ 50% reduction in seizure frequency (response rate)				
Schubert-Bast (2018)	18/28 (64%)	-	-	-
SP0969	-	56/168 (33%)	90/170 (53%)	1.59 (1.23, 2.05)

Source: Table 2.29, p77, Table 2.31, p31 of the submission; Table 10-2, p139 of study N01263 CSR

CI = confidence interval; CSR = clinical study report

^a Excluded patients who did not experience seizure during the one-week baseline period

6.10 Different measures of seizure response were reported in the studies. Study N01263 reported that 31% of patients with partial onset seizures experiencing a 50% or greater reduction in seizure-days. This outcome may not be comparable with a 50% or greater reduction in seizure frequency because the baseline seizure frequency was not reported, and its impact on any comparison was not clear. Despite this, the reduction in response detected in N01263 was substantially lower than 53% response rate (a 50% or greater reduction in seizure frequency) for lacosamide in SP0969. The naïve comparison was likely biased against brivaracetam because brivaracetam effectiveness was measured during a three-week period when brivaracetam was being titrated whereas lacosamide effectiveness was measured after dose titration. Additionally, there were differences in patients and disease characteristics between the studies.

6.11 Schubert-Bast (2018), the retrospective single-arm study, reported that 64% of brivaracetam patients experienced a 50% or greater reduction in seizure frequency (response) after three months of brivaracetam treatment. This was higher than the 53% response rate for lacosamide patients reported in SP0969. The results from the naïve comparison may not be fully comparable and should be interpreted with caution given:

- The number of prior AEDs trialled may differ due to differences in how prior treatments were reported. Inadequate response to previously trialled AEDs may be a poor prognostic factor for subsequent AED response;
- Fewer patients in Schubert-Bast (2018) had two or more other concurrent AEDs (46%) compared with SP0969 (83%). This may suggest patients in SP0969 have more severe disease;
- Biases in the before-and-after study design in Schubert-Bast (2018); and
- The accuracy of seizure frequency measurements from patients' clinical records used in Schubert-Bast (2018).

6.12 Results from two pharmacokinetic/pharmacodynamic (PK/PD) studies which were evaluated by the TGA for registration of brivaracetam in children were presented:

- Study CL0187 was a pharmacokinetic modelling study. The TGA Clinical Evaluation Report (CER, second round) considered this study supported the use of weight-based dosing in paediatric patients to achieve equivalent brivaracetam exposure to adults; and
- Study CL0258 was an exposure-response (pharmacokinetic-pharmacodynamics) modelling study that aimed to predict brivaracetam effectiveness in paediatric patients using i) an existing brivaracetam model for adults, and ii) a levetiracetam model for adult and paediatric patients to obtain the scaling factor to be applied to the existing brivaracetam model, assuming similarity between brivaracetam and levetiracetam. The TGA CER (second round, p18 and p37) raised concerns that the assumption of similarity between brivaracetam and levetiracetam was not well supported. It was unclear whether the findings were clinically validated.

6.13 Table 6 presents the indirect treatment comparisons on the 50% or greater reduction in seizure frequency in adults with partial onset epilepsy treated with brivaracetam or lacosamide. This was considered by the PBAC in its previous considerations of brivaracetam.

Table 6: 50% reduction in partial onset seizure frequency in adults – indirect comparison of brivaracetam and lacosamide

	Brivaracetam n/N (%)	Placebo n/N (%)	Lacosamide n/N (%)	RR (95% CI)
≥ 2 concomitant AEDs, 3+ previous AEDs (post hoc subgroup)				
Brivaracetam trials ^a	117/362 (32.3%)	38/206 (18.4%)	-	1.75 (1.3, 2.4)
Lacosamide trials ^b	-	55/271 (20.3%)	198/540 (36.7%)	1.80 (1.4, 2.3)
Indirect comparison	-	-	-	0.97 (0.66, 1.44)
Full trial population				
Indirect comparison ^c	-	-	-	1.06 (0.79, 1.43)

Source: Compiled during the evaluation from Table 2.25, p75, Table 2.28, p76 of the submission; Table 19, p23, statistical consulting report; Table 2, p10 of the November 2017 brivaracetam PSD

AED = antiepileptic drug; CI = confidence interval; n = number of patients in group; N = total patients; PSD = public summary document; RR = relative risk; **bold** = statistically significant

^a 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).

