Brivaget™

(Brivaracetam)

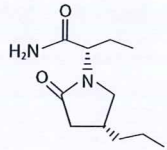
بریواگیٹ

Solution for Injection and Infusion 50mg/5mL

Film-coated Tablets 25mg, 50mg, 75mg & 100mg

DESCRIPTION

Brivaget (Brivaracetam) belongs to the class of antiepileptics. The chemical name of Brivaracetam is (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl] butanamide. Its molecular formula is $C_{11}H_{20}N_2O_2$ and the structural formula is:



Brivaracetam

QUALITATIVE & QUANTITATIVE COMPOSITION

Brivaget (Brivaracetam) is available for administration as:

Brivaget IV Solution for Injection and Infusion 50mg/5mL
Each 5mL ampoule contains:
Brivaracetam…50mg

Brivaget Tablets 25mg
Each film-coated tablet contains:
Brivaracetam...25mg

Brivaget Tablets 50mg
Each film-coated tablet contains:
Brivaracetam…50mg

Brivaget Tablets 75mg
Each film-coated tablet contains:
Brivaracetam…75mg

Brivaget Tablets 100mg
Each film-coated tablet contains:
Brivaracetam…100mg

CLINICAL PHARMACOLOGY

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. Binding to SV2A is believed to be the primary mechanism for Brivaracetam anticonvulsant activity.

Pharmacokinetics

Absorption

Brivaracetam is highly permeable and is rapidly and almost completely absorbed after oral administration. Pharmacokinetics is dose-proportional from 10mg to 600mg. The median T_{max} for tablets taken without food is 1 hour (range 0.25 hours to 3 hours). Co-administration with high-fat meal slowed the absorption, but the extent of absorption remains unchanged.

Distribution

Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5L/kg, a value close to that of the total body water. Brivaracetam is rapidly and evenly distributed in most tissues.

Metabolism

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of Brivaracetam itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. An additional hydroxy acid metabolite is created by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are 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. Fecal excretion accounts for less than 1% of the dose. Less than 10% of the dose is excreted unchanged in the urine. Thirty-four percent of the dose is excreted as the carboxylic acid metabolite in urine. The terminal plasma half-life ($t_{1/2}$) is approximately 9 hours. The total plasma clearance in patients was estimated to 3.6L/h.

Special Population

Pediatric Patients

A weight-based dosing regimen is necessary to achieve Brivaracetam exposures in pediatric patients 1 month to less than 16 years of age that are similar to those observed in adults treated at effective doses of Brivaracetam. The estimated plasma clearance was 1.09L/h, 1.81L/h, and 3.11L/h for pediatric patients weighing 11kg, 20kg, and 50kg, respectively.

Elderly

In a study in elderly subjects (65 to 79 years old; creatinine clearance 53 to 98mL/min/1.73m²) receiving Brivaracetam 200mg twice daily (2 times the highest recommended dosage), 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 (0.76mL/min/kg) than in young healthy controls (0.83mL/min/kg). No dose adjustment is required.

Patient with renal Impairment

A study in subjects with severe renal impairment (creatinine clearance <30mL/min/1.73m² and not requiring dialysis) revealed that the plasma AUC of Brivaracetam was moderately increased (21%) relative to healthy controls, while the AUCs of the acid, hydroxy, and hydroxyacid metabolites were increased 3-fold, 4-fold, and 21-fold, respectively. The renal clearance of these inactive metabolites was decreased 10-fold. Brivaracetam has not been studied in patients undergoing hemodialysis.

Patient with hepatic Impairment

A pharmacokinetic study in subjects with hepatic cirrhosis, Child-Pugh grades A, B, and C, showed 50%, 57%, and 59% increases in Brivaracetam exposure, respectively, compared to matched healthy controls. The effect of hepatic impairment on Brivaracetam pharmacokinetics in pediatric patients is expected to be comparable to the effect observed in adults.

THERAPEUTIC INDICATIONS

Brivaget (Brivaracetam) is indicated for the treatment of partial-onset seizures in patients 1 month of age and older.

DOSAGE AND ADMINISTRATION

The physician should prescribe the most appropriate formulation and strength according to weight and dose.

The recommended dosage for patients 1 month of age and older is included in table below. In pediatric patients weighing less than 50kg, the recommended dosing regimen is dependent upon body weight. When initiating treatment, gradual dose escalation is not required. Dosage should be adjusted based on clinical response and tolerability.

Recommended dosage for patients 1 month of age and older

Age and Body Weight	Initial Dosage	Minimum and Maximum Maintenance Dosage
Adults (16 years and older)	50mg twice daily (100mg per day)	25mg to 100mg twice daily (50mg to 200mg per day)
Pediatric patients weighing 50kg or more	25mg to 50mg twice daily (50mg to 100mg per day)	25mg to 100mg twice daily (50mg to 200mg per day)
Pediatric patients weighing 20kg to less than 50kg	0.5mg/kg to 1mg/kg twice daily (1mg/kg to 2mg/kg per day)	0.5mg/kg to 2mg/kg twice daily (1mg/kg to 4mg/kg per day)
Pediatric patients weighing 11kg to less than 20kg	0.5mg/kg to 1.25mg/kg twice daily (1mg/kg to 2.5mg/kg per day)	0.5mg/kg to 2.5mg/kg twice daily (1mg/kg to 5mg/kg per day)
Pediatric patients weighing less than 11kg	0.75mg/kg to 1.5mg/kg twice daily (1.5mg/kg to 3mg/kg per day)	0.75mg/kg to 3mg/kg twice daily (1.5mg/kg to 6mg/kg per day)

Brivaget (Brivaracetam) Injection may be used when oral administration is temporarily not feasible. Brivaget (Brivaracetam) Injection should be administered intravenously at the same dosage and same frequency as Brivaget (Brivaracetam) Tablets.

