# PRODUCT INFORMATION

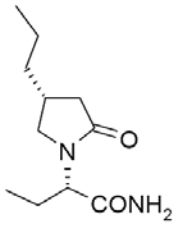
## BRIVIACT (brivaracetam) film-coated tablets and oral solution

## NAME OF THE MEDICINE

Non-proprietary name: Brivaracetam

Chemical name: (2*S*)-2-[(4*R*)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide

Chemical structure:




Molecular formula: $C_{11}H_{20}N_2O_2$
MW: 212.29
CAS number: [357336-20-0]

## DESCRIPTION

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.

**BRIVIACT film-coated tablets** contain the following excipients: croscarmellose sodium, lactose, betadex, lactose anhydrous, magnesium stearate and the proprietary film coating agents specified below:

10 mg tablets: Opadry II complete film coating system 85F18422 White (ARTG No: 11376)

25 mg tablets: Opadry II complete film coating system 85F275014 Grey (ARTG No: 110507)

50 mg tablets: Opadry II complete film coating system 85F38197 (ARTG No: Yellow 110509)

75 mg tablets: Opadry II complete film coating system 85F200021 Purple (ARTG No: 110513)

100 mg tablets: Opadry II complete film coating system 85F270000 Tan (ARTG No: 110508)

**BRIVIACT oral solution** contains the following excipients: sodium citrate, citric acid anhydrous, methyl hydroxybenzoate, carmellose sodium, sucralose, sorbitol solution (70 percent)(crystallising), glycerol, Raspberry Flavour 7557-A (ARTG No: 110532) and purified water.

# PHARMACOLOGY

## 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.

## 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.

***Elimination***
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 (t1/2) 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 Dosage and 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 Dosage and Administration).

***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 Dosage and Administration).

***Paediatric population (1 month to 16 years of age)***
In a pharmacokinetic study in 99 subjects aged 1 month to <16 years receiving BRIVIACT oral solution, 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. 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.

## 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 carbamzepine (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 1.

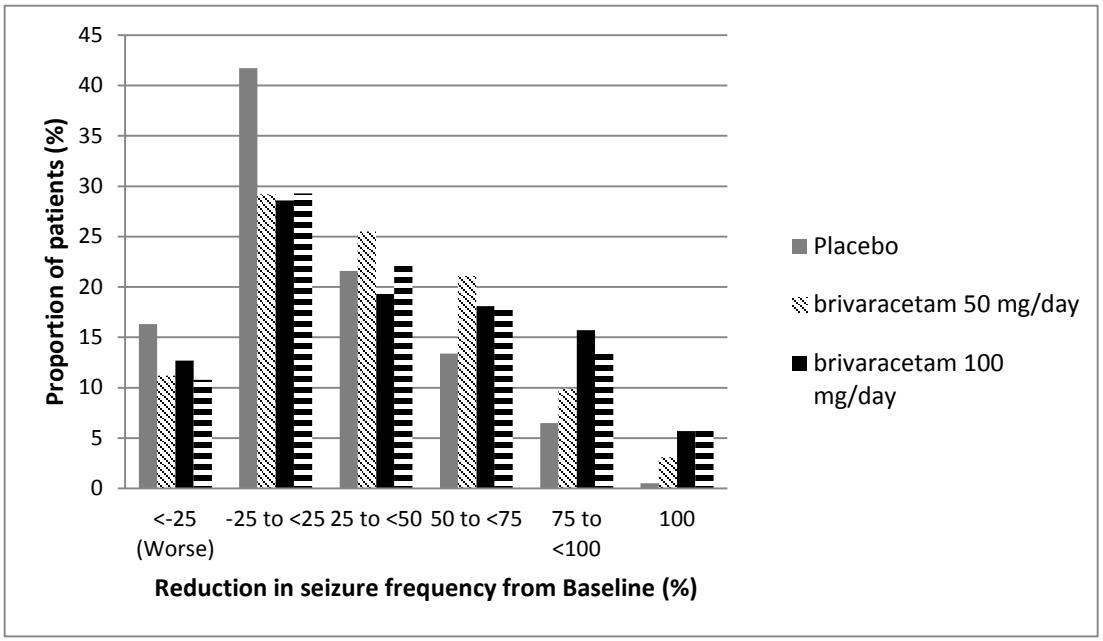
**Table 1: Percent Reduction in 7-Day, 28 day and over Treatment Period Partial Onset Seizure Frequency over Placebo (Studies 1 and 2)**

| | 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.