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

^c The included 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. Included patients receiving brivaracetam 50 mg to 200 mg per day or lacosamide 200 mg to 400 mg per day.

6.14 At the November 2017 PBAC meeting, the PBAC recalled that, among the trials included in the indirect comparison, the brivaracetam trials generally included less resistant patient populations. However, the PBAC noted the additional information provided for the post-hoc subgroup analyses from the March 2017 resubmission in which the brivaracetam and lacosamide trials were stratified according to concomitant medications and prior anti-epileptic drug history. The PBAC specifically noted the similar 50% responder rates in the placebo arms of the trials (18.4% in the brivaracetam trials; 20.3% in the lacosamide trials). Overall, the PBAC considered that, although transitivity issues across the trials remained, the claim of non-inferior

comparative effectiveness of brivaracetam and lacosamide was reasonable (paragraph 7.6, brivaracetam PSD, November 2017 PBAC Meeting).

- 6.15 Regulatory agencies including the TGA, EMA, and the United States Food and Drug Administration have accepted that, with a few exceptions, focal epilepsies in paediatric patients from 4 years of age may have a similar clinical expression to focal epilepsies in adolescents and adults. For focal epilepsies, the results of efficacy trials performed in adults may be extrapolated to children and adolescents provided that the PK/PD relationship in adults is established and that the dose regime proposed in children and adolescents results in similar exposure levels as in adults in all age categories (4 to 18 years) (EMA 2018 draft guideline).

Comparative harms

- 6.16 Table 7 presents a summary of adverse events in the paediatric brivaracetam studies and SP0969.

Table 7: Summary of adverse events in the studies

Study	Brivaracetam				Lacosamide
	Pooled ^a All patients n (%)	Pooled ^a POS < 4 years n (%)	Pooled ^a POS 4 to < 16 years n (%)	Schubert-Bast 2018 n (%)	SP0969 n (%)
N	206	15	141	34	171
Any TEAE	191 (93%)	15 (100%)	125 (89%)	4 (12%)	122 (71%)
Severe TEAE	27 (13%)	4 (27%)	13 (9%)	-	7 (4%)
Serious TEAEs	54 (26%)	6 (40%)	26 (18%)	-	11 (6%)
TEAEs leading to discontinuation	19 (9%)	1 (7%)	6 (4%)	3 (9%)	7 (4%)
Drug-related TEAEs	63 (31%)	5 (33%)	43 (31%)	-	58 (34%)
Drug-related serious TEAEs	5 (2%)	-	2 (1%)	-	6 (4%)
Deaths	4 (2%)	-	2 (1%)	-	-
Vomiting	43 (20%)	8 (50%)	22 (15%)	-	-
Diarrhoea	33 (15%)	3 (19%)	18 (12%)	-	-
Behavioural disorder	58 (27%)	8 (50%)	32 (22%)	2 (6%) ^b	-
Seizure worsening	58 (26%)	7 (44%)	32 (22%)	-	-
Irritability	25 (11%)	4 (25%)	15 (10%)	-	4 (2%)
Aggression	13 (6%)	1 (6%)	7 (5%)	-	-
Suicidal ideation	9 (4%)	-	7 (5%)	-	3 (2%)
Decreased appetite	26 (12%)	3 (19%)	15 (10%)	-	6 (4%)
Psychomotor hyperactivity	7 (3%)	-	7 (5%)	-	-

Source: Tables 2.18 - 2.19, pp64-65, Table 2.32, p80 of the submission; and Table 8, p11 November 2018 lacosamide PBAC PSD
n = number of participants reporting data; PBAC = Pharmaceutical Benefits Advisory Committee; POS = partial onset seizures; PSD = public summary document; TEAE = treatment-emergent adverse event

^a Pooled data from N01263 and N01266. Includes patients with generalised seizures.

