▼This medicinal product is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

BRIVIACT (BRIVARACETAM) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Brivaracetam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Briviact is available as 50 mg brivaracetam per 5 mL solution.

The active ingredient brivaracetam is a white to off-white crystalline powder. It is very soluble in water, buffer (pH 1.2, 4.5 and 7.4), ethanol, methanol, and glacial acetic acid. It is freely soluble in acetonitrile and acetone and soluble in toluene. It is very slightly soluble in n-hexane.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Briviact solution for injection is packaged in a clear, colourless Type I glass vial with a grey rubber stopper and sealed with an aluminium cap fitted with a white polypropylene tear-off seal.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Briviact solution for injection is 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults
Briviact at doses between 50 and 200 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures. Initial dose titration to an effective dose is not required for tolerability.

The daily dose is administered in two equally divided doses, once in the morning and once in the evening. The recommended starting dose as per clinical trials is 100 mg/day. In accordance with good prescribing practice, Briviact may be initiated at a dose of 50 mg per day. Based on individual patient response, the dose may be adjusted between 50 mg/day and 200 mg/day in steps of 50 mg per day every 2 weeks. Briviact may be taken with or without food.

Brivaracetam may be initiated with either intravenous or oral administration. When converting from oral to intravenous administration or vice versa, the total daily dose and frequency of administration

should be maintained. Brivaracetam solution for injection is an alternative for patients when oral administration is temporarily not feasible.

In accordance with current clinical practice, if Briviact has to be discontinued, it is recommended to withdraw it gradually.

If patients missed one dose or more, it is recommended that they take a single dose as soon as they remember.

Briviact solution for injection may be administered as an intravenous bolus without dilution or may be diluted in a compatible diluent and administered as a 15-minute intravenous infusion.

After intravenous administration a bitter taste may be experienced.

This medicinal product is for single use in one patient only. Discard any residue.

Product with particulate matter or discoloration should not be used.

There is no experience with twice daily intravenous administration of Briviact for a period longer than 4 days.

Briviact solution for injection is physically compatible when mixed with the following diluents and other compounds commonly co-administered in patients with epilepsy.

Diluents:

- Sodium chloride 9 mg/mL (0.9%) solution for injection
- Glucose 50 mg/mL (5%) solution for injection
- Lactated Ringer's solution for injection

Other compounds:

- Lacosamide
- Valproate
- Phenytoin and fosphenytoin
- Clonazepam and diazepam
- Midazolam and lorazepam
- Propofol

Following dilution, Briviact solution for injection was found to be physically compatible and chemically stable for up to 24 hours and stored in PVC or polyolefin bags at a temperature up to 25°C. However to avoid microbiological contamination, the product should be used immediately after dilution. If this is not practicable, the diluted solution can be stored at room temperature for not more than 4 hours before use.

Use in patients with impaired renal function

The dose should be monitored in any form of renal impairment. Briviact is not recommended in end-stage renal disease patients undergoing dialysis due to lack of data.

Use in patients with impaired hepatic function

Exposure to brivaracetam was increased by 50%, 57% and 59% in adult patients with chronic liver disease belonging to Child-Pugh classes A, B and C, relatively to matched healthy controls. In adults, a 50 mg/day starting dose should be considered. In adolescents weighing 50kg or greater, a 50 mg/day

starting dose is recommended. A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment. In paediatric patients weighing less than 50 kg, a 1 mg/kg/day starting dose is recommended. The maximum dose should not exceed 3 mg/kg/day.

Use in elderly (65 years and older)
No dose reduction is necessary in elderly patients.

Use in children
Adolescents weighing 50 kg or greater
The daily dose is administered in two equally divided doses, once in the morning and once in the evening. The recommended starting dose is 50 mg/day. Brivaracetam may also be initiated at 100 mg/day based on physician assessment of need for seizure control. The recommended maintenance dose is 100 mg/day. Based on individual patient response, the dose may be adjusted between the effective dose range of 50 mg/day and 200 mg/day.

Children from 4 years of age or adolescents weighing less than 50 kg
The daily dose is administered in two equally divided doses, once in the morning and once in the evening. The recommended starting dose is 1 mg/kg/day. Brivaracetam may also be initiated at 2 mg/kg/day based on physician assessment of need for seizure control. The recommended maintenance dose is 2 mg/kg/day. Based on individual patient response, the dose may be adjusted between the effective dose range of 1 mg/kg/day and 4 mg/kg/day.

The physician should prescribe the most appropriate formulation and strength according to weight and dose.

