
BRITZILAM 25

1. Generic Name

Brivaracetam Tablets 25mg

2. Qualitative and quantitative composition

Brivaracetam Tablets 25mg

Each film coated tablet contains:

Brivaracetam.....25mg

Excipients.....q.s.

Colour: Titanium dioxide I.P., Yellow oxide of Iron and black oxide of Iron

The excipients used are Micro Crystalline Cellulose, Anhydrous Lactose (DCL 21), Lactose Monohydrate DCL11, Croscarmellose Sodium, Polyvinyl pyrrolidone (K30), Methanol, Purified Water, Magnesium Stearate.

3. Dosage form and strength

Dosage form: Film Coated Tablets

Strength: 25mg

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

The dose of brivaracetam 25mg tablets must be taken as prescribe by physician. The physician should prescribe the most appropriate formulation and strength according to weight and dose.

Adults

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.

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. In children and adolescents weighing 50 kg 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 adolescents weighing less than 50 kg, a 1 mg/kg/day starting dose is recommended. The maximum dose should not exceed 3 mg/kg/day. No reported clinical data are available in paediatric patients with hepatic impairment.

Children (from 4 years of age) and adolescents weighing 50 kg or more

The recommended starting dose is 50mg/day. Brivaracetam may also be initiated at 100 mg/day based on physician's assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening. The recommended maintenance dose is 100 mg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 50 mg/day to 200 mg/day.

Children (from 4 years of age) and adolescents weighing less than 50 kg

The recommended starting dose is 1 mg/kg/day. Brivaracetam may also be initiated at 2 mg/kg/day based on physician's assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening. The recommended maintenance dose is 2 mg/kg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 1 mg/kg/day to 4 mg/kg/day.

The following table summarises the recommended posology for children from 4 years of age and adolescents.

| | Children (≥4 years) and Adolescents ≥50 kg Administered in 2 equally divided doses | Children (≥4 years) and Adolescents <50 kg Administered in 2 equally divided doses |
|------------------------------|---|--|
| Therapeutic dose range | 50 - 200 mg/day | 50 - 200 mg/day |
| Recommended starting dose | 50 mg/day (or 100 mg/day)* | 1 mg/kg/day (or 2 mg/kg/day)* |
| Recommended maintenance dose | 100 mg/day | 2 mg/kg/day |

* Based on physician's assessment of need for seizure control

Method of administration

Brivaracetam film-coated tablets must be taken orally swallowed in whole with liquid and may be taken with or without food.

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 ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs), including brivaracetam, in several indications. A meta-analysis of randomized placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for brivaracetam.

Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should any signs of suicidal ideation or behaviour emerge.

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.

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 reported 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.

Strong 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 reported *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. lansoprazole, 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 phase 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}).

The following table shows 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 % ↓ No dose adjustment required | None |
| 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 reported 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 reported 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 reported data to determine the clinical significance.

Fertility

No reported 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 reported 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ 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 |
| 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.

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.

Paediatric population

The safety profile of brivaracetam observed in children was consistent with the safety profile observed in adults. In the reported open label, uncontrolled, long-term studies 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. The majority of events were mild or moderate in intensity, were non-serious, and did not lead to discontinuation of study drug. An additional adverse reaction reported in children was psychomotor hyperactivity (4.7 %).

There are limited reported safety data from open-label studies in children from 1 month to <4 years of age. Limited data are available on neurodevelopment in children <4 years of age. No clinical data are available in neonates.

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 suspected 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.

4.9 Overdose

Symptoms

There is limited reported 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 reported 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

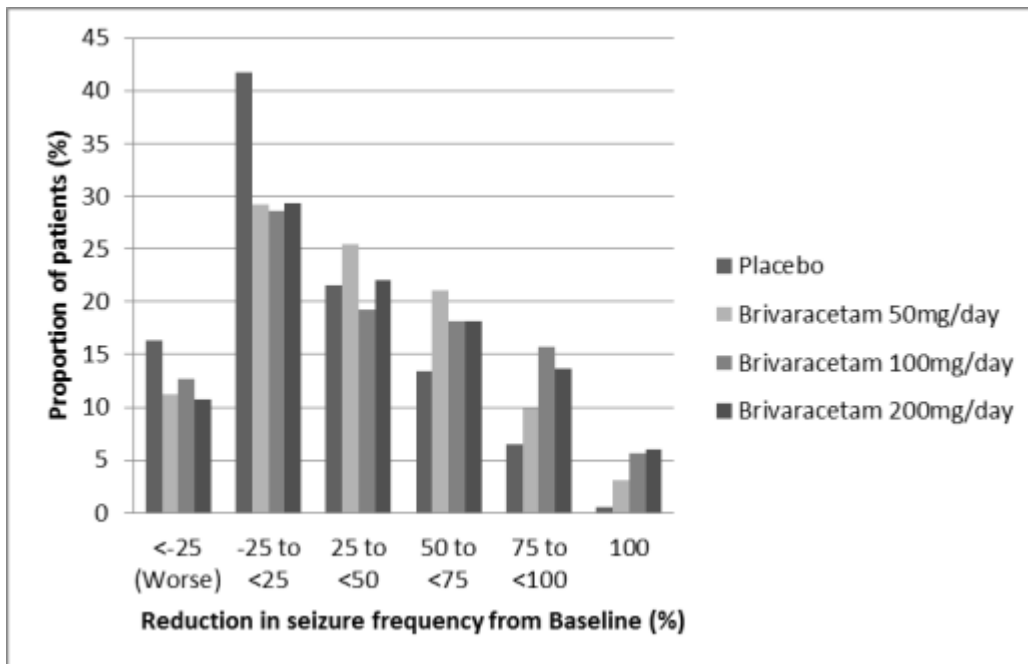
⁽¹⁾ Approximately 20 % of the patients were on concomitant levetiracetam

