To be sold by retail on the prescription of a RMP only

BRITZILAM

1. Generic Name

Brivacetam Injection I.P. 10 mg/ml

2. Qualitative and quantitative composition

BRITZILAM

Each ml contains:

Brivaracetam I.P. ….10 mg

Water for injection I.P. ……q.s.

The other ingredients are:

Sodium acetate trihydrate (injectable grade)
Sodium Chloride (injectable grade)
Glacial acetic acid

3. Dosage form and strength

Dosage form: Injection
Strength: 10mg

4. Clinical particulars

4.1 Therapeutic indication

As adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

4.2 Posology and method of administration

Posology

Adults

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/infusion is an alternative for patients when oral administration is temporarily not feasible.

The recommended starting dose is either 50 mg/day or 100 mg/day based on physician assessment of required seizure reduction versus potential side effects. The dose should be administered in two equally divided doses, once in the morning and once in the evening. Based on individual patient response and tolerability, the dose may be adjusted in the dose range of 50 mg/day to 200 mg/day.

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

Missed doses

If patients missed one dose or more, it is recommended that they take a single dose as soon as they remember and take the following dose at the usual morning or evening time. This may avoid the brivaracetam plasma concentration falling below the efficacy level and prevent breakthrough seizures from occurring.

Discontinuation

If brivaracetam has to be discontinued it is recommended to withdraw it gradually by 50 mg/day on a weekly basis. After 1 week of treatment at 50 mg/day, a final week of treatment at the dose of 20 mg/day is recommended.

Special populations

Elderly (65 years of age and above)

No dose adjustment is needed in elderly patients. The clinical experience in patients ≥ 65 years is limited.

Renal impairment

No dose adjustment is needed in patients with impaired renal function. Brivaracetam is not recommended in end-stage renal disease patients undergoing dialysis due to lack of data.

Hepatic impairment

Exposure to brivaracetam was increased in adult patients with chronic liver disease. In adults, 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.

Method of administration

- Intravenous bolus: brivaracetam may be administered as an intravenous bolus without dilution.
- Intravenous infusion: brivaracetam may be diluted in a compatible diluent and administered as a 15-minute intravenous infusion. This medicinal product must not be mixed with other medicinal products.

Brivaracetam bolus injection or intravenous infusion has not been studied in acute conditions; e.g. status epilepticus and is therefore not recommended for such conditions.

4.3 Contraindications

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.

4.4 Special warnings and precautions for use

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including BRIVARACETAM, increase the risk of suicidal thoughts or behavior 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 behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized 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 behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated

patients, representing an increase ofapproximately one case of suicidal thinking or behavior for every 530 patients treated.

There were four suicides in drug-treated patients in the trials and none in placebotreated patients, but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior 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 behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. 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 analyzed. Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Risk of Suicidal Thoughts or Behaviors by Indication for

Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 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 behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with 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 the risk of suicidal thoughts or behaviors 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 behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Neurological Adverse Reactions

BRIVARACETAM causes somnolence, fatigue, dizziness, and disturbance in coordination. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on BRIVARACETAM to gauge whether it adversely affects their ability to drive or operate machinery. Somnolence and Fatigue BRIVARACETAM causes dose-dependent increases in somnolence and fatigue-related adverse reactions (fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy).

In the Phase 3 controlled adjunctive epilepsy trials, these events were reported in 25% of patients randomized to receive BRIVARACETAM at least 50 mg/day (20% at 50 mg/day, 26% at 100 mg/day, and 27% at 200 mg/day) compared to 14% of patients who received

placebo. The risk is greatest early in treatment but can occur at any time. Dizziness and Disturbance in Gait and Coordination BRIVARACETAM causes adverse reactions related to dizziness and disturbance in gait and coordination (dizziness, vertigo, balance disorder, ataxia, nystagmus, gait disturbance, and abnormal coordination). In the Phase 3 controlled adjunctive epilepsy trials, these events were reported in 16% of patients randomized to receive BRIVARACETAM at least 50 mg/day compared to 10% of patients who received placebo. The risk is greatest early in treatment but can occur at any time.