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) 11 and 24 months (n=847), respectively.

# INDICATIONS

BRIVIACT tablets and oral solution are indicated as add-on therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy.

# CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (refer to DESCRIPTION).

# PRECAUTIONS

**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 2 shows absolute and relative risk by indication for all evaluated AEDs

**Table 2: 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.

**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.

**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 Interactions with other Medicines). 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.

**Use in children**
BRIVIACT is not recommended for use in children under 16 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.

**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.

**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.

**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.

**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 Dosage and 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.

**Effect on ability to drive or operate machinery**
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.

## INTERACTIONS WITH OTHER MEDICINES

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 Pharmacology). 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 (eg. CYP1A, 2C8, 2C9, 2C19, 2D6 and 3A4) or transporter (eg. 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 3.

**Table 3: 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<br>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<br>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.

# ADVERSE 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 4: 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 |

| 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) % |
|---|---|---|---|---|
| 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 |

| 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) % |
|---|---|---|---|---|
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | <1 | 3 | <1 | 2 |
| Hyponatraemia | <1 | 0 | 1 | 2 |
| **Musculoskeletal disorders** | | | | |
| Myalgia | 1 | 3 | 1 | <1 |
| 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 |

| 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) % |
|---|---|---|---|---|
| Pruritus | <1 | 2 | <1 | 2 |
| Eczema | 0 | <1 | 0 | 2 |

* Causality has been established

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

- Blood and lymphatic system disorders: neutropenia
- Psychiatric disorders: aggression

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.

## DOSAGE AND ADMINISTRATION

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 50mg 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.

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.

The film-coated tablets must be taken orally whole with liquid.

The oral solution does not need to be diluted before swallowing. A nasogastric tube or gastrostomy tube may be used when administering the oral solution.

**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 patients with chronic liver disease belonging to Child-Pugh classes A, B and C, relatively to matched healthy controls. A 50 mg/day starting dose should be considered. A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment.

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

**Use in children**
There are insufficient data to recommend the use of BRIVIACT in children under 16 years of age (see Precautions).

## OVERDOSAGE

**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 further information on the management of overdosage contact the Poisons Information Centre (telephone 13 11 26).

## PRESENTATION AND STORAGE CONDITIONS

**BRIVIACT film-coated tablets** are blister packed and available in strengths of 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg brivaracetam.

10 mg: White to off white, round, film-coated, and debossed with "u10" on one side. Available in blister packs containing 14, 56, 100^ tablets and a multipack of 168^ (3 x 56) tablets.

25 mg: Grey, oval, film-coated, and debossed with "u25" on one side. Available in blister packs containing 14, 56, 100^ tablets and a multipack of 168^ (3 x 56) tablets.

50 mg: Yellow, oval, film-coated, and debossed with "u50" on one side. Available in blister packs containing 14, 56, 100^ tablets and a multipack of 168^ (3 x 56) tablets.

75 mg: Purple, oval, film-coated, and debossed with "u75" on one side. Available in blister packs containing 14, 56, 100^ tablets and a multipack of 168^ (3 x 56) tablets.

100 mg: Green-grey, oval, film-coated, and debossed with "u100" on one side. Available in blister packs containing 14, 56, 100^ tablets and a multipack of 168^ (3 x 56) tablets.

**not all pack sizes may be marketed*
*^for hospital use only*

Store BRIVIACT film-coated tablets below 30°C.

**BRIVIACT oral solution** is packed in a 300 mL glass bottle and is available as 10 mg/mL strength. The pack also contains a 10 mL oral syringe and an adaptor for the syringe.

Store unopened BRIVIACT oral solution below 30°C. Once opened, store below 30°C and discard any remnants after 5 months.

## NAME AND ADDRESS OF THE SPONSOR

UCB Pharma
A division of UCB Australia Pty Ltd
Level 1, 1155 Malvern Road
Malvern VIC 3144, Australia

## POISON SCHEDULE OF THE MEDICINE

S4

Date of first inclusion in the Australian Register of Therapeutic Goods: 04 August 2016