⁽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 reported 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 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 Proportion of patients by category of seizure response for brivaracetam and placebo over 12 weeks across all three double-blind pivotal trials.



In a reported 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 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 reported 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 levetiracetam-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 three reported 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 reported studies, 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 reported study responded better than those who have terminated prematurely.

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 paediatric dose adaptations are established and safety has been demonstrated. Doses in patients from 4 years of age were defined by weight-based dose adaptations which have been established to achieve similar plasma concentrations to the ones observed in adults taking efficacious doses.

A reported long-term, uncontrolled, open-label safety study included children (from 4 years to less than 16 years) who continued treatment after completing the reported PK study and children directly enrolled into the reported 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 200 mg/day by weekly increments of 50 mg/day.

From the reported pooled open-label safety and PK studies in adjunctive therapy, 149 children with POS have received brivaracetam, of whom 116 have been treated for ≥ 6 months, 107 for ≥ 12 months, 58 for ≥ 24 months, and 28 for ≥ 36 months.

The efficacy and tolerability of brivaracetam in paediatric patients less than 4 years of age have not been established. Brivaracetam was evaluated in these patients in a short term reported open-label pharmacokinetic study and reported an ongoing open-label extension study, in 16 subjects from 1 month to <4 years of age.

The European Medicines Agency has deferred the obligation to submit the results of studies with brivaracetam in one or more subsets of the paediatric population in epilepsy with partial onset seizures.

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 bioavailability is approximately 100 %. 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 (median t_{max} 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 lipophilicity (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). The reported 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 ($t_{1/2}$) 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 Reported in vitro assays showed that brivaracetam disposition should not be significantly affected by CYP (eg. CYP1A, 2C8, 2C9, 2D6 and 3A4) inhibitors.

In Reported 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 to 79 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 reported 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 reported 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.

Paediatric population

In a reported pharmacokinetic study with a 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 mg/kg/day, 2 mg/kg/day, and 4 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 reported long-term follow-up study continuing on their last received dose. 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.

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 reported 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 reported 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 reported 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 in rats 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.

In reported 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 animal studies

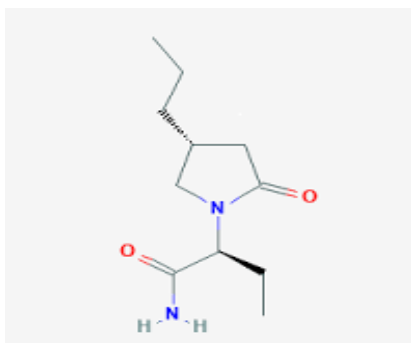
In reported juvenile rats, brivaracetam exposure levels 6- to 15-fold the clinical AUC exposure at the maximum recommended dose induced developmental adverse effects (i.e. mortality, clinical signs, decreased body weight and lower brain weight). There were no adverse effects on CNS function, neuropathological 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

BRIVARACETAM

Brivaracetam is (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl]butanamide. The empirical formula is $C_{11}H_{20}N_2O_2$ and its molecular weight is 212.29 g/mol. The chemical structure of Brivaracetam is:



Brivaracetam Tablets is

Grey coloured, biconvex, beveled edge, oval shape film-coated tablets with breakline on one side and plain on other side. . The excipients used are Micro Crystalline Cellulose, Anhydrous Lactose (DCL 21), Lactose Monohydrate DCL11, Croscarmellose Sodium, Polyvinyl pyrrolidone (K30), Methanol, Purified Water, Magnesium Stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

Blister pack of 15 Tablets

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, protected from light and moisture.

9. Patient Counselling Information

BRITZILAM 25

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What in this leaflet:

9.1 What Brivaracetam is and what it is used for

9.2 What you need to know before you take Brivaracetam

9.3 How to take Brivaracetam

9.4 Possible side effects

9.5 How to store Brivaracetam

9.6 Contents of the pack and other information

9.1 What BRITZILAM 25 is and what it is used for

The active substance brivaracetam belongs group of medicines called ‘anti-epileptics’.

Brivaracetam is used as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

9.2 What you need to know before you take BRITZILAM 25

Do not take Brivaracetam if:

- You are allergic to brivaracetam, other similar chemical compounds as levetiracetam or piracetam or any of the other ingredients of this medicine. If you are not sure, talk to your doctor or pharmacist before taking Brivaracetam.