Psychiatric Adverse Reactions

BRIVARACETAM causes psychiatric adverse reactions. In the Phase 3 controlled adjunctive epilepsy trials, psychiatric adverse reactions were reported in approximately 13% of patients who received BRIVARACETAM (at least 50 mg/day) compared to 8% of patients who received placebo. Psychiatric events included both non-psychotic symptoms (irritability, anxiety, nervousness, aggression, belligerence, anger, agitation, restlessness, depression, depressed mood, tearfulness, apathy, altered mood, mood swings, affect lability, psychomotor hyperactivity, abnormal behavior, and adjustment disorder) and psychotic symptoms (psychotic disorder along with hallucination, paranoia, acute psychosis, and psychotic behavior). A total of 1.7% of adult patients treated with BRIVARACETAM discontinued treatment because of psychiatric reactions compared to 1.3% of patients who received placebo. Psychiatric adverse reactions were also observed in open-label pediatric trials and were generally similar to those observed in adults Specific Populations.

Hypersensitivity: Bronchospasm and Angioedema

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

Withdrawal of Antiepileptic Drugs

As with most antiepileptic drugs, BRIVARACETAM should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus but if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

4.5 Drugs interactions

Formal interaction studies have only been performed in adults.

Pharmacodynamic interactions

Concomitant treatment with levetiracetam

In the clinical studies, although the numbers were limited, there was no observed benefit of brivaracetam versus placebo in patients taking levetiracetam concurrently. No additional safety or tolerability concern was observed.

Interaction with alcohol

In a pharmacokinetic and pharmacodynamic interaction study between brivaracetam 200 mg single dose and ethanol 0.6 g/L continuous infusion in healthy subjects, there was no pharmacokinetic interaction but brivaracetam approximately doubled the effect of alcohol on psychomotor function, attention and memory. Intake of brivaracetam with alcohol is not recommended.

Pharmacokinetic interactions

Effects of other agents on the pharmacokinetics of brivaracetam

In vitro data suggest that brivaracetam has a low interaction potential. The main disposition pathway of brivaracetam is by CYP-independent hydrolysis. A second disposition pathway involves hydroxylation mediated by CYP2C19.

Brivaracetam plasma concentrations may increase when coadministered with CYP2C19 strong inhibitors (e.g. fluconazole, fluvoxamine), but the risk of a clinically relevant CYP2C19-mediated interaction is considered to be low.

Rifampicin

In healthy subjects, coadministration with the strong enzyme inducer rifampicin (600 mg/day for 5 days), decreased brivaracetam area under the plasma concentration curve (AUC) by 45 %. Prescribers should consider adjusting the brivaracetam dose in patients starting or ending treatment with rifampicin.

trong enzyme inducing AEDs.

Brivaracetam plasma concentrations are decreased when coadministered with strong enzyme inducing AEDs (carbamazepine, phenobarbital, phenytoin) but no dose adjustment is required (see table 1).

Other enzyme inducers

Other strong enzyme inducers (such as St John´s wort (Hypericum perforatum)) may also decrease the systemic exposure of brivaracetam. Therefore, starting or ending treatment with St John's wort should be done with caution.

Effects of brivaracetam on other medicinal products

Brivaracetam given 50 or 150 mg/day did not affect the AUC of midazolam (metabolised by CYP3A4). The risk of clinically relevant CYP3A4 interactions is considered to be low.

In vitro studies have shown that brivaracetam exhibits little or no inhibition of CYP450 isoforms except for CYP2C19. Brivaracetam may increase plasma concentrations of medicinal products metabolised by CYP2C19 (e.g. lanzoprazole, omeprazole, diazepam). When tested *in vitro* brivaracetam did not induce CYP1A1/2 but induced CYP3A4 and CYP2B6. No CYP3A4 induction was found *in vivo* (see midazolam above). CYP2B6 induction has not been investigated *in vivo* and brivaracetam may decrease plasma concentrations of medicinal products metabolised by CYP2B6 (e.g. efavirenz). In vitro, interaction studies to determine the potential inhibitory effects on transporters concluded that there were no clinically relevant effects**,** except for OAT3**.** *In vitro*, brivaracetam inhibits OAT3 with a half maximal inhibitory concentration 42-fold higher than the C_{max} at the highest clinical dose. Brivaracetam 200mg/day may increase plasma concentrations of medicinal products transported by OAT3.