There are insufficient data to recommend the use of Briviact in children under 4 years of age (see Section 4.4 Special Warnings and Precautions for Use).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of Excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Suicidal behaviour and ideation
Antiepileptic drugs, including Briviact, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were

four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 - 100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events/1000 patients	Drug patients with events/1000 patients	Relative Risk: Incidence of events in Drug patients/incidence in Placebo patients	Risk Difference: Additional Drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing brivaracetam or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Hypersensitivity: bronchospasm and angioedema

Briviact can cause hypersensitivity reactions. Bronchospasm and angioedema have been reported in patients taking Briviact. If a patient develops hypersensitivity reactions after treatment with Briviact, the drug should be discontinued. Briviact is contraindicated in patients with a prior hypersensitivity reaction to brivaracetam or any of the inactive ingredients (see Section 4.3 Contraindications).

Discontinuation

In accordance with current clinical practice, if Briviact has to be discontinued it is recommended this be done gradually to minimise the potential for rebound seizures.

Use in hepatic impairment
There are limited clinical data on the use of brivaracetam in patients with pre-existing hepatic impairment. Dose adjustments are recommended for patients with hepatic impairment (see Section 4.2 Dose and Method of Administration).

No adverse liver changes were seen in rats and monkeys following chronic administration of brivaracetam at exposure well above (up to 33-fold) the mean human exposure at the clinical dose of 200 mg/day. In dogs, brivaracetam administration resulted in adverse liver changes, mainly porphyria, at an exposure level close to mean human exposure at the clinical dose of 200 mg/day. However, toxicological data accumulated on brivaracetam and on a structurally related compound indicate that the dog liver changes have developed through mechanisms not relevant for humans.

Use in renal impairment
See Section 4.2 Dose and Method of Administration.

Use in the elderly
The three pivotal double-blind placebo-controlled studies included 38 elderly patients aged between 65 and 80 years. Although data are limited, the efficacy was comparable to younger subjects. No dose adjustment is needed in elderly patients.

Paediatric use
Briviact is not recommended for use in children under 4 years of age as safety and efficacy has not yet been established in this population. Limited efficacy data is available from open-label studies in children 1 month to < 16 years of age with partial-onset seizures and other epilepsy syndromes.

The potential adverse effects of long-term oral administration of brivaracetam on neonatal growth and development were investigated in juvenile rats and dogs. In juvenile rats, the highest dose tested, 600 mg/kg/day, was associated with adverse developmental effects (i.e. mortality, clinical signs, decreased body weight, lower brain weight and non-reversible effects on auditory startle responses). There were no adverse neuropathological or brain histopathological findings. The NOAEL was considered to be 300 mg/kg/day. In juvenile dogs, the dose of 100 mg/kg/day induced adverse liver changes similar to those observed in adult animals. There were no adverse effects on growth, bone density or strength, brain and neurobehavioral assessments and neuropathology evaluation. Similar exposure to brivaracetam was achieved in adult vs juvenile animals at the NOAEL, except at post-natal day 4 where higher exposure was achieved in juveniles compared to adults.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interaction studies have only been performed in adults.

Effects of other substances on brivaracetam
The hydrolysis of brivaracetam is mediated by non-CYP-dependent amidase. The hydroxylation of brivaracetam appears to be a minor elimination pathway primarily mediated by CYP2C19 (see Section 5 Pharmacological Properties). CYP-mediated oxidation is responsible for a limited portion of brivaracetam's elimination.

Thus, coadministration with CYP inhibitors is unlikely to significantly affect brivaracetam exposure. Coadministration with CYP450 strong inducer, rifampicin decreases brivaracetam plasma concentrations by 45%. Prescribers should consider increasing the brivaracetam dose in patients starting treatment with rifampicin and decreasing when stopping rifampicin therapy. Brivaracetam concentrations were not significantly modified by CYP3A inhibitors and CYP2C19 inhibitors. *In vitro* assays showed that brivaracetam disposition should not be significantly affected by any CYP (e.g. CYP1A, 2C8, 2C9, 2C19, 2D6 and 3A4) or transporter (e.g. Pglycoprotein, BCRP, MRPs) inhibitors.

Effects of brivaracetam on other medicinal products
Brivaracetam is not expected to cause clinically significant inhibition or induction of the clearance of other drugs metabolized by CYP450 isoforms. *In vitro* studies have shown that brivaracetam exhibits little or no inhibition of CYP450 isoforms at plasma concentrations achieved following a therapeutic dose. Brivaracetam did not induce CYP enzymes at therapeutic concentrations. Interaction studies to determine the potential inhibitory effects on transporters concluded that there were no clinically relevant effects.

Antiepileptic drugs
Potential interactions between brivaracetam (50 mg/day to 200 mg/day) and other AEDs were investigated in a pooled analysis of plasma drug concentrations from all phase 2-3 studies and in a population exposure-response analysis of placebo-controlled phase-3 studies in adjunctive therapy in the treatment of partial onset seizures. The effect of the interactions on the plasma concentration is summarised in the Table 2.