Warnings and precautions

Talk to your doctor or pharmacist before taking Brivaracetam if:

- You have thoughts of harming or killing yourself. A small number of people being treated with anti-epileptic medicines such as Brivaracetam have had thoughts of harming or killing themselves. If you have any of these thoughts at any time, contact your doctor immediately.
- You have liver problems - your doctor may need to adjust your dose.

Children

Brivaracetam is not recommended for use in children under 4 years of age.

Other medicines and BRITZILAM 25

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking any of the following medicines – this is because your doctor may need to adjust your Brivaracetam dose:

- Rifampicin - a medicine used to treat bacterial infections.
- St John's wort (also known as *Hypericum perforatum*) - a herbal medicine used to treat depression and anxiety as well as other conditions.

BRITZILAM 25 with alcohol

- Combining this medicine with alcohol is not recommended.
- If you drink alcohol while taking BRITZILAM 25 the negative effects of alcohol may be increased.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not recommended to take BRITZILAM 25 if you are pregnant or breast-feeding, as the effects of BRITZILAM 25 on pregnancy and the unborn baby or the new-born child are not known.

- Do not stop treatment without talking to your doctor first. Stopping treatment could increase your seizures and harm your baby.

Driving and using machines

- You may feel sleepy, dizzy or tired while taking BRITZILAM 25.
- These effects are more likely at the start of the treatment or after a dose increase.
- Do not drive, cycle or use any tools or machines until you know how the medicine affects you.

9.3 How to take BRITZILAM 25

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You will take BRITZILAM 25 together with other medicines for epilepsy.

How much to take

Your doctor will work out the right daily dose for you. Take the daily dose in two equal divided doses

- one in the morning and one in the evening at about the same time each day.

Adults and adolescents weighing 50kg or more

- The recommended dose is from 25 mg to 100 mg taken twice a day. Your doctor may then decide to adjust your dose to find the best dose for you.

Adolescents weighing less than 50 kg

- The recommended dose is from 0.5 mg to 2 mg for each kg of bodyweight, taken twice a day. Your doctor may then decide to adjust your dose to find the best dose for you.

People with liver problems

If you have problems with your liver:

- As an adult, adolescent or child weighing 50 kg or more, the maximum dose you will take is 75 mg twice a day.
- As a child or adolescent weighing less than 50 kg, the maximum dose you will take is 1.5 mg for each kg of bodyweight twice a day.

How to take BRITZILAM 25 tablets

- Swallow the tablets whole with a glass of liquid.
- The medicine may be taken with or without food.

How long to take BRITZILAM 25 for

BRITZILAM 25 is a long term treatment – keep taking BRITZILAM 25 mg until your doctor tells you to stop.

If you take more BRITZILAM 25 than you should

If you have taken more BRITZILAM 25 than you should, talk to your doctor. You may feel dizzy and sleepy.

If you forget to take BRITZILAM 25

- If you miss a dose take it as soon as you remember.
- Then take your next dose at the time you would normally take it.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure what to do, ask your doctor or pharmacist.

If you stop taking BRITZILAM 25

- Do not stop taking this medicine unless your doctor tells you to. This is because stopping treatment could increase the number of fits you have.
- If your doctor asks you to stop taking this medicine they will lower your dose gradually. This helps to stop your fits coming back or getting worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people

- feeling sleepy or dizzy

Common: may affect up to 1 in 10 people

- flu
- feeling very tired (fatigue)
- convulsion, a feeling of ‘spinning’ (vertigo)
- feeling and being sick, constipation
- depression, anxiety, not being able to sleep (insomnia), irritability
- infections of the nose and throat (such as the ‘common cold’), cough

- decreased appetite

Uncommon: may affect up to 1 in 100 people

- allergic reactions
- abnormal thinking and/or loss of touch with reality (psychotic disorder), being aggressive, nervous excitement (agitation)
- thoughts or attempts of harming or killing yourself: tell your doctor straight away
- a decrease in white blood cells (called 'neutropenia') - shown in blood tests.

Common: may affect up to 1 in 10 people

- restlessness and hyperactivity (psychomotor hyperactivity)

Reporting of side effects

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.

9.5 How to store BRITZILAM 25

Store at a temperature not exceeding 30°C, protected from light and moisture.

9.6 Contents of the pack and other information

What BRITZILAM 25 contains

The active substance is Brivaracetam.

The other ingredients are:

Micro Crystalline Cellulose, Anhydrous Lactose (DCL 21), Lactose Monohydrate DCL11, Croscarmellose Sodium, Polyvinyl pyrrolidone (K30), Methanol, Purified Water, Magnesium Stearate.

What BRITZILAM 25 looks like and contents of the pack

BRITZILAM 25 is available in blister pack of 15 tablets

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

Village: Bhud & Makhnu Majra,

Tehsil: Baddi,-173205, Dist.: Solan (H.P.), India

11. Details of permission or licence number with date

Mfg Lic No.: MF/SND/22/000270 issued on 22/11/2022

12. Date of revision

Dec-2022

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/ BRITZILAM 25 /DEC-22/02/PI