For use in India only

To be sold by retail on the prescription of a Registered Medical Practitioner only.

PRESCRIBING INFORMATION

℞

Brivaracetam Injection 50 mg/5 ml (10 mg/ml)

Brivanext

1. GENERIC NAME

Brivaracetam Injection 50 mg/5 ml (10 mg/ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Brivaracetam Injection 50 mg/5 ml (10 mg/ml)
Each mL Contains
Brivaracetam IP.....10 mg

3. DOSAGE FORM AND STRENGTH

Brivaracetam is available as injection 50 mg/5 ml (10 mg/ml)

4. CLINICAL PARTICULARS

4.1. Indications

Brivaracetam injection is approved as an 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

Brivaracetam injection may be used for adult patients when oral administration is temporarily not feasible. The use of Brivaracetam injection in pediatric patients has not been studied.

Administration Instructions for Brivaracetam Injection for Adult Patients
Brivaracetam injection is for intravenous use only.

Preparation
Brivaracetam injection can be administered intravenously without further dilution or may be mixed with diluents listed below.

Diluents

0.9% Sodium Chloride injection, USP

Lactated Ringer's injection, USP

5% Dextrose injection, USP

It should be administered intravenously over 2 to 15 minutes. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Product with particulate matter or discoloration should not be used. Brivaracetam injection is for single dose only.

Storage and Stability
The diluted solution should not be stored for more than 4 hours at room temperature and may be stored in polyvinyl chloride (PVC) bags. Discard any unused portion of the Brivaracetam injection vial contents.

Discontinuation of Brivaracetam
Avoid abrupt withdrawal from Brivaracetam in order to minimize the risk of increased seizure frequency and status epilepticus.

Patients with Hepatic Impairment
For all stages of hepatic impairment, the recommended starting dosage for adults patients weighing 50 kg or more is 50 mg per day), and the recommended maximum dosage is 150 mg per day.

Co-administration with Rifampin
Increase the Brivaracetam dosage in patients on concomitant rifampin by up to 100% (i.e., double the dosage).

4.3. Contraindications

Hypersensitivity to Brivaracetam or any of the inactive ingredients in Brivaracetam (bronchospasm and angioedema have occurred).

4.4. Special Warnings and Precautions for Use

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

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.

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. 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). The risk is greatest early in treatment but can occur at any time.

Psychiatric Adverse Reactions
Brivaracetam causes psychiatric adverse reactions. 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 behaviour, and adjustment disorder) and psychotic symptoms (psychotic disorder along with hallucination, paranoia, acute psychosis, and psychotic behaviour).

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. Drug 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.

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.

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

Pregnancy
There are no adequate data on the developmental risks associated with use of Brivaracetam in pregnant women. In animal studies, Brivaracetam produced evidence of developmental toxicity (increased embryofetal mortality and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, and long-term neurobehavioral changes in rat offspring) at maternal plasma exposures greater than clinical exposures.

Oral administration of Brivaracetam (0, 150, 300, or 600mg/kg/day) to pregnant rats during the period of organogenesis did not produce any significant maternal or embryofetal toxicity.

Oral administration of Brivaracetam (0, 30, 60, 120, or 240 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in embryofetal mortality and decreased fetal body weights at the highest dose tested, which was also maternally toxic. When Brivaracetam (0, 150, 300, or 600 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation (female), and long-term neurobehavioral changes were observed in the offspring at the highest dose.

Brivaracetam was shown to readily cross the placenta in pregnant rats after a single oral (5 mg/kg) dose of ^{14}C-brivaracetam. *[Reference: BRIVIACT US FDA Label. Dated: May 2018].*

Lactation
No data are available regarding the presence of Brivaracetam in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Studies in lactating rats have shown excretion of Brivaracetam or metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Brivaracetam and any potential adverse effects on the breast fed infant from Brivaracetam or from the underlying maternal condition *[Reference: BRIVIACT US FDA Label. Dated: May2018].*

Pediatric Use
Safety of Brivaracetam injection in pediatric patients has not been established.