Table 2: Median percent reduction from baseline over treatment period

AED Coadministered	Influence of AED on brivaracetam plasma concentration	Influence of brivaracetam on AED plasma concentration
Clobazam	No data	None
Clonazepam	No data	None
Carbamazepine	26% decrease	None Increased carbamazepine-epoxide (See below)
Lacosamide	No data	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None (monohydroxy derivative, MHD)
Phenobarbital	19% decrease	None
Phenytoin	21% decrease	None 20% increase*
Pregabalin	No data	None
Topiramate	None	None
Valproic acid	None	None

Zonisamide	No data	None

* based on a study involving the administration of a supratherapeutic dose of 400 mg/day brivaracetam

Brivaracetam is a moderate reversible inhibitor of epoxide hydrolase resulting in an increased concentration of carbamazepine epoxide, an active metabolite of carbamazepine. In controlled studies, the carbamazepine epoxide plasma concentration increased by a mean of 37%, 62% and 98% with little variability at brivaracetam doses of 50 mg/day, 100 mg/day and 200 mg/day respectively. No toxicity was observed, however, if tolerability issues arise when co-administered, carbamazepine dose reduction should be considered.

Oral contraceptives
Co-administration of brivaracetam (100 mg/day) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) did not influence the pharmacokinetics of either substance. When brivaracetam was coadministered at a dose of 400 mg/day (twice the recommended maximum daily dose) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg), a reduction in estrogen and progestin AUCs of 27% and 23%, respectively, was observed without impact on suppression of ovulation (no change was observed in the endogenous markers estradiol, progesterone, luteinizing hormone, follicle stimulating hormone, and sex hormone binding globulin). No study with lower doses of oral contraceptives has been performed.

Alcohol
Brivaracetam increased the effect of alcohol on psychomotor function, attention and memory in a pharmacokinetic and pharmacodynamic interaction study in healthy subjects. There was no pharmacokinetic interaction.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No human data on the effect of brivaracetam on fertility are available. In rats, there was no adverse effect on male or female fertility following oral administration of brivaracetam at doses at least 15 times the maximal recommended human dose based on body surface area and plasma concentrations.

Use in pregnancy
(Category B3)

There are no adequate data on the use of brivaracetam in pregnant women. Brivaracetam was used as adjunctive therapy in clinical studies and when used with carbamazepine, it induced a dose-related increase in the concentration of an active metabolite, carbamazepine-epoxide (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). There is insufficient data to determine the clinical significance of this effect in pregnancy. There are no data on human placental transfer. In rats, brivaracetam was shown to readily cross the placenta. The potential risk for humans is unknown.

As a precautionary measure, brivaracetam should not be used during pregnancy unless clinically necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus. If a woman decides to become pregnant, the use of brivaracetam should be carefully re-evaluated. To monitor outcome of pregnancy in women exposed to Briviact,

doctors are encouraged to register pregnant patients taking Briviact on the Australian Pregnancy Register for Women on Antiepileptic Medication with Epilepsy and Allied Conditions by calling 1800 069 722.

Animal studies did not detect any teratogenic potential of brivaracetam in either the rat or the rabbit. There were no adverse effects on embryofetal development following oral administration of brivaracetam to rats during the period of organogenesis at doses up to 600 mg/kg/day (AUC exposure 25 times clinical exposure at the MRHD), or following intravenous administration of the brivaracetam metabolite ucb-107092-1 at doses up to 1000 mg/kg/day (plasma concentration at least 40 times the plasma C_{max} in healthy or renally impaired subjects). In rabbits, adverse effects on embryofetal development were not apparent at oral doses up to 120 mg/kg/day (AUC exposure 3 times clinical exposure at the MRHD) during organogenesis despite the presence of overt maternotoxicity. Maternotoxic exposure at 6 times the clinical AUC at the MRHD resulted in increased post-implantation loss, fewer live fetuses and reduced fetal bodyweight. The potential risk for humans is unknown.

Use in lactation
It is unknown whether brivaracetam is excreted in human milk. Studies in rats have shown excretion of brivaracetam and/or its metabolites in milk where levels are similar to the plasma level. Oral administration of brivaracetam to rats from early gestation to weaning was associated with mild developmental delays (plasma AUC 14 times clinical exposure at the MRHD); the no-effect dose was 5 times clinical exposure. Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue brivaracetam, taking into account the benefit of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised not to drive a car or to operate other potentially hazardous machines until they are familiar with the effects of brivaracetam on their ability to perform such activities, as brivaracetam treatment has been associated with somnolence and other CNS related symptoms.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies
In all controlled and uncontrolled trials in patients with epilepsy, 2388 subjects have received brivaracetam, of whom 1740 have been treated for ≥ 6 months,1363 for ≥ 12 months, 923 for ≥ 24 months, 733 for ≥ 36 months and 569 for ≥ 60 months (5 years).

