7.09 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 minor resubmission requested a Section 85, Authority Required (STREAMLINED) listing for brivaracetam for the treatment of intractable partial epileptic seizures. The first submission was considered in July 2016, and a following resubmission was considered in March 2017.

2 Requested listing

2.1 The resubmission requested the following listing, unchanged from the March 2017 resubmission other than the inclusion of treatment criteria for brivaracetam to not be given concomitantly with levetiracetam, and application of a Special Pricing Arrangement.

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	5	Published price: $[redacted] Effective price: $[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

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	5	Published price: $[redacted] Effective price: $[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:	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. 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 liquid 10 mg/mL	300 mL	5	Published price: $[redacted] Effective price: $[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 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

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BRIVARACETAM Oral liquid 10 mg/mL	300 mL	5	Published price: $[redacted] Effective price: $[redacted]	Briviact® UCB Pharma

Category / Program	GENERAL – General Schedule (Code GE)
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Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	Patient must have previously been treated with PBS-subsidised treatment with this drug. AND 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
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

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 as a major submission by PBAC in July 2016, and again as a major resubmission in March 2017. A summary of the previous submissions and the current resubmission is presented in the table below.

Table 1: Summary of previous brivaracetam submissions and the current resubmission

Component	July 2016 submission	March 2017 resubmission	Current resubmission
Requested PBS restriction and place in therapy	Third or later line in refractory population not controlled by at least one first-line agent and at least two second-line agents; and also for patients who cannot tolerate levetiracetam.	Use of briva with ≥ 2 AEDs which includes one second-line adjunctive agent; and in patients not adequately controlled on ≥ 3 AEDs. Third-line adjunctive therapy in same population as PBS listings for lacosamide and perampanel.	Unchanged from March 2017 other than inclusion of requirement that briva must not be given concomitantly with levetiracetam.
	PBAC comment: July 2016 PSD, paragraph 7.3; March 2017 PSD, paragraph 7.3: The appropriate place in therapy for briva was earlier in treatment algorithm, in a similar way to levetiracetam.		-
Requested price	Published price: $[redacted] tablets Published price: $[redacted] liquid Effective price: $[redacted] tablets Effective price: $[redacted] liquid	Published price: $[redacted] tablets Published price: $[redacted] liquid No Special Pricing Arrangement proposed so published and effective prices the same.	Published price: $[redacted] tablets Published price: $[redacted] liquid Effective price (as per prePBAC response): $[redacted] tablets Effective price (as per prePBAC response): $[redacted] liquid
Nominated comparator	Lacosamide	Lacosamide	Lacosamide
	PBAC comment: July 2016 PSD, paragraph 7.4, March 2017 PSD paragraph 7.4: Nomination of lacosamide was not appropriate and a comparison with levetiracetam and other similar listed AEDs (lamotrigine, topiramate) would be more appropriate.		-
Key evidence	Indirect comparison of 3 briva trials and 3 lacosamide trials with placebo as common reference.	Same as July 2016 with a post-hoc subgroup analysis.	Same as March 2017
Clinical claim	Briva non-inferior to lacosamide for comparative effectiveness and comparative safety	Same as July 2016	No clinical claim made (assumed to be the same as previously).
	PBAC comment: July 2016 PSD, paragraph 7.6; Mar 2017, paragraph 7.6: The claim of non-inferior efficacy was not adequately supported; July 2016, paragraph 7.7: the claim of non-inferior safety was not adequately supported given short-term trials and know psychological issues (suicidal thoughts) with briva and other AEDs.		-
Economic evaluation	Cost-minimisation; equi-effective doses of 124.55mg brivaracetam to 291.35mg lacosamide Dose relativity: 2.34	Cost-minimisation; equi-effective doses of 117.6mg brivaracetam to 316.2mg lacosamide. Dose relativity: 2.69[a]	Equi-effective doses same as March 2017 Dose relativity: 2.69
	PBAC comment: July 2016 PSD, paragraph 7.9: Cost minimisation vs. lacosamide not appropriate given lack of evidence comparing the two treatments in patients of similar resistant therapy; July paragraph 7.10; Mar 2017 paragraph 7.8: uncertainty around equi-effective doses.		-
Estimated patient numbers	Year 1: less than 10,000 Year 5: less than 10,000	Year 1: less than 10,000 Year 5: less than 10,000	Year 1: less than 10,000 Year 5: less than 10,000
Cost to Govt	$10-20 million over first 5 years	Saving of less than $10 million over first 5 years	Saving of $10 - $20 million over first 5 years (as per prePBAC response)
	PBAC comment: July 2016 PSD, paragraph 6.31; Mar 2017 PSD, paragraph 7.9: Financial implications to the Government health budget could vary greatly; estimated net cost to PBS/RPBS is uncertain		-
PBAC outcome	Reject	Reject	-