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 phases 2-3 studies in a population pharmacokinetic analysis of placebo-controlled phase 2-3 studies, and in dedicated drug-drug interaction studies (for the following AEDs: carbamazepine, lamotrigine, phenytoin and topiramate). The effect of the interactions on the plasma concentration is summarised in table 1 (increase is indicated as "↑" and decrease as "↓", area under the plasma concentration versus time curve as "AUC", maximum observed

concentration as C_{max}).

Table 1: Pharmacokinetic interactions between brivaracetam and other AEDs

AED coadministered	Influence of AED on brivaracetam plasma concentration	Influence of brivaracetam on AED plasma concentration
Carbamazepine	AUC 29 % ↓ C_{max} 13 % ↓ No dose adjustment required	Carbamazepine - None Carbamazepine- epoxide ↑ (See below) No dose adjustment required.
Clobazam	No data available	None
Clonazepam	No data available	None
Lacosamide	No data available	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None (monohydroxy derivative, MHD)
Phenobarbital	AUC 19 % ↓	None
	No dose adjustment required	
Phenytoin	AUC 21 % ↓ No dose adjustment required	None [a] AUC 20% ↑ [a] C_{max} 20% ↑
Pregabalin	No data available	None
Topiramate	None	None
Valproic acid	None	None
Zonisamide	No data available	None

[a] based on a study involving the administration of a supratherapeutic dose of 400 mg/day brivaracetam.

Carbamazepine

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 safety risks were observed. There was no additive effect of brivaracetam and valproate on the AUC of carbamazepine epoxide.

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. There was generally no change in the concentration-

time profiles of the endogenous markers estradiol, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and sex hormone binding globulin (SHBG).

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Women of childbearing potential

Physicians should discuss family planning and contraception with women of childbearing potential taking brivaracetam (see Pregnancy).

If a woman decides to become pregnant, the use of brivaracetam should be carefully re-evaluated.

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general.

For all anti-epileptic drugs, it has been shown that in the offspring of treated women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3 % in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the underlying condition is responsible has not been elucidated.

Discontinuation of anti-epileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Risk related to brivaracetam.

There is a limited amount of data from the use of brivaracetam in pregnant women. There is no data on placental transfer in humans, but brivaracetam was shown to readily cross the placenta in rats. The potential risk for humans is unknown. Animal studies did not detect any teratogenic potential of brivaracetam.

In clinical studies, brivaracetam was used as adjunctive therapy and when it was used with carbamazepine, it induced a dose-related increase in the concentration of the active metabolite, carbamazepine-epoxide. There is insufficient data to determine the clinical significance of this effect in pregnancy.

As a precautionary measure, brivaracetam should not be used during pregnancy unless clinically necessary i.e. (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

It is unknown whether brivaracetam is excreted in human breast milk. Studies in rats have shown excretion of brivaracetam in breast milk. A decision should be made whether to discontinue breastfeeding or to discontinue brivaracetam, taking into account the benefit of the medicinal product to the mother. In case of co- administration of brivaracetam and carbamazepine, the amount of carbamazepine- epoxide excreted in breast milk could increase. There is insufficient data to determine the clinical significance.

Fertility

No human data on the effect of brivaracetam on fertility are available. In rats, there was no effect on fertility with brivaracetam.

4.7 Effects on ability to drive and use machines.

Brivaracetam has minor or moderate influence on the ability to drive and use machines.

Due to possible differences in individual sensitivity some patients might experience

somnolence, dizziness, and other central nervous system (CNS) related symptoms. 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.

4.8 Undesirable effects

Summary of the safety profile

In all controlled and uncontrolled trials in patients with epilepsy, 2,388 subjects have received brivaracetam, of whom 1,740 have been treated for ≥ 6 months,1,363 for ≥ 12 months, 923 for ≥24 months and 569 for ≥ 60 months (5 years).

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 (8.2 %) were reported at a higher incidence with increasing dose. The types of adverse reactions reported during the first 7 days of treatment were similar to those reported for the overall treatment period.

The discontinuation rate due to adverse reactions was 3.5 %, 3.4 % and 4.0 % for patients randomized to brivaracetam at respectively the dose of 50 mg/day, 100 mg/day and 200 mg/day and 1.7 % for patients randomized to placebo. The adverse reactions most frequently resulting in discontinuation of brivaracetam therapy were dizziness (0.8 %) and convulsion (0.8 %).