In pooled placebo-controlled adjunctive therapy studies involving 1558 adult patients with partial-onset seizures (1099 patients treated with brivaracetam and 459 treated with placebo), 68.3% of patients treated with brivaracetam and 62.1% of patients treated with placebo experienced adverse events.

The most frequently reported adverse reactions (> 10%) with brivaracetam treatment were: somnolence (14.3%) and dizziness (11.0%). They were usually mild to moderate in intensity. Somnolence and fatigue were reported at a higher incidence with increasing dose. The types of adverse events reported during the first 7 days of treatment were similar to those reported for the overall treatment period.

The discontinuation rate due to adverse events was 6.0%, 7.4% and 6.8% for patients randomized to brivaracetam at respectively the dose of 50 mg/day, 100 mg/day and 200 mg/day and 3.5% for patients randomized to placebo. The adverse reaction most frequently resulting in discontinuation of brivaracetam therapy was dizziness.

Table 3: Incidence of treatment-emergent adverse event in double-blind, placebo-controlled phase 3 partial-onset seizure studies (events ≥ 2% of patients in brivaracetam and more frequent than in the placebo group)

System Organ Class/ Preferred Term	PLACEBO (N=459) %	BRIVARACETAM 50 mg/day (N=200) %	BRIVARACETAM 100 mg/day (N=353) %	BRIVARACETAM 200 mg/day (N=250) %
Ear and labyrinth disorders				
Vertigo*	2	2	3	2
Eye disorders				
Vision blurred	<1	2	<1	2
Diplopia	<1	2	<1	<1
Gastrointestinal disorders				
Nausea*	2	4	4	4
Diarrhoea	3	4	2	3
Vomiting*	<1	5	1	1
Constipation*	<1	3	1	2
Abdominal pain upper	<1	3	1	1
Toothache	1	2	<1	2
General disorders and administration site conditions				
Fatigue*	4	7	8	12
Irritability*	1	5	3	3
Infections and infestations				
Nasopharyngitis	3	3	3	4
Upper respiratory tract infection*	2	<1	2	2
Influenza*	1	2	2	<1
Bacteriuria	<1	<1	<1	2
Oral herpes	0	2	0	<1
Injury, poisoning and procedural complications				
Fall	1	2	1	1
Excoriation	1	2	<1	<1
Head injury	<1	2	<1	<1
Investigations				
Weight decreased	<1	2	<1	1
Gamma-glutamyltransferase increased	1	2	<1	1
Weight increased	<1	2	<1	<1
Metabolism and nutrition disorders				
Decreased appetite*	<1	3	<1	2
Hyponatraemia	<1	0	1	2
Musculoskeletal disorders				
Myalgia	1	3	1	<1

System Organ Class/ Preferred Term	PLACEBO (N=459) %	BRIVARACETAM 50 mg/day (N=200) %	BRIVARACETAM 100 mg/day (N=353) %	BRIVARACETAM 200 mg/day (N=250) %
Back pain	<1	3	1	<1
Pain in extremity	1	3	<1	<1
Nervous system disorders				
Somnolence*	9	12	16	17
Dizziness*	7	12	9	14
Headache	10	16	7	8
Convulsion	2	3	3	1
Tremor	1	2	<1	2
Balance disorder	<1	2	<1	1
Memory impairment	1	2	<1	1
Paraesthesia	1	2	1	<1
Ataxia	<1	2	<1	<1
Sedation	0	0	0	2
Psychiatric disorders				
Insomnia*	2	5	2	2
Anxiety*	1	2	1	3
Depression*	1	5	1	1
Nervousness	<1	2	<1	<1
Respiratory, thoracic and mediastinal disorders				
Cough*	2	2	3	2
Dyspnoea	0	2	<1	<1
Skin and subcutaneous tissue disorders				
Rash	1	2	1	<1
Pruritus	<1	2	<1	2
Eczema	0	<1	0	2

* Causality has been established.

Paediatric population

A long-term, uncontrolled, open-label safety study included children (from 4 years to less than 16 years) who continued treatment after completing the PK study (see Pharmacology) and children directly enrolled into the safety study. Children who directly enrolled received a brivaracetam starting dose of 1 mg/kg/day and depending on response and tolerability, the dose was increased up to 5 mg/kg/day by doubling the dose at weekly intervals. No child received a dose greater than 200 mg/day. For children weighing 50 kg or greater the brivaracetam starting dose was 50 mg/day and depending on response and tolerability, the dose was increased up to a maximum of 200mg/day by weekly increments of 50mg/day.