^b Depression, aggression, irritability

- 6.17 The submission noted the following AEs occurred more commonly in patients aged 4 - 15 years compared with patients aged 16 years and older (pooled adult data): seizure worsening, behavioural disorder, and suicidality. Additionally, decreased

appetite and psychomotor hyperactivity were proposed as adverse events for the paediatric population in the Summary of Clinical Safety. The TGA CER (second round, p35) considered that ‘...diarrhoea and/or vomiting in a 4 year old is a matter of concern particularly in summer from Brisbane north and inland west of the Great Dividing Range’. AEs were more frequently reported in children younger than 4 years of age compared with those aged 4 - 15 years.

- 6.18 The submission did not present a comparison of brivaracetam with its main comparator lacosamide in terms of safety for the less than 4 years age group.

Clinical claim

- 6.19 The submission described brivaracetam as non-inferior in terms of effectiveness and non-inferior in terms of safety compared with lacosamide.
- 6.20 The rationale for the effectiveness claim was that 1) the PBAC had previously accepted, despite some transitivity concerns, this clinical claim for patients aged 16 years and older, and 2) that this could be extrapolated to patients aged 4 - 15 years based on TGA acceptance of the efficacy extrapolation.
- 6.21 The evaluation considered that the claim of non-inferior comparative safety was not fully supported by the naïve comparison as brivaracetam appeared to have more AEs and a potentially inferior safety profile compared with lacosamide in the paediatric population, with the exception of drug-related TEAEs.
- 6.22 The PBAC considered that the claim of non-inferior effectiveness of brivaracetam and lacosamide in the paediatric population was reasonable, noting the difficulty in obtaining reliable evidence for the paediatric population.
- 6.23 The PBAC considered that the claim of non-inferior safety compared with lacosamide to be uncertain but reasonable.

Economic analysis

- 6.24 The submission requested the current brivaracetam prices be maintained for the proposed extension to the PBS-listing. This implicitly assumed that the equi-effective doses for the population aged 16 years and older would apply to the paediatric population. The current equi-effective doses in adults are 117.6 mg brivaracetam and 316.2 mg lacosamide (paragraph 6.16, brivaracetam PSD, November 2017 PBAC Meeting).
- 6.25 A cost comparison of brivaracetam and lacosamide doses was performed during the evaluation to assess whether brivaracetam and lacosamide treatment at equivalent doses would result in similar costs at the AEMP price. For the purposes of the analysis equivalent doses were 4 mg/kg/day of brivaracetam and 8 mg/kg/day of lacosamide. The brivaracetam dose was selected because it was the maximum of the effective dose range in the brivaracetam Product Information despite the data from study N01266 suggesting that a higher dose may be used. The lacosamide dose used for the

cost comparison was the average of median maintenance doses from trial SP0969. The results of the analysis are presented in Table 8.

Table 8: Cost comparison of brivaracetam and lacosamide

Component	Brivaracetam	Lacosamide
Mean dose used in paediatric clinical evidence	4 mg/kg/day ^a	8.0 mg/kg/day ^b
Mean daily dose ^c	124 mg	248 mg
Cost per daily dose at AEMP (tablets)	\$6.15 ^d	\$6.48 ^e
Cost per daily dose at AEMP (oral liquid)	\$7.17 ^d	\$7.12 ^e
Difference in cost (tablets)		-\$0.33
Difference in cost (oral liquid)		\$0.05

Source: Constructed during the evaluation

AEMP = approved ex-manufacturer price

^a Based on study N01266 modal dose and brivaracetam dosing in the Product Information

^b Average of median maintenance doses

^c Based on a weight of 31 kg as per weight of patients weighing less than 50 kg (and using weight-based dosing) in the financial estimates.

^d Based on brivaracetam tablet AEMP of \$0.05/mg (50 mg tablets) or \$0.06/mg for oral solution. Brivaracetam AEMP for 25 mg tablets is \$0.10/mg and \$0.02/mg for 100 mg tablets.

^e Based on lacosamide tablet AEMP of \$0.02611/mg and oral solution AEMP of \$0.028725/mg.

6.26 The analysis found that the daily cost of brivaracetam and lacosamide were similar for the assumed equivalent doses of 4 mg/kg/day of brivaracetam and 8 mg/kg/day for lacosamide. However, the limitations of this analysis included:

- the doses not being established as equi-effective because study N01266 did not report effectiveness to enable comparison;
- uncertainty regarding the dose of brivaracetam because:
 - the mean dose of brivaracetam was not reported in study N01266, and
 - doses up to 5 mg/kg/day (higher than the range in the Product Information) could be used. These higher doses may also be used in clinical practice; and
- SP0969 had a strict dosing protocol that required patients to use specified target lacosamide doses. This may have resulted in less dose variability than study N01266.

