# Brivatam

( B r i v a r a c e t a m )

Tablet

# بریواٹیم

**COMPOSITION:**
***Brivatam Tablet 25 mg:***
Each film coated tablet contains:
Brivaracetam ..... 25 mg.

**Product Specs.:** BP

***Brivatam Tablet 50 mg:***
Each film coated tablet contains:
Brivaracetam ..... 50 mg.

**Product Specs.:** BP

***Brivatam Tablet 100 mg:***
Each film coated tablet contains:
Brivaracetam ..... 100 mg.

**Product Specs.:** BP

**CLINICAL PARTICULARS:**
***Therapeutic Indications:***
Brivaracetam is indicated for the treatment of partial-onset seizures in patients 1 month of age and older.
***It may be used:***
- As monotherapy
- As adjunctive therapy with other antiepileptic drugs

***Posology and Method of Administration:***
Treatment should be initiated by physicians experienced in the management of epilepsy.
***Adults and Adolescents (16 years and older):***
***Recommended starting dose:***
- 50 mg twice daily (100 mg/day)

**Dose range:**
- 25 mg twice daily to 100 mg twice daily
- Total daily dose: 50–200 mg/day

Dose adjustments should be based on clinical response and tolerability.
Gradual dose escalation is not required.
***Hepatic Impairment:***
Dose adjustment is recommended.
***Recommended starting dose:***
- 25 mg twice daily

***Maximum recommended dose:***
- 75 mg twice daily (150 mg/day)

***Renal Impairment:***
No dose adjustment is required in patients with impaired renal function.
There is limited experience in patients with end-stage renal disease undergoing dialysis; use is not recommended.
***Elderly:***
No dose adjustment required solely on the basis of age.

**METHOD OF ADMINISTRATION:**
- For oral use
- Tablets should be swallowed whole with liquid
- Tablets should not be chewed or crushed
- May be taken with or without food

**CONTRAINDICATIONS:**
- Hypersensitivity to brivaracetam or any component of the formulation
- Hypersensitivity reactions to other pyrrolidone derivatives

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE:**
***Suicidal Behavior and Ideation:***
Antiepileptic drugs, including brivaracetam, may increase the risk of suicidal thoughts or behavior.
***Patients should be monitored for:***
- Depression
- Mood changes
- Suicidal ideation
- Unusual behavioral changes

***Psychiatric Reactions:***
*Psychiatric adverse reactions reported include:*
- Irritability
- Anxiety
- Aggression
- Agitation
- Psychotic symptoms

Use caution in patients with psychiatric history.
***Dizziness and Somnolence:***
***Brivaracetam may cause:***
- Dizziness
- Fatigue
- Sedation
- Somnolence

Patients should avoid hazardous activities until the effect of the medicine is known.
***Hypersensitivity Reactions:***
Bronchospasm and angioedema have been reported rarely.
Discontinue treatment if hypersensitivity occurs.
***Withdrawal of Antiepileptic Drugs:***
Abrupt discontinuation should be avoided due to risk of increased seizure frequency.
Dose reduction should generally be gradual.

**INTERACTION WITH OTHER MEDICINAL PRODUCTS:**
***Rifampin:***
Rifampin may significantly reduce plasma concentrations of brivaracetam.
Dose adjustment may be required.
***Carbamazepine:***
Brivaracetam may increase concentrations of carbamazepine-epoxide.
Clinical monitoring is recommended.
**Alcohol and CNS Depressants:**
***Concomitant use may increase:***
- Sedation
- Cognitive impairment
- Psychomotor impairment

***Oral Contraceptives:***
No clinically significant interaction observed at therapeutic doses.

**FERTILITY, PREGNANCY AND LACTATION:**
***Pregnancy:***
Limited human data are available.
Brivaracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
***Lactation:***
Brivaracetam is excreted into human breast milk.
A decision should be made whether to discontinue breastfeeding or discontinue therapy.
***Fertility:***
Animal studies showed no adverse effects on fertility.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:**
Brivatam may impair the ability to drive or operate machinery.
***Patients should be cautioned regarding:***
- Drowsiness
- Dizziness
- Reduced alertness