From the pooled open-label safety and PK studies in adjunctive therapy, 149 children with partial onset seizures in the age range of 4-<16 years of age have received brivaracetam, of whom 116 have been treated for ≥6 months, 104 for ≥12 months, 58 for ≥24 months, 20 for ≥36 months. The safety profile of brivaracetam observed in children was consistent with the safety profile observed in adults. As has been seen in patients with epilepsy, behavioural adverse reactions were more common in children than in adults. The types of events were, in general, consistent with the established brivaracetam safety profile in adults. The majority of events were mild or moderate in intensity, were non-serious, and did not lead to dose reduction or discontinuation of study drug. An additional

adverse reaction reported in children was psychomotor hyperactivity (4.7%). As these are uncontrolled data, definitive causality cannot be concluded.

Suicidal ideation was reported in 4.7 % of paediatric patients (more common in adolescents) compared with 2.4 % of adults and behavioural disorders were reported in 24.8 % of paediatric patients compared with 15.1 % of adults.

Other adverse reactions (< 1%)
Other adverse reactions with a lower incidence rate which are considered important are listed below.

Immune system disorders: Hypersensitivity including bronchospasm and angioedema (see Section 4.4 Special Warnings and Precautions for Use).

Blood and lymphatic system disorders: Neutropenia.

Psychiatric disorders: Aggression, agitation, psychotic disorder.

Suicidal ideation has been reported in 0.3% (3/1099) brivaracetam patients and 0.7% (3/459) placebo patients. In the short-term clinical studies of brivaracetam in epilepsy patients, there were no cases of completed suicide and suicide attempt, however both have been reported in open-label extension studies.

Intravenous administration
Adverse reactions with intravenous administration were generally similar to those with oral administration. Intravenous administration was associated with infusion site pain in 2.8% of the patients.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms
There is limited clinical experience with Briviact overdose in humans. Somnolence and dizziness have been reported in a healthy subject taking a single dose of 1400 mg of Briviact.

Management of overdose
There is no specific antidote for overdose with Briviact. Treatment of an overdose should include general supportive measures. Since less than 10% of brivaracetam is excreted in urine, haemodialysis is not expected to significantly enhance brivaracetam clearance.

For information on the management of overdose, contact the Poisons Information Centre on 131 126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is considered to be the primary mechanism for brivaracetam anticonvulsant activity, however, the precise mechanism by which brivaracetam exerts is anticonvulsant activity has not been fully elucidated.

Effects on QT interval
The effect of brivaracetam on QTc prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled parallel group study of brivaracetam (150 mg/day and 800 mg/day in two daily intakes) in 184 healthy subjects. There was no evidence that brivaracetam prolongs the QT interval.

Seizure frequency
A statistically significant correlation has been demonstrated between brivaracetam plasma concentration and seizure frequency reduction from baseline in confirmatory clinical studies in adjunctive treatment of partial onset seizures. The EC50 (brivaracetam plasma concentration corresponding to 50% of the maximum effect) was estimated to be 0.57 mg/L. This plasma concentration is slightly above the median exposure obtained after brivaracetam doses of 50 mg/day. Further seizure frequency reduction is obtained by increasing the dose to 100 mg/day and reaches a plateau at 200 mg/day.

Clinical trials
The efficacy of Briviact as adjunctive therapy in partial-onset seizures with or without secondary generalization was established in 3 fixed-dose, randomized, double-blind, placebo-controlled, multicenter studies (Studies 1, 2 and 3) which included 1558 patients. Patients enrolled had partial onset seizures and were not adequately controlled with 1 to 2 concomitant AEDs. In Studies 1 and 2, approximately 80% of patients were taking 2 concomitant AEDs, and in Study 3, 71% were taking 2 concomitant AEDs with or without vagal nerve stimulation. The most commonly used AEDs across the three studies were carbamazepine (41%), lamotrigine (25%), valproate (21%), oxcarbazepine (16%), topiramate (14%), phenytoin (10%) and levetiracetam (10%). Patients on levetiracetam were excluded from Study 3. In Study 3, approximately 19% of the patients had a history of 0-1 previous AEDs, 34% with a history of 2-4 AEDs, and 47% with a history of 5 or more AEDs. The median baseline seizure frequency across the 3 studies was 9 seizures per 28 days. Patients had a mean duration of epilepsy of approximately 23 years.

All trials had an 8-week baseline period, during which patients were required to have at least 8 partial-onset seizures. The baseline period was followed by a 12-week treatment period.There was no titration period in these studies. Study N01252 compared doses of Briviact 50 mg/day and 100 mg/day with placebo. Study N01253 compared a dose of Briviact 50 mg/day with placebo. Study N01358 compared doses of Briviact 100 mg/day and 200 mg/day with placebo.