6.27 However, this would not fully apply to paediatric patients because:

- a large proportion of paediatric patients would be expected to use the oral liquid, which would incur a proportionally larger cost; and
- paediatric patients using tablets would use lower strength tablets resulting a proportionally higher brivaracetam cost.

6.28 Currently, brivaracetam tablets have a flat pricing structure. At its November 2017 consideration of brivaracetam for adult patients, 'The PBAC noted that the flat pricing structure across dose strengths for brivaracetam tablets ameliorated the economic uncertainty regarding the mean daily dose of brivaracetam; however, uncertainty for

the equi-effective dose of lacosamide remained.’ (paragraph 7.8, brivaracetam PSD, November 2017 PBAC Meeting).

Drug cost/patient/year: \$1,425

6.29 The drug cost per patient-year for brivaracetam and lacosamide estimated in the submission is presented in Table 9.

6.30 The submission requested the existing brivaracetam prices be maintained for the proposed extension to the PBS-listing.

Table 9: Drug cost per patient for proposed and comparator drugs

	Trial dose and duration	Economic evaluation	Financial estimates
Brivaracetam			
Dose (daily)	124 mg ^a	117.6 mg	81 mg
Duration (mean)	23 months	NA	chronic
Cost/patient/year			
Tablet	\$3,139 ^b	No cost presented	\$1,425 ^c
Oral liquid	\$3,014 ^b	No cost presented	
Lacosamide			
Dose (daily)	248 mg ^d	316.2 mg	161 mg
Duration (mean)	10 weeks ^e	NA	chronic
Cost/patient/year			
Tablet	\$2,784 ^e	No cost presented	\$1,725 ^f
Oral liquid	\$2,957 ^e	No cost presented	

Source: Compiled and calculated during the evaluation from Section 4 spreadsheet; Table 8-2, p80 of the study N01266 CSR; Lacosamide November 2018 PBAC PSD

CSR = clinical study report; DPMQ = dispensed price for maximum quantity; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document

^a Brivaracetam dose of 4 mg/kg/day was based on study N01266 modal dose and calculated for a patient weighing 31 kg as per weight of patients weighing less than 50 kg (and using weight-based dosing) in the financial estimates.

^b Daily dose rounded up to 125 mg brivaracetam to enable calculation. Tablet cost calculated as \$160.54 (50 mg brivaracetam DPMQ) × 13.04 + \$160.54 (25 mg brivaracetam DPMQ) × 13.04/2. Oral solution calculated as 365.25/(3,000(brivaracetam mg per bottle)/125) × \$198.06 (brivaracetam oral solution DPMQ).

^c Weighted average based on 60% of prescription for oral solution (167 mg daily), 4%, 10%, 18% and 8% of patients using 50 mg, 100 mg, 150 mg and 200 mg brivaracetam daily, respectively, with 75% adherence (calculated from Section 4 spreadsheet: '3b. Impact - PUB!C28/Dosing!C6).

^d Based on a daily dose of 8 mg/kg/day from the 10 week maintenance phase of lacosamide trial SP0969 and patient weight of 31 kg.

^e Dose rounded to 250 mg lacosamide to enable calculation. Tablet cost calculated as \$168.57 (100 mg lacosamide DPMQ) × 13.04 + \$89.93 (50 mg lacosamide DPMQ) × 13.04/2. Oral solution calculated as 365.25/(12,000(lacosamide mg prescription)/250) × \$388.65 (lacosamide oral solution DPMQ).

^f Weighted average based on 12%, 66%, 17% and 5% of patients using 100 mg, 200 mg, 300 mg and 400 mg lacosamide daily, respectively, with 75% adherence (calculated from Section 4 spreadsheet: '4b. Displaced - PUB!C27/Dosing!C6).