Geriatric Use
In general, dose selection for an elderly patient should be judicious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment
Dose adjustments are not required for patients with impaired renal function. There are no data in patients with end-stage renal disease undergoing dialysis, and use of Brivaracetam is not recommended in this patient population

Hepatic Impairment
Because of increases in Brivaracetam exposure, dosage adjustment is recommended for all stages of hepatic impairment

DRUG ABUSE AND DEPENDENCE

Abuse
Brivaracetam at the recommended single dose (50 mg) caused fewer sedative and euphoric effects than alprazolam; however, Brivaracetam at supratherapeutic single doses (200mg 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 Brivaracetam in a pooled review of placebo-controlled adjunctive therapy studies

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

Adverse reactions are listed by System Organ Class (SOC) and within each frequency grouping [Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000)] the adverse reactions 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

Other adverse events that occurred in patients who received Brivaracetam injection included dysgeusia, euphoric mood, feeling drunk, and infusion site pain.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

There is limited clinical experience with Brivaracetam overdose in humans. Somnolence and dizziness were reported in a patient taking a single dose of 1400 mg (14 times the highest recommended single dose) of Brivaracetam. The following adverse reactions were reported with Brivaracetam overdose: vertigo, balance disorder, fatigue, nausea, diplopia, anxiety, and bradycardia. In general, the adverse reactions associated with Brivaracetam overdose were consistent with the known adverse reactions.

There is no specific antidote for overdose with Brivaracetam. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rate and rhythm and vital signs is recommended. Acertified poison control center should be contacted for updated information on the management of overdose with Brivaracetam. There are no data on the removal of Brivaracetam using hemodialysis, but because less than 10% of Brivaracetam is excreted in urine, hemodialysis is not expected to enhance Brivaracetam clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

The precise mechanism by which Brivaracetam exerts its anticonvulsant activity is not known. Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the anticonvulsant effect.

5.2 Pharmacodynamic Properties

Interaction with Alcohol
In a pharmacokinetic and pharmacodynamic interaction study in healthy subjects, co-administration of Brivaracetam (single dose 200 mg [2 times greater than the highest recommended single dose]) and ethanol (continuous intravenous infusion to achieve a blood alcohol concentration of 60 mg/100 mL during 5 hours) increased the effects of alcohol on psychomotor function, attention, and memory. Co-administration of Brivaracetam and ethanol caused a larger decrease from baseline in saccadic peak velocity, smooth pursuit, adaptive tracking performance, and Visual Analog Scale (VAS) alertness, and a larger increase from baseline in body sway and in saccadic reaction time compared with Brivaracetam alone or ethanol alone. The immediate word recall scores were generally lower for Brivaracetam when co-administered with ethanol.

Cardiac Electrophysiology
At a dose 4 times the maximum recommended dose, Brivaracetam did not prolong the QT interval to a clinically relevant extent *[Reference: BRIVIACT US FDA Label. Dated: May 2018].*

5.3 PHARMACOKINETIC PROPERTIES

Brivaracetam exhibits linear and time-independent pharmacokinetics at the approved doses.

The pharmacokinetics of Brivaracetam is similar when used as monotherapy or as adjunctive therapy for the treatment of partial onset seizures.

Absorption
Brivaracetam is highly permeable and is rapidly and almost completely absorbed after oral administration. Pharmacokinetics is dose-proportional from 10 to 600 mg (a range that extends beyond the minimum and maximum single-administration dose levels. The median T_{max} for tablets taken without food is 1 hour (range 0.25 to 3 hours). Co-administration with a high-fat meal slowed absorption, but the extent of absorption remained unchanged. Specifically, when a 50 mg tablet was administered with a high-fat meal, C_{max} (maximum Brivaracetam plasma concentration during a dose interval, an exposure metric) was decreased by 37% and T_{max} was delayed by 3 hours, but AUC (area under the Brivaracetam plasma concentration versus time curve, an exposure metric) was essentially unchanged (decreased by 5%)

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.

