# Cubriva™ (Brivaracetam)

25mg, 50mg, 75mg, 100mg Tablets
10mg/mL oral solution
10mg/mL injection

# کیوبریوا (بریواریسیٹیم)

۲۵ ملی گرام، ۵۰ ملی گرام، ۷۵ ملی گرام، ۱۰۰ ملی گرام ٹیبلٹس
۱۰ ملی گرام/ملی لیٹر اورل سلوشن
۱۰ ملی گرام/ملی لیٹر انجکشن

## QUALITATIVE AND QUANTITATIVE COMPOSITION

**Cubriva 25mg Tablets:** Each film-coated tablet contains: Brivaracetam ..... 25mg (Innovator's specification)
**Cubriva 50mg Tablets:** Each film-coated tablet contains: Brivaracetam ..... 50mg (Innovator's specification)
**Cubriva 75mg Tablets:** Each film-coated tablet contains: Brivaracetam ..... 75mg (Innovator's specification)
**Cubriva 100mg Tablets:** Each film-coated tablet contains: Brivaracetam ...100mg (Innovator's specification)
**Cubriva Oral Solution:** Each mL contains: Brivaracetam ……..10mg (Innovator's specification)
**Cubriva Injection:** Each mL contains: Brivaracetam ….....10mg (Innovator's specification)

## 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 injection can be used interchangeably. Bri-varacetam 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 with-out 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 expo-sure metric) was decreased by 37% and Tmax was delayed by 3 hours, but AUC (area under the Bri-varacetam plasma concentration versus time curve, an exposure metric) was essentially unchanged (decreased by 5%).
**Distribution:** Brivaracetam is weakly bound to plasma proteins (≤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 corre-sponding 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 hydrox-ylation 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 addi-tional 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 excre-

tion 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 (t1/2) 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 effectives 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 $m^2$) 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.

**Race/Ethnicity:** A population pharmacokinetic analysis comparing Caucasian and non-Caucasian patients showed no significant pharmacokinetic difference.

Renal Impairment: In severe renal impairment patients (creatinine clearance<30 mL/min/1.73$m^2$ 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 hydroxyacidmetaboliteswereincreased3-fold,4-fold, and 21-fold, respectively. There nal clearance of these inactive metabolites was decreased 10-fold.

**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. Brivarace-tam weakly inhibited CYP2C19 and would not be expected to cause significant inhibition of CYP2C19 in hu-mans. Brivaracetam was an inhibitor of epoxide hydrolase, (IC50 = 8.2 $\mu$M), suggesting that Brivaracetam can inhibit the enzyme in vivo.

**Drug-Metabolizing Enzyme Induction:** The concentrations up to 10 $\mu$M 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 un-likely 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 max-imum daily dosage) with an oral contraceptive containing ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg) reduced estrogen and progestin AUCs by 27% and 23%, respectively, without impact on suppres-sion 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 in Cubriva.

## 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 of Brivaracetam injection in pediatric patients has not been established.
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 recommend-ed 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, Hypersensi-tivity 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 Injection Dosage in Adult Patients (16 years and older):** Brivaracetam injection may be used for adult patients when oral administration is temporarily not feasible. Brivaracetam injection should be administered intravenously to adult patients at the same dosage and same frequency as Brivaracetam tablets and oral solution. The use of Brivaracetam injection in pediatric patients has not been studied. The clinical study experience with Brivaracetam injection is limited to 4 consecutive days of treatment.
Administration Instructions for Brivaracetam Tablets and Brivaracetam Oral **Solution:** Brivaracetam can be initiated with either intravenous or oral administration. Brivaracetam tablets and oral solution may be taken with or without food.
**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.
**Preparation and 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 5% Dextrose injection, USP
**Administration:** 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 ad-ministration, whenever solution and container permit.
**Storage and Stability:** The diluted solution should not be stored for more than 4 hours at room temperature and may be stored in 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 and pediatric patients weighing 50 kg or more is 25 mg twice daily, and the recommended max-imum 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. Protect from heat, light and moisture.
The diluted solution should not be stored for more than 4 hours at room temperature and may be stored in polyvinyl chloride (PVC) bags. Keep all medicines out of the reach of children.
To be sold on the prescription of registered medical practitioner only.

## PRESENTATION
**Cubriva 25mg Tablets:** Cubriva (Brivaracetam) 25mg tablets are available in Alu-Alu blister/s of fourteen tablets (14's) in a carton.
**Cubriva 50mg Tablets:** Cubriva (Brivaracetam) 50mg tablets are available in Alu-Alu blister/s of fourteen tablets (14's) in a carton.
**Cubriva 75mg Tablets:** Cubriva (Brivaracetam) 75mg tablets are available in Alu-Alu blister/s of fourteen tablets (14's) in a carton.
**Cubriva 100mg Tablets:** Cubriva (Brivaracetam) 100mg tablets are available in Alu-Alu blister/s of fourteen tablets (14's) in a carton.
**Cubriva Oral Solution:** Cubriva (Brivaracetam) 10mg/mL oral solution is packed in 60mL labeled amber PET bottle in a carton with syringe dropper.
**Cubriva Injection:** Cubriva (Brivaracetam) 10mg/mL injection is packed in printed 5mL clear glass vial in a carton.

**خوراک:** ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
**ہدایات:** ۳۰ ڈگری سینٹی گریڈ سے کم پر رکھیں۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

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