[a] Corrected during the March 2017 evaluation (316.20/117.63); the March 2017 resubmission had presented a dose relativity of 2.77.
AED=antiepileptic drug; briva=brivaracetam; PSD=public summary document
Source; 5.04 brivaracetam COM; 7.01 brivaracetam COM; July 2016 PSD; March 2017 PSD.

3.3 The effective price proposed in the current resubmission for brivaracetam tablets ($[redacted]) was [redacted]% lower than the price proposed in the March 2017 resubmission ($[redacted]) but similar to the price proposed in the July 2016 submission ($[redacted]).

3.4 In the pre-PBAC response, the sponsor proposed an additional [redacted]% price reduction, increasing the price reduction to [redacted]% compared with the price proposed in the March 2017 resubmission.

4 Clinical place for the proposed therapy

4.1 Brivaracetam is an anti-epileptic drug which exerts its anticonvulsant activity by binding to synaptic vesicle protein 2A (SV2A) in the brain. It is the 4-n-propyl analogue of levetiracetam.

4.2 As in the March 2017 resubmission, the current resubmission proposed brivaracetam to be used as 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).

4.3 The resubmission argued that the clinical place for brivaracetam is in highly refractory epilepsy and the use of levetiracetam in Australia is in a different population. The resubmission presented a report assessing levetiracetam use in Australia. According to the report, in March 2017 a total of 33,480 patients were on levetiracetam treatment, and of these patients, 57% were on monotherapy, 4% were on combination therapy with lacosamide, 1% were on combination therapy with perampanel and 40% were on combination therapy with other epilepsy drugs. The resubmission claimed that these data demonstrate that the combination of levetiracetam and lacosamide is extremely low in the refractory epilepsy space, indicating that patients have used levetiracetam earlier in the treatment of their epilepsy.

4.4 The resubmission also cited a 2016 Quintiles report on claims data for the USA which indicated that 55% of brivaracetam patients received no recent levetiracetam and 10% - 12% of levetiracetam-treated patients switched to brivaracetam. It appears that 252 patients (of 777) discontinued levetiracetam before starting brivaracetam. This represents 32% of patients and does not correspond to the resubmission's statement that 10-12% of levetiracetam-treated patients switched to brivaracetam. The resubmission reported that timing of levetiracetam discontinuations varies considerably but many levetiracetam discontinuations are ≥90 days apart from brivaracetam, indicating there is not a direct switch from levetiracetam to brivaracetam. The resubmission also stated that the Steinhoff abstract (2017a) indicated that 19% of patients (20 of 109 patients) switched from levetiracetam to brivaracetam due to adverse events. These data cited by the resubmission were sourced from an abstract, and most could not be confirmed. Given the lack of detail provided by the resubmission, it is difficult to determine the likely proportion of patients that may switch from levetiracetam to brivaracetam.

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 unchanged from the original submission (July 2016) and the March 2017 resubmission.

5.2 Lacosamide has a lower price than that of perampanel, which was recommended for listing on a cost-minimisation basis with lacosamide. While both drugs are listed in the F1 formulary, a 5% statutory price reduction has been applied to lacosamide but not 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 as it was a minor submission.

Consumer comments

6.2 There PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The resubmission did not present any new comparative clinical trials. The previous resubmission, and the original submission used 3 brivaracetam trials (Trial 1252 (N=399); Trial 1253 (N=400); Trial 1358 (N=768)) and 3 lacosamide trials (SP667 (N=497); SP754 (N=489); SP755 (N=546)) to provide an indirect comparison of brivaracetam and lacosamide using placebo as the common reference.

