For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

BRITZILAM SR

1. Generic Name

Brivaracetam Sustained Release Tablets 200 mg

2. Qualitative and quantitative composition

Each film coated sustained release tablet contains:

Brivaracetam I.P. …..200 mg

Excipients …….q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Hypromellose (HPMC), Purified Water, Poly Ethylene Oxide, Magnesium Stearate, Purified Talc, Colloidal Silicon Dioxide, Ready mix (EP-S-199), Isopropyl Alcohol, Methylene chloride

3. Dosage form and strength

Dosage form: Film Coated Sustained Release Tablets

Strength: 200mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated 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 Sustained Release 200 mg Tablets is recommended once daily in patients who require the dose of 200 mg/day in equally divided doses based on the physician's assessment and dose range recommendation.

The recommended starting dose is either 50 mg/day or 100 mg/day based on physician's 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.

Method of administration

Oral use Brivaracetam Sustained Release 200 mg Tablets must be taken orally swallowed in whole with liquid and may be taken with or without food. Do not chew, crush or break Brivaracetam Sustained Release 200 mg Tablets.

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.

Excipients

Lactose intolerance

Brivaracetam film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5 Drugs interactions

Rifampin

Co-administration with rifampin decreases BRIVARACETAM plasma concentrations likely because of CYP2C19 induction. Prescribers should increase the BRIVARACETAM dose by up to 100% (i.e., double the dosage) in patients while receiving concomitant treatment with rifampin.

Carbamazepine

Co-administration with carbamazepine may increase exposure to carbamazepine-epoxide, the active metabolite of carbamazepine. Though available data did not reveal any safety concerns, if tolerability issues arise when co-administered, carbamazepine dose reduction should be considered**.**

Phenytoin

Because BRIVARACETAM can increase plasma concentrations of phenytoin, phenytoin levels should be monitored in patients when concomitant BRIVARACETAM is added to or discontinued from ongoing phenytoin therapy.

Levetiracetam

BRIVARACETAM provided no added therapeutic benefit to levetiracetam when the two drugs were co-administered

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.

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.

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

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 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
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

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:

https://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

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.

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

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.

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.

5.3 Pharmacokinetic properties

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.

Metabolism 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.

6. Nonclinical properties

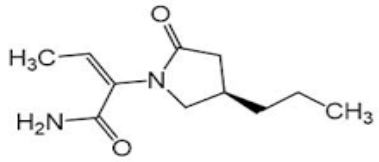
6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis In a carcinogenicity study in mice, oral administration of brivaracetam (0, 400, 550, or 700 mg/kg/day) for 104 weeks increased the incidence of liver tumors (hepatocellular adenoma and carcinoma) in male mice at the two highest doses tested. At the dose (400 mg/kg) not associated with an increase in liver tumors, plasma exposures (AUC) were approximately equal to those in humans at the maximum recommended dose (MRD) of 200 mg/day. Oral administration (0, 150, 230, 450, or 700 mg/kg/day) to rats for 104 weeks resulted in an increased incidence of thymus tumors (benign thymoma) in female rats at the highest dose tested. At the highest dose not associated with an increase in thymus tumors, plasma exposures were approximately 9 times those in humans at the MRD. Mutagenesis Brivaracetam was negative for genotoxicity in in vitro (Ames, mouse lymphoma, and CHO chromosomal aberration) and in vivo (rat bone marrow micronucleus) assays. Impairment of Fertility Oral administration of brivaracetam (0, 100, 200, or 400 mg/kg/day) to male and female rats prior to and throughout mating and early gestation produced no adverse effects on fertility. The highest dose tested was associated with plasma exposures approximately 6 (males) and 13 (females) times those in humans at the MRD.

7. Description

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 212.3 g/mol. The chemical structure of Brivaracetam is:



BRITZILAM SR 200

White to off white coloured, round shaped, biconvex, film coated sustained release tablet having both sides plain.

The excipients used are Microcrystalline Cellulose, Hypromellose (HPMC), Purified Water, Poly Ethylene Oxide, Magnesium Stearate, Purified Talc, Colloidal Silicon Dioxide, Ready mix (EP-S-199), Isopropyl Alcohol, Methylene chloride

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

Available in blister pack of 10 tablets.

8.4 Storage and handing instructions

Store Protected from moisture, at a temperature not exceeding 30°C.

Keep all the medicines out of reach of children.

9. Patient Counselling Information

BRITZILAM SR

Brivaracetam Sustained Release Tablets 200 mg

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 BRITZILAM SR 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 SR

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 BRITZILAM SR 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 SR

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.

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 SR if you are pregnant or breast-feeding, as the effects of BRITZILAM SR 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.

9.3 How to take BRITZILAM SR

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

BRITZILAM SR Tablets must be taken orally swallowed in whole with liquid and may be taken with or without food. Do not chew, crush or break BRITZILAM SR

How much to take

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

Adults

- The recommended dose is 200 mg once a daily. Your doctor may then decide to adjust your dose to find the best dose for you. A patients who require the dose of 200 mg/day in equally divided doses based on the physician's assessment and dose range recommendation.

People with liver problems

If you have problems with your liver:

- Exposure to brivaracetam was increased in adult patients with chronic liver disease. In adults, a 50 mg/day starting dose should be considered. No clinical data are available in paediatric patients with hepatic impairment.

People with renal problems

- 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.

How to take BRITZILAM SR tablets

- Swallow the tablets whole with a glass of liquid. and not chewed or crushed.
- The medicine may be taken with or without food.

How long to take BRITZILAM SR for

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

If you take more BRITZILAM SR than you should

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

If you forget to take BRITZILAM SR

- 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 SR

- 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:

https://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 SR

Store Protected from moisture, at a temperature not exceeding 30°C

9.6 Contents of the pack and other information

What BRITZILAM SR contains

The active substance is Brivaracetam.

The other ingredients are: used Microcrystalline Cellulose, Hypromellose (HPMC), Purified Water, Poly Ethylene Oxide, Magnesium Stearate, Purified Talc, Colloidal Silicon Dioxide, Ready mix (EP-S-199), Isopropyl Alcohol, Methylene chloride.

What BRITZILAM SR looks like and contents of the pack

BRITZILAM SR Available in blister pack of 10 tablets.

10. Details of manufacturer

Ravenbhel Healthcare Pvt. Ltd.

At: EPIP, SIDCO, Kartholi,

Bari Brahmana, Jammu-181133

11. Details of permission or licence number with date

Mfg Lic No.: JK/01/17-18/LL/251 issued on 06/01/2023

12. Date of revision

NA

MARKETED BY

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IN/BRITZILAM SR 200 mg/FEB-23/01/PI