**UNDESIRABLE EFFECTS:**
***Very Common (>1/10)***
- Somnolence
- Dizziness

***Common***
- Fatigue
- Nausea
- Vomiting
- Irritability
- Anxiety
- Insomnia
- Depression
- Convulsion
- Vertigo

***Uncommon***
- Aggression
- Psychotic disorder
- Suicidal ideation
- Neutropenia

***Rare***
- Angioedema
- Hypersensitivity reactions

Most adverse reactions are mild to moderate in severity.

**PHARMACOLOGICAL PROPERTIES:**
***Pharmacodynamic Properties:***
***Pharmacotherapeutic group:*** Antiepileptics for partial-onset seizures
**ATC code:** N03AX23
Brivaracetam is a selective, high-affinity synaptic vesicle protein 2A (SV2A) ligand with anticonvulsant activity.
***Mechanism of Action:*** Although the precise mechanism by which brivaracetam exerts its antiepileptic activity is not fully understood, it is believed to act primarily through selective binding to synaptic vesicle protein 2A (SV2A) in the brain.
SV2A is a transmembrane glycoprotein located on presynaptic vesicles and plays an important role in neurotransmitter release and synaptic transmission.
***Brivaracetam binds selectively and reversibly to SV2A, leading to:***
- Modulation of synaptic vesicle exocytosis
- Stabilization of neuronal electrical activity
- Reduction in abnormal hypersynchronous neuronal firing
- Suppression of seizure propagation

***Brivaracetam demonstrates:***
- Approximately 15–30-fold higher affinity for SV2A compared with levetiracetam
- Rapid penetration across the blood-brain barrier
- Rapid receptor occupancy in the central nervous system

***Unlike some antiepileptic agents, brivaracetam does not significantly affect:***
- Voltage-gated sodium channels at therapeutic concentrations
- GABAergic neurotransmission directly
- Glutamate receptor binding

**Pharmacodynamic Effects:**
***Anticonvulsant Activity:***
***Brivaracetam demonstrated broad-spectrum anticonvulsant activity in multiple animal seizure models including:***
- Focal seizures
- Generalized seizures
- Audiogenic seizures
- Kindling models

***Electrophysiological Effects:***
Brivaracetam reduces neuronal hyperexcitability and suppresses epileptiform discharges without causing major impairment of normal neuronal signaling.
***CNS Effects:***
***Dose-related central nervous system effects may include:***
- Somnolence
- Sedation
- Fatigue
- Dizziness

***Behavioral Effects:***
***Psychiatric and behavioral adverse reactions have been reported, including:***
- Irritability
- Anxiety
- Aggression
- Mood changes

***Clinical Efficacy:***
***Clinical studies demonstrated statistically significant reductions in seizure frequency in patients with partial-onset seizures when brivaracetam was used:***
- As adjunctive therapy
- As monotherapy

Therapeutic response has been observed as early as the first day of treatment due to rapid onset of action.
***Resistance and Dependence:***
***No evidence of:***
- Pharmacologic tolerance
- Physical dependence
- Drug-seeking behavior

has been observed during therapeutic use.
**Pharmacokinetic Properties:**
Brivaracetam exhibits linear, predictable, and dose-proportional pharmacokinetics over the therapeutic dose range.
Pharmacokinetic variability between individuals is low to moderate.
***Absorption:*** Brivaracetam is rapidly and almost completely absorbed following oral administration.
***Key absorption characteristics:***
- Absolute oral bioavailability: approximately 100%
- Rapid gastrointestinal absorption
- Peak plasma concentration ($C_{max}$) achieved within approximately 1 hour after administration under fasting conditions
- $T_{max}$ may be delayed by food intake, but overall exposure (AUC) is not significantly affected