6.4 In March 2017, the PBAC had noted the transitivity concerns between the brivaracetam and lacosamide trials (paragraph 7.5, March 2017 PSD). The resubmission provided argument that the brivaracetam and lacosamide trial populations were similar. The resubmission provided a description of the steps taken in the March 2017 resubmission in the post-hoc analysis, when subgroups in the brivaracetam and lacosamide trials were stratified according to concomitant medications and prior antiepileptic drug (AED) history. The resubmission argued that the patient populations were similar, given the 50% responder rates in the placebo arms of the trials (18.4% in the brivaracetam trials; 20.3% in the lacosamide trials).

6.5 The resubmission stated that the patient populations from brivaracetam and levetiracetam trials have been compared and that these populations are less comparable then the brivaracetam and lacosamide trials. The resubmission added that the brivaracetam and levetiracetam datasets cannot be matched for use in an indirect comparison as the patients in the brivaracetam trials are more heavily pre-

treated and refractory than the patients in the levetiracetam trials. To substantiate this claim, the resubmission provided a report prepared for the sponsor assessing indirect comparisons of brivaracetam and levetiracetam. The resubmission summarised key points from this report, as follows:

- The analysis pooled patient-level clinical trial data for the comparison of brivaracetam and levetiracetam for adjunctive treatment of partial onset seizures.
- Patients were selected from the two sets of trials such that inclusion/exclusion criteria were consistent across trials.
- Patient baseline characteristics were matched between the brivaracetam and levetiracetam trials, outcomes were defined and were assessed during the first 12 weeks following randomisation (including any titration), thus reducing the potential for bias.
- Even after the adjustments described above, differences remained between the placebo arm outcomes in the brivaracetam and levetiracetam trials, indicating the presence of unobserved confounding factors. Similar results were observed for a subgroup analysis of refractory patients.
- The populations and placebo response rates in the brivaracetam and levetiracetam trials are so different that matching was not successful.
- There are unobserved confounding factors. As such, comparisons between brivaracetam and levetiracetam using these trials is problematic.
- It is not possible to conclude that brivaracetam and levetiracetam are equivalent, nor that one is better than the other.

6.6 The resubmission did not provide the report (which was prepared in 2015) and therefore the statements made in the resubmission regarding the potential comparison between the brivaracetam and levetiracetam trials could not be verified. The resubmission did indicate that the report is available upon request.

Comparative effectiveness

6.7 The resubmission provided a summary of the clinical evidence presented in the previous resubmission and original submission as an attachment to the resubmission. The key results as presented in the March 2017 resubmission are provided in the table below.

Table 2: 50% responder rate for partial onset seizure frequency - indirect comparison of brivaracetam and lacosamide

	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 3, p14 of the March 2017 PSD

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.

Comparative harms

6.8 The resubmission provided no new comparative safety data, however it did provide a discussion of issues around comparative safety as well post-marketing data.

6.9 The resubmission stated the trial durations represent the standard for add-on therapies in epilepsy (European Medicines Agency 2010). While the EMA 2010 Guidelines cited by the resubmission stated that the maintenance period of add-on trials should last at least 12 weeks in order to establish that efficacy is not short lasting, for safety the EMA document stated that long-term data should be generated by continuation or extension of add-on studies in order to assess absence of tolerance on the long term and maintenance of safety. The EMA document indicated that one-year study duration is considered the minimum.

6.10 The resubmission presented results of a multinational, non-interventional, post-marketing European study sourced from a conference abstract (Steinhoff 2017a), in which patients (N=109) received adjunctive brivaracetam according to normal clinical practice. Interim analysis of 6-month data from the study provided the following results:

- Incidence of treatment-emergent adverse events (TEAEs): 46/109 (42.2%).
  - Serious TEAEs: 8/109 (7.3%).
  - Discontinuation due to TEAEs: 17/109 (15.6%).
  - Drug-related TEAEs: 28/109 (25.7%)
- Most frequent adverse events (>5%) were fatigue (6/109; 5.5%) and seizure (discontinuation due to seizure worsening, seizure increase, seizure worsening, seizures; 6/109; 5.5%).

The resubmission concluded that these results suggested that brivaracetam had good tolerability in a highly refractory population.