Estimated PBS usage & financial implications

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

6.32 The submission estimated that 0.65% of the population aged 4 - 15 years had epilepsy, of which 57% had partial onset epilepsy and 9.4% would be eligible for fourth line adjunctive treatment. The submission assumed more patients aged 4 - 11 years would

be treated with brivaracetam than patients aged 12 - 15 years because perampanel was not registered for use in the younger population. The approach used was consistent with the approach used to estimate the financial implications in the November 2018 lacosamide submission for the same population. The submission may have overestimated the prevalence of epilepsy, and use of the oral solution, because incidence of epilepsy and treated epilepsy increases over childhood (Hollingsworth and Eadie, 2010, Wallace et al., 1998).

6.33 The submission did not include dose titration because brivaracetam is initiated at a therapeutically active dose. Table 10 summarises the estimated use and financial implications of listing brivaracetam in patients aged 4 - 15 years of age.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Market share ^a	%	%	%	%	%	%
Number of patients treated						
Number of scripts dispensed						
Estimated financial implications of brivaracetam						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
Estimated financial implications for lacosamide						
Saving to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Saving to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to PBS/RPBS less co-payments	-\$	-\$	-\$	-\$	-\$	-\$

Source: Table 4.7, p95; Table 4.12, p97; Table 4.14, p97; Table 4.18, p4.18 of the submission

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

^a From lacosamide-brivaracetam market. This did not include perampanel which has a similar place in therapy.

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

6.34 The submission estimated that the proposed brivaracetam listing would result in a small net savings to the PBS of less than \$10 million in Year 1, increasing to savings of less than \$10 million in Year 6 (net of patient co-payments). The small net saving was due to brivaracetam having a flat price structure across strengths and replacing lacosamide which was more costly at higher strengths. The net savings to the PBS and RPBS may be higher or lower because:

- the eligible and treated population for fourth line adjunctive treatment may have been overestimated (decrease costs for brivaracetam and savings due to reduced use of lacosamide);

- the treated population may be older, and heavier, than assumed in the submission because the prevalence of epilepsy increases over childhood and patients require sufficient opportunity to trial earlier lines of treatment (increase brivaracetam cost); and
- the older patient group may require less oral solution use, and a smaller proportion would use brivaracetam due to the availability of perampanel in this group (decrease brivaracetam cost).

On balance, the PBAC considered there would be no significant financial impact to the PBS, as the population is low and overall, the financial uncertainties were unlikely to significantly increase financial risk.

- 6.35 The submission assumed brivaracetam would only replace lacosamide. Brivaracetam may also replace perampanel in patients aged 12 to 16 years old. Additionally, the requested restriction change to continuation treatment listings would allow discontinuation of ineffective AEDs, further reducing the use of other AEDs.
- 6.36 Further to this, estimates of patient numbers may not be accurate since the time required to complete early line treatments could mean patients treated with brivaracetam tend to be older, resulting in a higher per-patient dose, preferred use of tablet over oral solution formulation, and greater displacement of perampanel in patients over 12 years of age.
- 6.37 The PBAC considered that it would be appropriate to include substitution for perampanel in the financial estimates based on the current market share of perampanel on the PBS for patients 12 to 16 years, while maintaining the same total market share assumptions.

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

7 PBAC Outcome

- 7.1 The PBAC recommended changing the Authority Required (STREAMLINED) listing for brivaracetam for treatment of intractable partial onset epileptic seizures, to include patients aged 4 to 15 years. Its recommendation was based on, among other matters, its assessment that the cost-effectiveness of brivaracetam would remain acceptable with the extended listing implemented at the current price, where the listing results in an overall saving to Government.
- 7.2 In making its recommendation, the PBAC acknowledged the clinical need for drugs that are effective in reducing seizure frequency for paediatric patients who have failed other lines of AED treatment.
- 7.3 The PBAC accepted lacosamide was the main comparator. The PBAC considered perampanel was also a comparator for patients aged 12 to 15 years.