Tabulated list of adverse reactions

In the table below, adverse reactions, which were identified based on review of the three placebo-controlled, fixed-dose studies safety database in subjects ≥ 16 years of age, are listed by System Organ Class and frequency.

The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reactions from clinical trials**
Infections and infestations	Common	Influenza
Blood and lymphatic system disorders	Uncommon	Neutropenia
Metabolism and nutrition disorders	Common	Decreased appetite
Immune system disorders	Uncommon	Type I hypersensitivity
Psychiatric disorders	Common	Depression, anxiety, insomnia, irritability
	Uncommon	Suicidal ideation, psychotic disorder, aggression, agitation
Nervous system disorders	Very common	Dizziness, somnolence
	Common	Convulsion, vertigo

System organ class	Frequency	Adverse reactions from clinical
Respiratory, thoracic, and mediastinal disorders	Common	Upper respiratory tract infections, cough
Gastrointestinal disorders	Common	Nausea, vomiting, constipation
General disorders and administration site conditions	Common	Fatigue

Description of selected adverse reactions

Neutropenia has been reported in 0.5 % (6/1099) brivaracetam patients and 0 % (0/459) placebo patients. Four of these subjects had decreased neutrophil counts at baseline, and experienced additional decrease in neutrophil counts after initiation of brivaracetam treatment. None of the 6 cases of neutropenia were severe, required any specific treatment or led to discontinuation of brivaracetam and none had associated infections. 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.

Reactions suggestive of immediate (Type I) hypersensitivity have been reported in a small number of brivaracetam patients (9/3022) during clinical development.

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

Open-label extension studies

It has been reported that in patients who were followed up in the open-label extension studies for up to 8 years, the safety profile was similar to that observed in the short- term, placebo-controlled studies.

Elderly

Of the 130 elderly subjects enrolled in the brivaracetam phase 2/3 development program (44 with epilepsy), 100 were 65-74 years of age and 30 were 75-84 years of age. The safety profile in elderly patients appears to be similar to that observed in younger adult patients.

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this Medicine.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

BRITZILAM contains brivaracetam and is listed as a Schedule V controlled substance.

Abuse

In a human abuse potential study, single doses of BRITZILAM at therapeutic and supratherapeutic doses were compared to alprazolam (C-IV) (1.5 mg and 3 mg). BRITZILAM at the recommended single dose (50 mg) caused fewer sedative and euphoric effects than alprazolam; however, BRITZILAM at supratherapeutic single doses (200 mg and 1000 mg) was similar to alprazolam on other measures of abuse.

Dependence

There was no evidence of physical dependence potential or a withdrawal syndrome with BRITZILAM in a pooled review of placebo-controlled adjunctive therapy studies.

4.9 Overdose

Symptoms

There is limited clinical experience with brivaracetam overdose in humans. Somnolence and dizziness have been reported in a healthy subject taking a single dose of 1,400 mg of brivaracetam.

Management of overdose

There is no specific antidote for overdose with brivaracetam. 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.

5. Pharmacological properties

5.1 Mechanism of Action

Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A), a transmembrane glycoprotein found at presynaptic level in neurons and in endocrine cells. Although the exact role of this protein remains to be elucidated it has been shown to modulate exocytosis of neurotransmitters. Binding to SV2A is believed to be the primary mechanism for brivaracetam anticonvulsant activity.

5.2 Pharmacodynamic properties

Clinical efficacy and safety

It has been reported that the efficacy of brivaracetam for the adjunctive therapy of partial onset seizures (POS) was established in 3 randomized, double-blind, placebo-controlled, fixed-dose, multi-center studies in subjects 16 years of age and older. The daily dose of

brivaracetam ranged from 5 to 200 mg/day across these studies. All studies had an 8- week baseline period followed by a 12-week treatment period with no up-titration. 1,558 patients received study drug of which 1,099 received brivaracetam. Study enrollment criteria required that patients have uncontrolled POS despite treatment with either 1 or 2 concomitant AEDs. Patients were required to have at least 8 POS during the baseline period. The primary endpoints in the phase 3 studies were the percent reduction in POS frequency over placebo and the 50 % responder rate based on 50 % reduction in POS frequency from baseline.