6.11 The resubmission also presented results of a multicentre, retrospective cohort study from Germany (Steinig 2017) assessing 262 patients treated with brivaracetam. The

length of exposure ranged from 1 day to 12 months, with a median retention time of 6.1 months.

- TEAEs were observed in 37.8% of the patients, with the most common being somnolence, dizziness and behavioural adverse events (BAEs).
- BAEs that presented under previous levetiracetam treatment improved upon switch to brivaracetam in 57.1% (20/35) of patients and levetiracetam-induced somnolence improved in 70.8% of patients (17/24). These improvement rates were based on relatively small sample sizes.

6.12 A third retrospective study using data from a single epilepsy referral centre in Germany (Steinhoff 2017), with a minimum observation period of 6 months, reported that of 101 patients treated with brivaracetam, 37 (37%) patients had adverse events, with the most frequent events being dizziness (16%) and somnolence (11%). Psychiatric events including irritability, aggression, depression and psychosis were observed in single cases.

6.13 The PBAC previously noted uncertainty remained around the compounding of neuropathic side effects when brivaracetam is used concomitantly with levetiracetam (paragraph 7.2, March 2017 brivaracetam PSD). The resubmission asserted that the comment relating to compounding the neuropsychological effects is unsubstantiated, and furthermore immediate discontinuation from an anti-epileptic drug poses several safety risks to the patient. The resubmission stated that the standard of care is to cross-titrate and this would be the preferred methodology for use of brivaracetam in patients in Australia.

Clinical claim

6.14 The resubmission did not present a clinical claim. The March 2017 resubmission made the same claim as the July 2016 submission, that brivaracetam was non-inferior to lacosamide in terms of comparative effectiveness, and non-inferior in terms of comparative safety.

Economic analysis

6.15 A cost-minimisation analysis of brivaracetam versus lacosamide in patients with refractory partial epileptic seizures was conducted. The same approach as that applied in the previous resubmission was used, with the only difference being the 25% decrease in brivaracetam price. Key features of the cost-minimisation analysis are provided below.

6.16 The trial based equi-effective daily doses in the resubmission were estimated as 117.6mg for brivaracetam and 316.2mg for lacosamide. Dose relativity was calculated to be 2.69. The resubmission 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). The proposed equi-effective doses were the same as those presented in the March 2017 resubmission. In March 2017, 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.

6.17 The minor resubmission proposed a [redacted]% price decrease compared with the cost-minimised price, again as a flat pricing structure for all dosage strengths, to address the economic uncertainty surrounding the mean daily dose of brivaracetam. The [redacted]% reduction in price was also proposed to cover the possibility of an early switch to brivaracetam from levetiracetam.

6.18 In its pre-PBAC response, the sponsor proposed an additional [redacted]% price reduction, to position brivaracetam at [redacted]% below the cost-minimised price of lacosamide, in a greater effort to reduce the uncertainties noted above.

6.19 The table below provides a summary of the equi-effective doses and AEMP and DPMQ for brivaracetam.

Table 3: Brivaracetam cost per pack calculations

	Equi-effective dose	Cost per day (AEMP)	Days of therapy per pack	AEMP	DPMQ
Lacosamide tablets	316.2 mg	$8.26	28	NC[a]	NC[a]
Brivaracetam tablets: 25 mg, 50 mg, 75 mg, 100 mg, x 56	117.6 mg	$[redacted]	28	published price (based on cost-minimised price: $[redacted] effective price ([redacted]% discount on cost-minimised price): $[redacted]	published price: $[redacted] effective price: $[redacted]
Brivaracetam liquid: 10 mg/mL, 300 mL	-	-		published price: $[redacted] effective price: $[redacted]	published price: $[redacted] effective price: $[redacted]

[a] Since lacosamide has a linear price per mg each presentation has a different price per pack
Source: Tables 15-16, pp44 of the resubmission and prePBAC response
AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; NC=not calculated

6.20 Under the Special Pricing Arrangement proposed by the resubmission, the monthly costs of brivaracetam tablets were: AEMP = $[redacted]; and DPMQ = $[redacted]. The costs of the oral solution were: AEMP = $[redacted]; and DPMQ = $[redacted]. The higher proposed price for the oral solution was not justified in the resubmission. Special Pricing Arrangements are only available for new drugs seeking listing on a cost-minimisation basis with a currently listed drug, if the currently listed drug already has a Special Pricing Arrangement. Listing is proposed on a cost-minimisation basis with lacosamide that does not have Special Pricing Arrangement. Perampanel also does not have a Special Pricing Arrangement.