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.

Specific Populations

Age
Pediatric Patients: Brivaracetam plasma concentrations were shown to be dose-proportional. A weight-based dosing regimen is necessary to achieve Brivaracetam exposures in pediatric patients 4 years to less than 16 years of age. The estimated plasma clearance was 1.61 L/h; 2.18 L/h; 3.19 L/h for pediatric patients 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).

Geriatric Population: The plasma half-life of Brivaracetam was 7.9 hours and 9.3 hours in the 65 to 75 and >75 years groups, respectively. The steady-state plasma clearance of Brivaracetam was slightly lower (0.76 mL/min/kg) than in young healthy controls (0.83 mL/min/kg).

Sex

There were no differences observed in the pharmacokinetics of Brivaracetam between male and female subjects.

Race/Ethnicity
No significant pharmacokinetic difference was showed in Caucasian and non-Caucasian patients.

Renal Impairment
In patients with severe renal impairment (creatinine clearance<30 mL/min/1.73m² and not requiring dialysis) the plasma AUC of Brivaracetam was moderately increased (21%), while the AUCs of the acid, hydroxy and hydroxyacidmetabolitesweireincreased3-fold,4-fold,and21-fold,respectively.Therenal clearance of these inactive metabolites was decreased10-fold. Brivaracetam has not been studied in patients undergoing hemodialysis.

Hepatic Impairment
In patients with hepatic cirrhosis, Child-Pugh grades A, B, and C, showed 50%, 57%, and 59% increases in Brivaracetam exposure, respectively. The effect of hepatic impairment on brivaracetam pharmacokinetics in pediatric patients is expected to be comparable to the effect observed in adults.

Drug Interaction Studies
In Vitro Assessment of Drug Interactions

Drug-Metabolizing Enzyme Inhibition
Brivaracetam did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, or 3A4. Brivaracetam weakly inhibited CYP2C19 and would not be expected to cause significant inhibition of CYP2C19 in humans. Brivaracetam was an inhibitor of epoxide hydrolase, (IC50 = 8.2 µM), suggesting that Brivaracetam can inhibit the enzyme *in vivo*.

Drug-Metabolizing Enzyme Induction
Brivaracetam at concentrations up to 10 µM caused little or no change of mRNA expression of CYP1A2, 2B6, 2C9, 2C19, 3A4, and epoxide hydrolase. It is unlikely that Brivaracetam will induce these enzymes *in vivo*.

Transporters
Brivaracetam was not a substrate of P-gp, MRP1, or MRP2. Brivaracetam did not inhibit or weakly inhibit BCRP, BSEP, MATE1, MATE2/K, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or P-gp, suggesting that Brivaracetam is unlikely to inhibit these transporters *in vivo.*

In Vivo Assessment of Drug Interactions

Drug Interaction Studies with Antiepileptic Drugs (AEDs)
The in vivo drug interactions are listed in below table.

Concomitant AED	Influence of AED on Brivaracetam	Influence of Brivaracetam on AED
Carbamazepine	26% decrease in plasma concentration	None for carbamazepine Increase of carbamazepine-epoxide metabolite*
Lacosamide	No data	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None on the active monohydroxy metabolite derivative (MHD)
Phenobarbital	19% decrease in plasma concentration	None
Phenytoin	21% decrease in plasma concentration	Up to 20% increase in plasma concentration**
Pregabalin	No data	None
Topiramate	None	None
Valproic acid	None	None
Zonisamide	No data	None

** Brivaracetam is a reversible inhibitor of epoxide hydrolase resulting in an increased concentration of carbamazepine epoxide, an active metabolite of carbamazepine. The carbamazepine epoxide plasma concentration increased up to 198% at a Brivaracetam dose of 100 mg twice daily.*
*** At a supratherapeutic dose of 400 mg/day brivaracetam, there was a 20% increase in phenytoin plasma concentration.*

Drug Interaction Studies with Other Drugs
Effect of Other Drugs on Brivaracetam
Co-administration with CYP inhibitors or transporter inhibitors is unlikely to significantly affect Brivaracetam exposure. Co-administration with rifampin decreases brivaracetam plasma concentrations by 45%, an effect that is probably the result of CYP2C19 induction.