The most commonly taken AEDs at the time of study entry were carbamazepine (40.6 %), lamotrigine (25.2 %), valproate (20.5 %), oxcarbazepine (16.0 %), topiramate (13.5 %), phenytoin (10.2 %) and levetiracetam (9.8 %). 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.

The efficacy outcomes are summarized in the following Table. Overall, brivaracetam was efficacious for the adjunctive treatment of partial onset seizures in patients 16 years of age and older between 50 mg/day and 200 mg/day.

Key Efficacy Outcomes for Partial Onset Seizure Frequency per 28 Days

Study	**Placebo**	**Brivaracetam** * Statistically significant **(p-value)**		
		50 mg/day	**100 mg/day**	**200 mg/day**
Study N01253(1)				
	n= 96	n= 101		
50 % Responder rate	16.7	32.7* (p=0.008)	~	~
Percent reduction over placebo (%)	NA	22.0* (p=0.004)	~	~
Study N01252(1)				
	n = 100	n = 99	n = 100	
50 % Responder rate	20.0	27.3 (p=0.372)	36.0(2) (p=0.023)	~
Percent reduction over placebo (%)	NA	9.2 (p=0.274)	20.5(2) (p=0.010)	~
Study N01358				
	n = 259		n = 252	n = 249
50% Responder rate	21.6	~	38.9* (p<0.001)	37.8* (p<0.001)
Percent reduction over placebo (%)	NA	~	22.8* (p<0.001)	23.2* (p<0.001)

n = randomised patients who received at least 1 dose of study medication

~ Dose not studied.

* Statistically significant

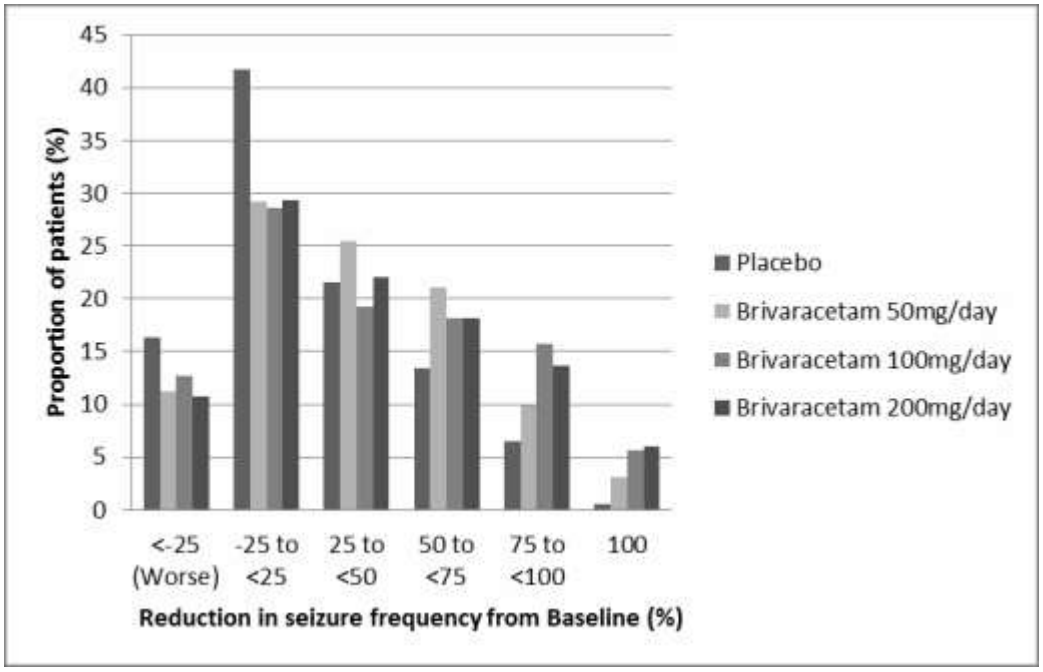
(1) Approximately 20 % of the patients were on concomitant levetiracetam (2) The primary outcome for N01252 did not achieve statistical significance based on the sequential testing procedure. The 100 mg/day dose was nominally significant.

In clinical studies, a reduction in seizure frequency over placebo was higher with the dose of 100 mg/day than with 50 mg/day. Apart from dose-dependent increases in incidences of somnolence and fatigue brivaracetam 50 mg/day and 100 mg/day had a similar safety profile including CNS-related AEs and with long-term use.