Drug cost/patient/year: $[redacted]

6.21 The cost of brivaracetam tablets per year would be $[redacted], based on the price proposed in the prePBAC response and assuming 100% compliance. The original submission estimated a yearly cost of $[redacted] for brivaracetam tablets, and the March 2017 resubmission had an estimated yearly cost of $[redacted] for tablets.

6.22 The yearly cost of lacosamide, was calculated to be $2,194.30 based on a daily dose of 200mg, and $4,304.39 based on a daily dose of 400mg, assuming 100% compliance.

Estimated PBS usage & financial implications

6.23 The resubmission used a market share approach to estimate the use and financial implications for the requested listing of brivaracetam on the PBS.

6.24 The uptake rate of brivaracetam was the same as that assumed in the March 2017 resubmission, 25% in Year 1 increasing by 5% for the next two years and then increasing by 2.5% for the final two years.

6.25 The resubmission stated that the replacement of lacosamide by brivaracetam was determined by calculating the equivalent lacosamide dose and then assuming that the lacosamide therapy being replaced will equal the equi-effective dose on average. As an example, for patients taking 50mg/day of brivaracetam the equivalent lacosamide dose would be 50mg × dose relativity of 2.69=135mg. It was then assumed that the lacosamide therapy being replaced was 65% 100mg/day and 35% 200mg/day to arrive at 135mg/day. The resubmission also assumed that since dose titration is not required with brivaracetam there would be one less specialist consultation for every patient initiating brivaracetam therapy, generating MBS cost offsets.

6.26 The table below provides a summary of the expected number of patients treated with brivaracetam, number of scripts, cost offsets due to substitution of lacosamide and fewer specialist visits along with the total estimated net saving to the Government (based on 25% price reduction proposed in minor resubmission).

Table 4: Estimated use and financial implications of listing brivaracetam (based on [redacted]% price reduction proposed in minor resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of brivaracetam use					
Population treated with lacosamide/perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population not receiving concomitant levetiracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake	25.0%	30.0%	35.0%	37.5%	37.5%
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated - March 2017 resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam scripts[a] - March 2017 resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost					
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offsets due to reduced lacosamide use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offsets to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government - March 2017 resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 20, p49; Table 21, p52; Table 26, p52 of the resubmission; 7.01 brivaracetam COM.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] Annual number of PBS prescriptions per patient = 12.16, based on a script analysis conducted by IMS Health.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

6.27 The estimated patient numbers, and scripts, decreased from those estimated in the March 2017 resubmission. Patient numbers decreased by [redacted] in Year 1 and [redacted] in Year 5, with script numbers decreasing by [redacted] in Year 1 and [redacted] in Year 5. These decreases were due to exclusion of patients in the current estimates who were receiving concomitant levetiracetam. If a lower proportion of lacosamide and levetiracetam combination patients was used, then with the resultant increase in patient numbers, the estimated cost savings increase (see sensitivity analyses below).

6.28 The resubmission estimated that the net saving to Government would be less than $10 million per year in the first five years of listing; this compared with an estimated net saving to Government of less than $10 million per year in the March 2017 resubmission.

6.29 Table 5 presents the financial implications of listing brivaracetam based on the [redacted]% price reduction proposed in the prePBAC response. The estimated net saving to the Government over 5 years was $10 - $20 million per year, or a saving of $10 - $20 million per year over the first 6 years from listing.

Table 5: Financials with current additional [redacted]% price cut: total of [redacted]%

Net costs	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 1-6 total
PBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Govt.	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**

Source: Table 7, p5 of the pre-PBAC response.

6.30 Sensitivity analyses for the financial forecasts are presented in the Table below (based on [redacted]% price reduction proposed in minor resubmission).