The primary efficacy outcome for Study N01252 and Study N01253 was the percent reduction in 7-day partial onset seizure frequency over placebo. For Study N01358, the primary efficacy outcome was the percent reduction in 28-day partial onset seizure frequency over placebo and the 50% responder rate. The criteria for statistical significance for all 3 studies was $p < 0.05$. For Study

N01252 and N01253, a post-hoc analysis was conducted to evaluate the percent reduction in 28-day partial onset seizure frequency over placebo. The results of the post-hoc analysis for Study N01252 and N01253 were comparable to the 7-day prospective analysis.

In Study N01252, a sequential testing procedure, which required statistical significance at the 0.050 level for Briviact 50 mg/day versus placebo, was required prior to testing Briviact 100 mg/day. A statistically significant treatment effect was not observed for the 50 mg/day dose. The 100 mg/day dose was nominally significant. In Study N01253, the 50 mg/day dose showed a statistically significant treatment effect. In Study N01358, the 100 mg/day and 200 mg/day doses showed a statistically significant treatment effect.

The primary and secondary efficacy outcomes of all 3 studies are summarized in Table 4.

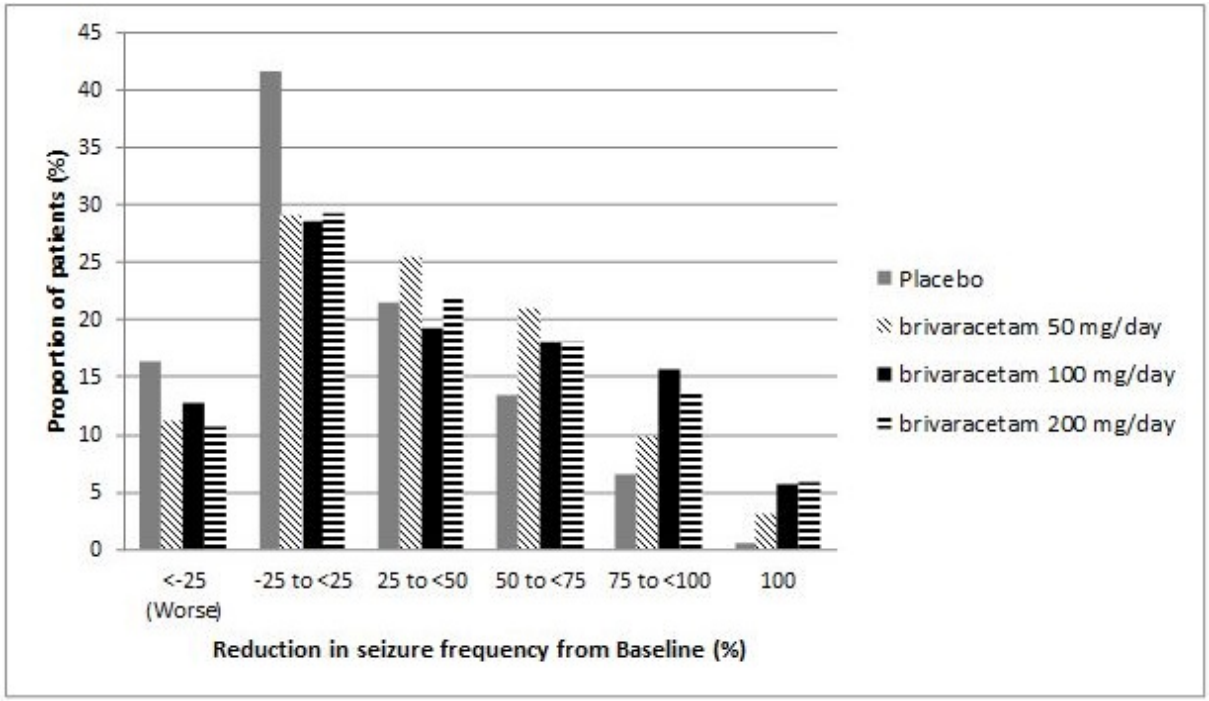
Table 4: Percent reduction in 7 day, 28 day and over treatment period partial onset seizure frequency over placebo (studies 1 and 2)

	Percent Reduction Over Placebo (%) per 7 days	**Percent Reduction Over Placebo (%) per 28 days**	**Median Percent Reduction from Baseline (%) over treatment period**	**50% Responder Rate 28 days**
Study N01252[(1)]				
Placebo (n=100)	-	-	17.0	20.0
50 mg/day (n=99)	6.5	9.2	26.8	27.3
100 mg/day (n=100)	11.7*	20.5*	32.5*[(2)]	36.0*[(2)]
Study N01253[(1)]				
Placebo (n=96)	-	-	17.8	16.7
50 mg/day (n=101)	12.8*	22.0*	30.5*	32.7*
Study N01358				
Placebo (n=259)	-	-	17.6	21.6
100 mg/day (n=252)	-	22.8*	37.2*	38.9*
200 mg/day (n=249)	-	23.2*	35.6*	37.8*

* Statistically significant (p-value < 0.05).
[(1)] Approximately 20% of the patients were on concomitant levetiracetam.
[(2)] The primary outcome for N01252 did not achieve statistical significance based on the sequential testing procedure, the 100 mg/day dose was nominally significant.