Figure 1 shows the percentage of patients (excluding patients with concomitant levetiracetam) by category of reduction from baseline in POS frequency per 28 days in all 3 studies. Patients with more than a 25 % increase in POS are shown at left as "worse". Patients with an improvement in percent reduction in baseline POS 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 brivaracetam and placebo over 12 weeks across all three double-blind pivotal trials



In a pooled analysis of the three pivotal trials, no differences in efficacy (measured as 50 % responder rate) was observed within the dose range of 50 mg/day to 200 mg/day when brivaracetam is combined with inducing or non-inducing AEDs. In clinical studies 2.5 % (4/161), 5.1 % (17/332) and 4.0% (10/249) of the patients on brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively became seizure free during the 12-week treatment period compared with 0.5 % (2/418) on placebo.

Improvement in the median percent reduction in seizure frequency per 28 days has been observed in patients with type IC seizure (secondary generalized tonic-clonic seizures) at baseline treated with brivaracetam (66.6 % (n=62), 61.2 % (n=100) and 82.1 % (n=75) of the patients on brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively as compared to placebo 33.3 % (n=115)).

the efficacy of brivaracetam in monotherapy has not been established. Brivaracetam is not recommended for use in monotherapy.

Treatment with levetiracetam

In the reported two phase 3 randomised placebo-controlled studies, levetiracetam was administered as concomitant AED in about 20 % of the patients. Although the number of subjects is limited, there was no observed benefit of brivaracetam versus placebo in patients taking levetiracetam concurrently which may reflect competition at the SV2A binding site. No additional safety or tolerability concerns were observed.

In a reported third study, a pre-specified analysis demonstrated efficacy over placebo for 100 mg/day and 200 mg/day in patients with prior exposure to levetiracetam. The lower efficacy observed in these patients compared to the leveticacetam-naïve patients was likely due to the higher number of prior AEDs used and higher baseline seizure frequency.

Elderly (65 years of age and above)

The reported 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.

Open label extension studies

Across all studies, it has been reported that 81.7 % of the patients who completed randomized studies were enrolled in the long-term open-label extension studies. From entry into the randomized studies, 5.3 % of the subjects exposed to brivaracetam for 6 months (n=1,500) were seizure free compared to 4.6 % and 3.7 % for subjects exposed for 12 months (n=1,188) and 24 months (n=847), respectively. However, as a high proportion of subjects (26%) discontinued from the open-label studies due to lack of efficacy, a selection bias may have occurred, as the subjects who stayed in the study responded better than those who have terminated prematurely.

5.3 Pharmacokinetic properties

Brivaracetam film-coated tablets, oral solution and solution for intravenous injection show the same AUC, while the maximum plasma concentration is slightly higher after intravenous administration. Brivaracetam exhibits linear and time-independent pharmacokinetics with low intra- and inter-subject variability, and features complete absorption, very low protein binding, renal excretion following extensive biotransformation, and pharmacologically inactive metabolites.

Absorption

Brivaracetam is rapidly and completely absorbed after oral administration and the absolute bioavailablity is approximately 100 %. The median tmax for tablets taken without food is 1 hour (tmax range is 0.25 to 3 h).

Coadministration with a high-fat meal slowed down the absorption rate (median tmax 3 h) and decreased the maximum plasma concentration (37 % lower) of brivaracetam, while the extent of absorption remained unchanged.

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 lipophylicity (Log P) brivaracetam has high cell membrane permeability.

Biotransformation

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid (approximately 60 % the elimination), and secondarily by hydroxylation on the propyl side chain (approximately 30 % the elimination). 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. In vitro, the hydroxylation of brivaracetam is mediated primarily by CYP2C19. Both metabolites, are further metabolised forming a common hydroxylated acid formed predominantly by hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). 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. The three 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. The total plasma clearance in patients was estimated to 3.6 L/h.

Linearity

Pharmacokinetics is dose-proportional from 10 to at least 600 mg.

Interactions with medicinal products

Brivaracetam is cleared by multiple pathways including renal excretion, non-CYP-mediated hydrolysis and CYP-mediated oxidations. In vitro, brivaracetam is not a substrate of human P-glycoprotein (P-gp), multidrug resistance proteins (MRP) 1 and 2, and likely not organic anion transporter polypeptide 1B1 (OATP1B1) and OATP1B3.