- 7.4 The PBAC noted that the TGA registered indications for both brivaracetam and lacosamide are as add-on therapy in the treatment of partial seizures in patients with epilepsy who are aged 4 years and older. The PBAC recommended removing the age criterion from the brivaracetam restriction, in line with the restriction for lacosamide.
- 7.5 The PBAC recommended that the continuation criteria ‘treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent’ be removed from the brivaracetam restriction, in line with the restriction for lacosamide. The PBAC recalled its decision to recommend the same change to the lacosamide listings at its November 2012 meeting to ‘allow patients to use lacosamide as eventual dual or monotherapy’ and that it was clinically appropriate to remove ineffective AEDs from a patient’s regimen.
- 7.6 The PBAC recalled it had previously considered that the claim of non-inferior comparative effectiveness of brivaracetam and lacosamide in adult patients was reasonable (paragraph 7.6, November 2017 PSD, brivaracetam). The PBAC noted the current submission extrapolated results of adult studies as evidence of non-inferiority in paediatric patients. It acknowledged that this method was accepted by the TGA and other international regulators for this population and condition, and considered this approach to be reasonable.
- 7.7 The PBAC noted the naïve comparison of two single arm brivaracetam studies and one single arm study of lacosamide, in the paediatric population, included by the evaluation. This comparison showed a reduction of 31% seizure days (n=11) and 64% reduction in seizure frequency (n=28) for brivaracetam compared with 53% reduction in seizure frequency (n=170) for lacosamide.
- 7.8 The PBAC considered it was reasonable to extend its previous consideration that brivaracetam is non-inferior to lacosamide in terms of efficacy in adults to the paediatric population, while noting the certainty regarding non-inferior efficacy to be only moderate due to low participant numbers, study design and trial population differences.
- 7.9 The PBAC noted the rate of some adverse events appeared higher in the paediatric population treated with brivaracetam compared with lacosamide on the basis of the naïve indirect comparison, particularly in patients less than 4 years of age. Accordingly, the PBAC considered that the claim of non-inferior safety compared with lacosamide was uncertain but reasonable, particularly in the context of a high clinical need for an additional late-line AED treatment for paediatric patients.
- 7.10 The PBAC noted that maintaining the current price of brivaracetam with the extension of the listing would result in the adult equi-effective doses of 117.6 mg brivaracetam and 316.2 mg lacosamide also applying to the paediatric population. The PBAC recalled it previously considered that the flat pricing structure across dose strengths for brivaracetam tablets ameliorated the economic uncertainty regarding the mean daily dose of brivaracetam; however, uncertainty for the equi-effective dose of

lacosamide remained.’ (paragraph 7.8, brivaracetam PSD, November 2017 PBAC Meeting). The PBAC considered that the flat pricing structure of brivaracetam also reduced the economic uncertainty regarding the mean daily dose of brivaracetam that may be required in the paediatric population using the tablet formulation.

- 7.11 The PBAC noted that brivaracetam is currently subject to a RSA, which is shared with perampanel and lacosamide. The PBAC was of the view that as the current RSA already accounts for paediatric use for the other agents, no increase in the Subsidisation Cap should be applied as a result of this listing.
- 7.12 The PBAC considered cost estimates to be moderately uncertain because of the issues discussed in paragraphs 6.34 to 6.36. However, overall, the PBAC considered the implications of the proposed changes would be cost-neutral to the PBS.
- 7.13 The PBAC considered it may be beneficial for DUSC to review the listing in 5 years, with a particular focus on use in patients aged less than 4 years.
- 7.14 The PBAC advised that nurse practitioner prescribing for continuing therapy only should continue to apply.
- 7.15 The PBAC recommended that the Early Supply Rule should continue to apply.
- 7.16 The PBAC recalled that it has previously advised that, under subsection 101(3BA) of the *National Health Act 1953*, brivaracetam should be treated as interchangeable on an individual patient basis with lacosamide and perampanel.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing listings as follows (with deletions in strikethrough):

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
BRIVARACETAM Tablets 25 mg, 50 mg, 75 mg and 100 mg	56	5	Briviact®	UCB Pharma

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Initial treatment

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> 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, except for cross titration.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition, AND The treatment must not be given concomitantly with levetiracetam.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
BRIVARACETAM Oral solution, 10 mg/mL, 300 mL	1	5	Briviact®	UCB Pharma

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a neurologist

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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, AND The treatment must not be given concomitantly with levetiracetam, except for cross titration.
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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Intractable partial epileptic seizures
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition, AND Patient must be unable to take a solid dose form of this drug, AND The treatment must not be given concomitantly with levetiracetam.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.