

Briplat

(Brivaracetam)

بریلپلٹ
(بریوراسیٹیم)

۲۵ ملی گرام، ۵۰ ملی گرام، ۱۰۰ ملی گرام ٹیبلیٹس
۱۰ ملی گرام / ملی لیٹر اورل سلوشن

25mg 50mg 100mg Tablets

10mg/ml Oral Solution

COMPOSITION

Briplat 25mg Tablet

Each film-coated tablet contains:
Brivaracetam 25mg
Product Complies B.P. Specs.

Briplat 50mg Tablet

Each film-coated tablet contains:
Brivaracetam 50mg
Product Complies B.P. Specs.

Briplat 100 mg Tablet

Each film-coated tablet contains:
Brivaracetam 100 mg
Product Complies B.P. Specs.

Briplat Oral Suspension

Each ml contains:
Brivaracetam 10mg
Product Complies B.P. Specs.

CLINICAL PHARMACOLOGY

Mechanism of Action: Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the anti-convulsant effect.

Pharmacodynamics: Interactions with Alcohol: Co-administration of Brivaracetam (single dose 200 mg) and ethanol 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 pro-long the QT interval to a clinically relevant extent.

Pharmacokinetics: Brivaracetam tablets, oral solution, and can be used interchangeably. Brivaracetam exhibits linear and time-independent pharmacokinetics at the approved doses.

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 Tmax 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, Cmax (maximum Brivaracetam plasma concentration during a dose interval, an exposure metric) was decreased by 37% and Tmax 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 to plasma proteins ($\leq 20\%$). The volume of distribution is 0.5 L/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. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. 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.

Specific Populations

Age: Pediatric Patients: 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 that are similar to those observed in adults treated at effective doses of Brivaracetam. 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: In elderly subjects (65 to 79 years old; creatinine clearance 53 to 98 mL/min/1.73 m² receiving Brivaracetam 200 mg 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 (0.76 mL/min/kg) than in young healthy controls (0.83 mL/min/kg).

Sex: No differences observed in the pharmacokinetics of Brivaracetam between male and female subjects.

Hepatic Impairment: In hepatic cirrhosis patients, 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 in pediatric patients is expected to be comparable to the effect observed in adults.

Drug Interaction Studies

In Vitro Assessment of Drug Interaction

Drug-Metabolizing Enzyme Inhibition: It 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, ($IC_{50} = 8.2 \mu M$), suggesting that Brivaracetam can inhibit the enzyme in vivo.

Drug-Metabolizing Enzyme Induction: The 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 it will induce these enzymes in vivo.

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

In Vivo Assessment of Drug Interaction

Drug Interaction Studies with Antiepileptic Drugs (AEDs): Potential interactions between Brivaracetam (25 mg twice daily to 100 mg twice daily) and other AEDs were investigated in a pooled analysis of plasma drug concentrations. None of the interactions require changes in the dose of Brivaracetam. Interactions with carbamazepine and phenytoin can be clinically important.

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.

Oral Contraceptives: Co-administration of Brivaracetam 200 mg twice daily (twice the recommended maximum daily dosage) with an oral contraceptive containing ethinyl estradiol (0.03 mg) and levo-norgestrel (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 ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg) did not significantly influence the pharmacokinetics of either substance.

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to Brivaracetam or any of the inactive ingredients in Briplat.

INTERACTIONS

Rifampin: Co-administration with rifampin decreases Brivaracetam plasma concentrations.

Carbamazepine: Co-administration with carbamazepine may increase exposure to carbamazepine-epoxide, the active metabolite of carbamazepine.

Phenytoin: Because Brivaracetam can increase plasma concentrations of phenytoin, phenytoin levels should be monitored.

Levetiracetam: Brivaracetam provided no added therapeutic benefit to levetiracetam when the two drugs were co-administered.

USE IN SPECIFIC POPULATION

Pregnancy: Risk Summary: 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 at maternal plasma exposures greater than clinical exposures.

Lactation: Risk Summary: 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.

Pediatric Use: Safety and effectiveness of Brivaracetam tablets and oral solution have been established in pediatric patients 4 years to less than 16 years of age.

Safety and effectiveness in pediatric patients below the age of 4 years have 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.

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

Suicidal Behavior and Ideation, Neurological Adverse Reactions, Psychiatric Adverse Reactions, Hypersensitivity including Bronchospasm and Angioedema, Withdrawal of Antiepileptic Drugs.

DOSAGE AND ADMINISTRATION

Monotherapy or Adjunctive Therapy: The recommended dosage for patients 1 month of age and older is included in Table 1. 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

Age and Body Weight	Initial Dosage	Minimum and Maximum Maintenance Dosage
Adults (16 years and older)	50 mg twice daily	25 mg to 100 mg twice daily
Paeds weighing 50 kg or more	25 mg to 50 mg twice daily	25 mg to 100 mg twice daily
Paeds weighing 20 kg to 50 kg	0.5 mg/kg to 1 mg/kg twice daily	0.5 mg/kg to2 mg/kg twice daily
Paeds weighing 11 kg to 20 kg	0.5 mg/kg to 1.25 mg/kg twice daily	0.5 mg/kg to 2.5 mg/kg twice daily
Pediatric patients weighing less than 11 kg	0.75 mg/kg to 1.5 mg/kg twice daily	0.75 mg/kg to 3 mg/kg twice daily

Brivaracetam Tablets: Brivaracetam tablets should be swallowed whole with liquid. Brivaracetam tablets should not be chewed or crushed.

Brivaracetam Oral Solution: A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. When using Brivaracetam oral solution, no dilution is necessary. Brivaracetam oral solution may also be administered using a nasogastric tube or gastrostomy tube.

Discard any unused Brivaracetam oral solution remaining after 5 months of first opening the bottle.

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 and pediatric patients weighing 50 kg or more is 25 mg twice daily, and the recommended maximum dosage is 75 mg twice daily. The recommended starting dosage for pediatric patients with hepatic impairment weighing 11 kg to less than 50 kg is 0.5 mg/kg twice daily. The maximum dosage for pediatric patients with hepatic impairment weighing 20 kg to less than 50 kg is 1.5 mg/kg twice daily. The maximum dosage for pediatric patients with hepatic impairment weighing 11 kg to less than 20 kg is 2 mg/kg twice daily.

Co-administration with Rifampin: Increase the Brivaracetam dosage in patients on concomitant rifampin by up to 100%.

DOSAGE: As directed by the physician.

INSTRUCTIONS:

Store below 30°C in a dry place, protect from light. To be dispensed on the prescription of a registered medical practitioner only. Keep out of the reach of children.

PRESENTATION

Briplat 25mg Tablets: Briplat 25mg tablets are available in 2x7 blisters in a carton.

Briplat 50mg Tablets: Briplat 50mg tablets are available in 2x7 blisters in a carton.

Briplat 100mg Tablets: Briplat 100mg tablets are available in 2x7 blisters in a carton.

Briplat Oral Solution: Briplat 10mg/ml oral solution is packed in 60ml labeled pet bottle in a carton with syringe dropper.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ پر رکھیں،
روشنی سے بچائیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

نوٹ: بریپلیٹ ٹیبلیٹ میں لیکٹوز شامل ہے۔

Briplat tablets contain lactose.

Manufactured by:

 **Platinum**
Pharmaceuticals (Pvt.) Ltd.

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