Figure 1 shows the percentage of patients (excluding patients with concomitant levetiracetam) by category of reduction from baseline in partial onset seizure frequency per 28 days across all 3 studies. Patients with more than a 25% increase in partial onset seizure are shown at left as “worse.” Patients with an improvement in percent reduction from baseline in partial onset seizure frequency are shown in the 4 right-most categories. The percentages of patients with at least a 50% reduction in seizure frequency were 20.3%, 34.2%, 39.5%, and 37.8% for placebo, 50 mg/day, 100 mg/day, and 200 mg/day, respectively.

Figure 1: Proportion of patients by category of seizure response for BRIVIACT and placebo across all three double-blind trials



Treatment with levetiracetam

In Studies N01252 and N01253, approximately 20% of the patients were on concomitant levetiracetam. Although the number of subjects is limited, there was no observed benefit versus placebo when brivaracetam was added to levetiracetam. No additional safety or tolerability concerns were observed.

In Study N01358, a pre-specified analysis of median percent reduction in partial onset seizure frequency by levetiracetam status demonstrated efficacy over placebo in patients with prior exposure to levetiracetam.

Paediatric population

In children aged 4 years and older, partial-onset seizures have a similar clinical expression to those in adolescents and adults. Experience with epilepsy medicines suggests that the results of efficacy studies performed in adults can be extrapolated to children down to the age of 4 years provided the dose is established (see 5.2 Pharmacokinetic properties). The results of efficacy have also been extrapolated to the IV route of administration on the basis of comparison with oral availability. Doses in patients from 4 years of age were defined by dose adaptations which have been established to achieve plasma concentrations in the range observed in adults taking efficacious doses (see 5.2 Pharmacokinetic properties).

Open label extension studies

Across all studies, 81.7% of the patients who completed randomized studies were enrolled in the longterm open-label extension studies. From entry into the randomized studies, 5.3% of the subjects exposed to brivaracetam for 6 months (n=1500) were seizure free compared to 4.6% and 3.7% for subjects exposed for 12 months (n=1188) and 24 months (n=847), respectively.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Brivaracetam is rapidly and completely absorbed after oral administration. Pharmacokinetics is dose proportional from 10 to 600 mg.

The median t_{max} for tablets taken without food is 1 hour (t_{max} range is 0.25 to 3 h).

Coadministration with a high-fat meal slowed down the absorption rate of brivaracetam while the extent of absorption remained unchanged.

The extent of absorption of brivaracetam is unchanged by food.

Distribution
Brivaracetam is weakly bound (≤ 20%) to plasma proteins. The volume of distribution is 0.5 L/kg, a value close to that of the total body water.

Due to its favourable lipophylicity (Log P) resulting in high cell membrane permeability, brivaracetam penetrates rapidly into the brain. Brivaracetam is rapidly and evenly distributed in most tissues. In rodents, the brain-to-plasma concentration ratio equilibrates rapidly, indicating fast brain penetration, and is close to 1, indicating absence of active transport.

Metabolism
Brivaracetam is primarily metabolised by hydrolysis of the amide moiety to form the corresponding carboxylic acid, and secondarily by hydroxylation on the propyl side chain. The hydrolysis of the amide moiety leading to the carboxylic acid metabolite (34% of the dose in urine) is supported by hepatic and extra-hepatic amidase (E.C.3.5.1.4). *In vitro,* the hydroxylation of brivaracetam is mediated primarily by CYP2C19. *In vivo,* in human subjects possessing ineffective mutations of CYP2C19, production of the hydroxy metabolite is decreased 10-fold while brivaracetam itself is increased by 22% or 42% in individuals with one or both mutated alleles. Therefore, inhibitors of CYP2C19 are unlikely to have a significant effect on brivaracetam. The 3 metabolites are not pharmacologically active.

Excretion
Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in the urine within 72 hours after intake. Less than 1% of the dose is excreted in faeces and less than 10% of brivaracetam is excreted unchanged in urine. The terminal plasma half-life ($t_{1/2}$) is approximately 9 hours.

Pharmacokinetics in special patient groups
Gender
There are no differences in the pharmacokinetics of brivaracetam by gender.

Renal impairment
A study in subjects with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m² and not requiring dialysis) revealed that the plasma AUC of brivaracetam was moderately increased (+21%) relative to healthy controls, while the AUC of the acid, hydroxy and hydroxyacid metabolites were increased 3-, 4-, and 21-fold, respectively. The renal clearance of these non-active metabolites was decreased 10-fold. Human exposure of the 3 metabolites, hydroxy, acid and hydroxyacid, at the maximum therapeutic dose of brivaracetam was sufficiently covered by levels achieved at the no observed adverse effect level (NOAEL) in repeated-dose toxicity studies in animals, including for patients with severe renal impairment. The hydroxyacid metabolite did not reveal any safety concerns

in non-clinical studies. Brivaracetam has not been studied in patients undergoing hemodialysis (see 4.2 Dose and Method of Administration).