Missed Dose

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

For patients from 16 years of age, if Brivaget (Brivaracetam) has to be discontinued, it is recommended that the dose is reduced gradually by 50mg/day on a weekly basis.

For patients below the age of 16 years, if Brivaget (Brivaracetam) has to be discontinued, it is recommended that the dose is reduced by a maximum of half the dose every week until a dose of 1mg/kg/day (for patients with a body weight less than 50kg) or 50mg/day (for patients with body weight of 50kg or more) is reached.

After 1 week of treatment at 50mg/day, a final week of treatment at the dose of 20mg/day is recommended.

Special Population

Patient with 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. No dose adjustment is necessary in pediatric patients with impaired renal function.

Patients with hepatic Impairment
The recommended dosage for patients with hepatic impairment is included in table below:

Recommended dosage for patients with hepatic impairment

Age and Body Weight	Initial Dosage	Minimum and Maximum Maintenance Dosage
Adults (16 years and older)	25mg twice daily (50mg per day)	75mg twice daily (150mg per day)
Pediatric patients weighing 50kg or more		
Pediatric patients weighing 20kg to less than 50kg	0.5mg/kg twice daily (1mg/kg per day)	1.5mg/kg twice daily (3mg/kg per day)
Pediatric patients weighing 11kg to less than 20kg	0.5mg/kg twice daily (1mg/kg per day)	2mg/kg twice daily (4mg/kg per day)
Pediatric patients weighing less than 11kg	0.75mg/kg twice daily (1.5mg/kg per day)	2.25mg/kg twice daily (4.5mg/kg per day)

Method of Administration
Brivaget (Brivaracetam) can be initiated with either intravenous or oral administration.

Tablets
Brivaget (Brivaracetam) Tablets may be taken with or without food.
Brivaget (Brivaracetam) Tablets should be swallowed whole with liquid and should not be chewed or crushed.

Injection / Infusion
Brivaget (Brivaracetam) Injection is for intravenous use only.
Brivaget (Brivaracetam) Injection can be administered intravenously without further dilution or may be mixed with diluents listed below:
- 0.9% Sodium Chloride Injection
- Lactated Ringer's Injection
- 5% Dextrose Injection

Brivaget (Brivaracetam) Injection 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.
The diluted solution should not be stored for more than 4 hours at controlled room temperature (15°C-30°C).

ADVERSE REACTIONS
Very Common: Dizziness and somnolence.
Common: Influenza, decreased appetite, depression, anxiety, insomnia, irritability, convulsion, vertigo, upper respiratory tract infections, cough, nausea, vomiting, constipation and fatigue.
Uncommon: Suicidal ideation, psychotic disorder, aggression, agitation, neutropenia and type I hypersensitivity.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Brivaracetam is contraindicated in patients with known hypersensitivity to the active substance or other pyrrolidone derivatives or to any excipient of the product.

PRECAUTIONS
Suicidal Ideation and Behaviour
Antiepileptic drugs, 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 behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

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.

Psychiatric Adverse Reactions
Behavioral reactions including psychotic symptoms, irritability, depression, aggressive behavior, and anxiety are observed, monitor patients for symptoms.

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.

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.

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

Pregnancy
Brivaracetam should not be used during pregnancy unless clinically necessary.

Nursing Mothers
Brivaracetam is excreted in human 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.

DRUG INTERACTIONS
Alcohol
Brivaracetam approximately doubles the effect of alcohol on psychomotor function, attention and memory. Intake of Brivaracetam with alcohol is not recommended.

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.

OVERDOSAGE
Symptoms
Somnolence and dizziness have been reported in a healthy subject taking a single dose of 1400mg of Brivaracetam. The following adverse reactions were reported with Brivaracetam overdose: nausea, vertigo, balance disorder, anxiety, fatigue, irritability, aggression, insomnia, depression, and suicidal ideation in the post-marketing experience. In general, the adverse reactions associated with Brivaracetam overdose were consistent with the known adverse reactions.

Treatment
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. 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.

STORAGE
Brivaget (Brivaracetam) Tablets 25mg, 50mg, 75mg & 100mg
Do not store above 30°C.
Protect from sunlight and moisture.

Brivaget IV (Brivaracetam) Solution for Injection or Infusion 50mg/5mL
Do not store above 30°C.
Protect from sunlight.
Do not freeze.
The diluted solution should not be stored for more than 4 hours at controlled room temperature (15°C-30°C).

HOW SUPPLIED
Brivaget (Brivaracetam) Tablets 25mg are available in blister pack of 14's.
Brivaget (Brivaracetam) Tablets 50mg are available in blister pack of 14's.
Brivaget (Brivaracetam) Tablets 75mg are available in blister pack of 14's.
Brivaget (Brivaracetam) Tablets 100mg are available in blister pack of 14's.
Brivaget IV (Brivaracetam) Solution for Injection and Infusion 50mg/5mL is available in a pack of 1's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

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