In vitro assays showed that brivaracetam disposition should not be significantly affected by CYP (eg. CYP1A, 2C8, 2C9, 2D6 and 3A4) inhibitors.

In vitro, brivaracetam was not an inhibitor of the CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 3A4, or the transporters P-gp, BCRP, BSEP MRP2, MATE-K, MATE-1, OATP1B1, OATP1B3, OAT1 and OCT1 at clinically relevant concentrations. In vitro, brivaracetam did not induce CYP1A2.

Pharmacokinetics in special patient groups

Elderly (65 years of age and above)

In a reported study in elderly subjects (65 to79 years old; with creatinine clearance 53 to 98 ml/min/1.73 m²) receiving brivaracetam 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 similar (0.76 ml/min/kg) to young healthy male subjects (0.83 ml/min/kg)

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. The hydroxyacid metabolite did not reveal any safety concerns in non-clinical studies. Brivaracetam has not been studied in patients undergoing hemodialysis.

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 %, 7 % and 59 %), relative to matched healthy controls.

Body weight

A 40 % decrease in steady-state plasma concentration has been estimated across a body weight range from 46 kg to 115 kg. However, this is not considered to be a clinically relevant difference.

Gender

There are no clinically relevant differences in the pharmacokinetics of brivaracetam by gender.

Race

The pharmacokinetics of brivaracetam was not significantly affected by race (Caucasian, Asian) in a population pharmacokinetic modeling from epilepsy patients. The number of patients with other ethnic background was limited.

Pharmacokinetic/pharmacodynamics relationship

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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

In safety pharmacology studies, the predominant effects were CNS related (mainly transient CNS depression and decreased spontaneous locomotor activity) seen at multiples (greater than 50-fold) of the pharmacologically active dose of brivaracetam, 2 mg/kg. Learning and memory function were not affected.

Findings not observed in clinical studies but seen in the repeated-dose toxicology dog studies at exposure similar to the clinical plasma AUC, were hepatotoxic effects (mainly porphyria). 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. No adverse liver changes were seen inrats and monkeys following chronic administration of brivaracetam at 5- and 42-fold the clinical AUC exposure. In monkeys, CNS signs (prostrate, loss of balance, clumsy movements) occurred at 64-fold the clinical Cmax, these effects being less apparent over time.

Genotoxicity studies have not detected any mutagenic or clastogenic activity. Carcinogenicity studies did not indicate any oncogenic potential in rats, whereas increased incidences of hepatocellular tumors in male mice are considered to result of a non-genotoxic, mode of action linked to a phenobarbitone-like liver enzyme induction, which is a known rodent specific phenomenon.

Brivaracetam did not affect male or female fertility and has demonstrated no teratogenic potential in either rat or rabbit. Embryotoxicity was observed in rabbits at a maternal toxic dose of brivaracetam with an exposure level 8-fold the clinical AUC exposure at the maximum recommended dose. In rats, brivaracetam was shown to readily cross the placenta and to be excreted in milk of lactating rats with concentrations similar to maternal

plasma levels. Brivaracetam did not show any dependence potential in rats.

Juvenile animals' studies

In juvenile rats, brivaracetam exposure levels 6- to 15-fold the clinical AUC exposure at the maximum recommended dose induced developmental adverse effects (i.e. mortality, clinical signs, decreased body weight and lower brain weight). There were no adverse effects on CNS function, neuropathological and brain histopathological examination. In juvenile dogs, the brivaracetam-induced changes at the exposure level 6- fold the clinical AUC were similar to those observed in adult animals. There were no adverse effects in any of the standard developmental or maturation endpoints.

7. Description

Britzilam Injection 10mg/ml

Clear colorless solution in type I glass vial with 20 mm rubber stopper and aluminum seals

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

24 months.

8.3 Packaging information

Sterile single dose 5ml vial

8.4 Storage and handing instructions.

Store at a temperature not exceeding 30ºC. Do not freeze.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Torrent Pharmaceuticals Ltd.

At: Plot no. 2-5, Sector- 6B, IIE,

SIDCUL, Ranipur Haridwar (UK) -249403

11. Details of permission or license number with date

5/UA/LL/SC/P-2018

12. Date of revision

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MARKETED BY

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IN/BRITZILAM 10mg/ml/SEP-2024/03/PI