Table 6: Sensitivity analyses of estimated cost savings (based on [redacted]% price reduction proposed in minor resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5 total
Net cost to Government - base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A presented in the minor resubmission						
Uptake decreased by 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake increased by 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Substitution of lacosamide reduced to 70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily brivaracetam dosage increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional analyses						
Lacosamide and levetiracetam combination 4.33% (base case 37.66%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake 35%, 45%, 50%, 55%, 60% Years 1 to 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide substitution 65%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Briva dosage: 14.3% 50mg, 100mg; 33.3% 150mg, 200mg; 2.5% oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 27, p53 of the resubmission and Excel workbook 'UCB Brivaracetam Section 4 workbook minor submission August 2017 Final'.

6.31 Increasing or decreasing uptake by 10% increased or decreased the estimated savings by 10%, as would be expected. An additional analysis, assuming uptake of 35% in Year 1, 45% in Year 2, 50% in Year 3, 55% in Year 4 and 60% in Year 5 showed an increase in estimated savings to $10 - $20 million. Reduction in the substitution of lacosamide from the base case assumption of 100% to 70% almost eliminated the cost savings (saving of less than $10 million over 5 years). Cost savings were also eliminated if the substitution of lacosamide drops below 70% (net cost of less than $10 million over 5 years with lacosamide substitution of 69%; less than $10 million with 65% substitution).

6.32 For the sensitivity analysis assessing increase in brivaracetam dose, the increase in estimated savings (from less than $10 million in the base case to $10 - $20 million) was driven by the assumption that the proportion using 50mg/day would decrease from 15.6% to 14.3%; the proportion using 100mg/day would decrease from 24.4% to 19.0%; the proportion using 150mg/day would decrease from 50.7% to 28.5%;

and the proportion using 200mg/day would increase from 6.8% to 33.3%. As such, while the use of 200mg/day has increased from less than 10% of patients to a third of patients, the usage of all other doses has decreased, with a considerable decrease in usage of the 150mg dose. Another analysis assuming that usage of the 150mg/day and 200mg/day dosages were equal (both at 33.3%) had little impact on the estimated savings, with the saving over the first 5 years of $10 - $20 million similar to that estimated by the resubmission's analysis ($10 - $20 million).

6.33 As previously noted (paragraph 6.34, March 2017 PSD) there remained 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 was 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.

Financial Management – Risk Sharing Arrangements

6.34 The minor resubmission stated that a Risk Share Arrangement contains the cost to the Government of lacosamide and perampanel. The resubmission acknowledged brivaracetam would be added to the lacosamide/perampanel Risk Share Arrangement and if this is exceeded, the sponsor would bear the financial risk.

6.35 While the resubmission has excluded patients in the lacosamide/perampanel population who would be on concomitant levetiracetam in the determination of its financial estimates and has included a statement in the requested restriction not permitting the concomitant use of brivaracetam and levetiracetam, the resubmission did not include any description of a proposed Risk Share Arrangement to address the risk of patients inappropriately moving from levetiracetam to brivaracetam. The statement added to the requested restriction only addressed concomitant use of brivaracetam and levetiracetam and did not address the possibility of early use of brivaracetam in place of levetiracetam.

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

7 PBAC Outcome

7.1 The PBAC recommended an Authority Required (Streamlined) listing of brivaracetam for the treatment of intractable partial epileptic seizures. The PBAC's recommendation for listing was based on, among other matters, that the cost-effectiveness of brivaracetam would be acceptable if it were cost-minimised against lacosamide. In addition, the following measures are to be implemented to contain risks associated with the cost of the drug to the PBS: the price reduction as proposed in the sponsor's prePBAC response and joining the current Risk Sharing Arrangement for lacosamide and perampanel for the same indication.

7.2 The PBAC noted, unchanged from the March 2017 resubmission, the current resubmission proposed listing brivaracetam as a third-line adjunctive therapy for use in the same population eligible for lacosamide and perampanel.

7.3 The PBAC recalled the March 2017 resubmission for brivaracetam was rejected based on a lack of a comparison with levetiracetam or other similarly listed anti-epileptic drugs, which the PBAC considered would be replaced by brivaracetam.

7.4 The PBAC noted the usage data included in the minor resubmission supporting levetiracetam and brivaracetam being used in different patient populations, and that the treatments have been studied in different patient populations that prevents a robust comparison of the efficacy and safety of levetiracetam and brivaracetam. The PBAC further noted that the financial risk associated with the use of brivaracetam in less refractory patients was mitigated by the proposed price reduction and Risk Sharing Arrangement. Overall, the PBAC considered the positioning of brivaracetam as a third-line adjunctive therapy was adequately supported.