Oral Contraceptives
Co-administration of Brivaracetam 200 mg twice daily (twice the recommended maximum daily dosage) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) reduced estrogen and progestin AUCs by 27% and 23%, respectively, without impact on suppression of ovulation. However, co-administration of Brivaracetam 50 mg twice daily with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) did not significantly influence the pharmacokinetics of either substance. The interaction is not expected to be of clinical significance.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

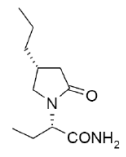
Carcinogenesis
In a carcinogenicity study in mice, oral administration of Brivaracetam (0, 400, 550, or 700 mg/kg/day) for 104 weeks increased the incidence of liver tumors (hepatocellular adenoma and carcinoma) in male mice at the two highest doses tested. At the dose (400 mg/kg) not associated with 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 *[Reference: BRIVIACT US FDA Label. Dated: May-2018].*

7. DESCRIPTION

Brivaracetam belongs to the chemical class of anti-epileptics. Brivaracetam is available as Injection 50 mg/5 ml (10 mg/ml). It has a molecular formula of $C_{11}H_{20}N_2O_2$ and a molecular weight of 212.29. Brivaracetam has the structural formula, as (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl] butanamide.



Brivaracetam is available as off-white crystalline powder and is non-hygroscopic. Brivaracetam is very soluble in water, hydrochloric acid buffer, acetate buffer, phosphate buffer, ethanol, methanol, glacial acetic acid. It is freely soluble in acetonitrile and acetone, soluble in toluene and very slightly soluble in n-hexane. The average pH of Brivaracetam is 5.64. Its average melting point is 75.35ºC.

Brivaracetam injection is a clear colorless free from visible particles.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

10 ml clear tubular glass vial.

8.3 Storage and Handling Instructions

Store at temperature not exceeding 30ºC.

9. PATIENT COUNSELING INFORMATION

Advise the patient to read package insert.

Suicidal Behavior and Ideation
Counsel patients, their caregivers, and/or families that antiepileptic drugs, including Brivaracetam, may increase the risk of suicidal thoughts and behavior, and advise patients to be alert for the emergence or worsening of symptoms of depression; unusual changes in mood or behavior or suicidal thoughts, behavior, or thoughts about self-harm. Advise patients, their care givers and/or families to report behaviors of concern immediately to a healthcare provider.

Neurological Adverse Reactions
Counsel patients that Brivaracetam causes somnolence, fatigue, dizziness, and gait disturbance. These adverse reactions, if observed, are more likely to occur early in treatment but can occur at any time. Advise patients 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.

Psychiatric Adverse Reactions
Advise patients that Brivaracetam causes changes in behavior (e.g., aggression, agitation, anger, anxiety, and irritability) and psychotic symptoms. Instruct patients to report these symptoms immediately to their healthcare provider.

Hypersensitivity: Bronchospasm and Angioedema
Advise patients that symptoms of hypersensitivity including bronchospasm and angioedema can occur with Brivaracetam. Instruct them to seek immediate medical care should they experience signs and symptoms of hypersensitivity.

Withdrawal of Antiepileptic Drugs
Advise patients not to discontinue use of Brivaracetam without consulting with their healthcare provider. Brivaracetam should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus.

Pregnancy
Advice patients to notify their health care provider if they become pregnant or intend to become pregnant during Brivaracetam therapy.

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division), Plot No. 42, Anrich Industrial Estate,
Bollaram, Sangareddy District - 502 325, Telangana, India.

B33252-00

11. DETAILS OF MANUFACTURING LICENCE NUMBER

Mfg. Lic. No.: 38/MD/AP/2007/F/CC

12. DATE OF REVISION

March 2023