***Food Effect:***
***Administration with a high-fat meal:***
- Delays $T_{max}$
- Reduces $C_{max}$ modestly
- Does not significantly alter extent of absorption

Therefore, brivaracetam may be administered with or without food.
***Steady State:*** Steady-state plasma concentrations are achieved within approximately 2 days of twice-daily dosing.
Accumulation is minimal due to relatively short elimination half-life.
***Distribution:*** Brivaracetam distributes rapidly into body tissues, including the central nervous system.
***Distribution characteristics:***
- Plasma protein binding: ≤20%
- Apparent volume of distribution: approximately 0.5 L/kg
- Rapid penetration across the blood-brain barrier
- Uniform tissue distribution

Low protein binding minimizes risk of displacement interactions with other drugs.
***Metabolism:*** Brivaracetam undergoes extensive metabolism.
***Major metabolic pathways include:***
- Hydrolysis of the acetamide moiety
- CYP2C19-mediated hydroxylation

***Primary metabolites include:***
- Acid metabolite (major inactive metabolite)
- Hydroxy metabolite
- Hydroxyacid metabolite

All major metabolites are pharmacologically inactive.
***Cytochrome P450 Involvement:***
The CYP2C19 enzyme contributes partially to metabolism.
Patients with reduced CYP2C19 activity may exhibit moderately increased plasma concentrations.
Brivaracetam has low potential for clinically significant CYP-mediated drug interactions.
***Elimination:*** Brivaracetam is eliminated primarily through metabolism followed by renal excretion of metabolites.
***Elimination characteristics:***
- Terminal elimination half-life: approximately 9 hours
- Total plasma clearance: approximately 3.6 L/hour
- Less than 10% excreted unchanged in urine
- More than 95% of administered dose recovered in urine within 72 hours, primarily as metabolites

Fecal excretion is minimal.
***Linearity:***
Pharmacokinetics are linear across the therapeutic dose range.
Systemic exposure increases proportionally with dose.
No clinically significant autoinduction or accumulation occurs with repeated dosing.
**Special Populations:**
***Hepatic Impairment:*** Brivaracetam exposure is increased in patients with hepatic impairment due to reduced metabolic clearance.
***Observed changes include:***
- Increased AUC
- Prolonged elimination half-life
- Reduced total clearance

Dose adjustment is recommended in all stages of hepatic impairment.
***Renal Impairment:***
Mild to moderate renal impairment has limited impact on parent drug exposure.
***However.***
- Metabolite exposure may increase
- Data in end-stage renal disease are limited

Use in dialysis patients is generally not recommended.
***Elderly:***
No clinically significant pharmacokinetic differences solely related to age.
***Pediatric Population:***
Pharmacokinetics in pediatric patients are generally comparable to adults when adjusted for body weight.
***Gender and Race:***
***No clinically significant effects of:***
- Gender
- Ethnicity
- Race

on brivaracetam pharmacokinetics have been observed.
***Pharmacokinetic–Pharmacodynamic Relationship:*** Clinical efficacy correlates with systemic exposure and SV2A receptor occupancy.
***Higher plasma concentrations may increase risk of CNS adverse effects such as:***
- Somnolence
- Fatigue
- Dizziness

Therapeutic activity is achieved within the recommended dosage range without requirement for plasma concentration monitoring.

**INSTRUCTIONS:**
– Store below 30°C.
– Protect from heat, sunlight and moisture.
– Keep out of the reach of children.
– To be sold on the prescription of a registered medical practitioner only.

**PRESENTATION:**

| | | |
|---|---|---|
| **Brivatam Tablet 25 mg** | : | Pack of 2 x 7 tablets. |
| **Brivatam Tablet 50 mg** | : | Pack of 2 x 7 tablets. |
| **Brivatam Tablet 100 mg** | : | Pack of 2 x 7 tablets. |

**ہدایات:**
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

*FOR FURTHER INFORMATIONS PLEASE CONTACT:*

Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.