7.5 Based on the positioning being adequately supported, the PBAC accepted lacosamide as the appropriate comparator.

7.6 The PBAC recalled that the July 2016 submission and the March 2017 resubmission were based on an indirect comparison of three brivaracetam trials and three lacosamide trials using placebo as the common comparator, however the brivaracetam trials generally included less resistant patient populations. 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.

7.7 The PBAC noted the additional safety data presented in the minor resubmission and considered that the claim of non-inferior comparative safety was reasonable.

7.8 The PBAC advised that the equi-effective doses are 117.6 mg brivaracetam and 316.2 mg lacosamide. 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. The PBAC considered the [redacted]% price reduction for brivaracetam compared with the cost-minimised price adequately addressed this uncertainty.

7.9 The PBAC noted the estimated net saving to the PBS/RPBS/MBS of $10 - $20 million over the first 5 years of listing. The PBAC noted the estimated saving was reduced if the extent of substitution of lacosamide was less than 100%. The PBAC considered that some substitution for second-line anti-epileptic drugs was likely and that this would reduce the savings as the proposed price of brivaracetam is higher than the PBS-listed prices of second-line anti-epileptic drugs. However, the PBAC considered the financial risk to the PBS/RPBS was adequately mitigated by the proposed [redacted]% price reduction together with brivaracetam joining the current Risk Sharing Arrangement for lacosamide and perampanel.

7.10 The PBAC noted and accepted the brivaracetam oral solution had a higher proposed price compared with the tablets.

7.11 The PBAC recalled its previous concern regarding the compounding of neuropathic side effects when brivaracetam is used concomitantly with levetiracetam. The PBAC noted the comments in the minor resubmission that immediate discontinuation from an anti-epileptic drug poses several safety risks to the patient and that the standard of care is to cross-titrate. The PBAC considered that the PBS listing for brivaracetam should not allow concomitant use with levetiracetam, except for cross titration. The PBAC recommended that the restriction for levetiracetam be updated accordingly to not allow combination use with brivaracetam, except for cross titration.

7.12 The PBAC advised that brivaracetam is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners as continuing therapy only. Existing anti-epileptic drugs on the PBS such as lacosamide and perampanel are currently included for prescribing by nurse practitioners within collaborative arrangements for continuing treatment only.

7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

7.14 The PBAC recommended that the Early Supply Rule should apply.

7.15 The PBAC 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.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

8.2

Name, Restriction, Manner of administration and form	Max. Qty	№.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:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Intractable partial epileptic seizures
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial 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:	The 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.*
Population criteria:	Patients must be aged 16 years or older
Administrative Advice	Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	Max. Qty	№.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:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Intractable partial epileptic seizures
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial 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
Clinical criteria:	Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition. 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	Proprietary Name and Manufacturer
BRIVARACETAM Oral liquid 10 mg/mL	300 mL	5	Briviact® UCB Pharma

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Intractable partial epileptic seizures
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial 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:	The 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.*
Population criteria:	Patients must be aged 16 years or older
Administrative Advice	Special Pricing Arrangements apply

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Intractable partial epileptic seizures
Severity:	Intractable
Condition:	Epilepsy
PBS Indication:	Intractable partial 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
Clinical criteria:	Patient must have previously been treated with PBS-subsidised treatment with this drug. 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
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

8.3 Amend the listings for levetiracetam as follows:

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
LEVETIRACETAM Tablets 250 mg, 500 mg and 1 g	60	5

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Partial epileptic seizures
Treatment phase:	Initial / Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs *AND* *The treatment must not be given concomitantly with brivaracetam, except for cross titration.*
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.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts
LEVETIRACETAM 100 mg/mL oral liquid, 300 mL	1	5

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Partial epileptic seizures
Treatment phase:	Initial / Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs AND Patient must be unable to take a solid dose form of levetiracetam *AND* *The treatment must not be given concomitantly with brivaracetam, except for cross titration.*
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.

9 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.

10 Sponsor's Comment

The sponsor had no comment.