Hepatic impairment
A pharmacokinetic study in subjects with hepatic cirrhosis (Child-Pugh grades A, B, and C) showed similar increases in exposure to brivaracetam irrespective of disease severity (50%, 57% and 59%), relative to matched healthy controls. Dose adjustments are recommended for patients with hepatic impairment (see 4.2 Dose and Method of Administration).

No clinical data are available in paediatric patients with hepatic impairment.

Elderly (over 65 years of age)
In a study in elderly subjects (65 to79 years old; with creatinine clearance 53 to 98 mL/min/1.73 m²) receiving Briviact 400 mg/day in bid administration, the plasma half-life of brivaracetam was 7.9 hours and 9.3 hours in the 65 to 75 and > 75 years groups, respectively. The steady-state plasma clearance of brivaracetam was slightly lower (0.76 mL/min/kg) than in young healthy male subjects (0.83 mL/min/kg). No dose adjustment is required (see 4.2 Dose and Method of Administration).

Paediatric population (1 month to 16 years of age)
In a pharmacokinetic study with 3-week evaluation period and weekly fixed 3-step up-titration using the brivaracetam oral solution, 99 subjects aged 1 month to <16 years were evaluated. Brivaracetam was administered at weekly increasing doses of approximately 1.0 mg/kg/day, 2.0 mg/kg/day, and 4.0 mg/kg/day. All doses were adjusted by body weight, and did not exceed a maximum of 50 mg/day, 100 mg/day, and 200 mg/day. At the end of the evaluation period, subjects may have been eligible for entry into a long-term follow-up study continuing on their last received dose (see 4.8 Adverse Effects (Undesirable effects)). Plasma concentrations were shown to be dose-proportional in all age groups. Population pharmacokinetics modeling indicated that the dose of 2.0 mg/kg twice a day provides the same steady-state average plasma concentration as in adults receiving 100 mg twice daily. The estimated plasma clearance was 1.61 L/h, 2.18 L/h and 3.19 L/h for children weighing 20 kg, 30 kg and 50 kg, respectively. In comparison, plasma clearance was estimated at 3.58 L/h in adult patients (70 kg body weight). Currently, no clinical data are available in neonates.

Race
The pharmacokinetics of brivaracetam was not significantly affected by race (Caucasian, Black/African American, Asian, American Indian/Alaska Native, Hispanic/Latino) in a population pharmacokinetic modeling from epilepsy patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Genotoxicity was evaluated *in vitro* in bacterial (Ames test) and mammalian cells (mouse lymphoma assay, chromosomal aberration test in CHO cells) and *in vivo* in rats (bone marrow micronucleus assay) and mice (Muta mice). Brivaracetam showed no evidence of mutagenicity or clastogenicity.

Carcinogenicity
In a carcinogenicity study in mice, oral administration of brivaracetam for 104 weeks increased the incidence of liver tumours (hepatocellular adenoma and carcinoma) in males at the two highest doses (550, 700 mg/kg/day). At the no-effect dose (400 mg/kg/day), exposure (plasma AUC) was similar to clinical exposure at the MRHD. These findings are considered to result from a non-genotoxic mode of action linked to a phenobarbitone-like liver enzyme induction, a known rodent specific phenomenon.

In rats, oral administration of brivaracetam for 104 weeks (150, 230, 450, 700 mg/kg/day) resulted in an increased incidence of benign thymomas in females at the highest dose. At the no-effect dose, exposure (plasma AUC) was about eight times the clinical exposure at the MRHD. The human relevance of the findings in rats is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Briviact solution for injection contains the following excipients: sodium acetate trihydrate, glacial acetic acid, sodium chloride, water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

4 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store Briviact solution for injection below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Briviact solution for injection is packaged in a clear, colourless Type I glass vial with a grey rubber stopper and sealed with an aluminium cap fitted with a white polypropylene tear-off seal. Each single use vial contains 5 mL of solution for injection and is available in packs of 10 vials.

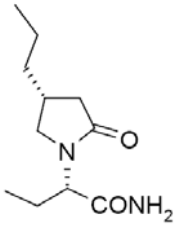
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: (2*S)*-2-[(4*R)*-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide
Molecular formula: $C_{11}H_{20}N_2O_2$
MW: 212.29

Chemical structure



CAS number
357336-20-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

4 August 2016

10 DATE OF REVISION

21 Dec 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.3	Change of shelf life from 3 to 4 years