BRITZILAM 25

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only
abbreviated prescribing information for BRIVARACETAM (Brivaracetam Tablets 25mg)
[Please refer the complete prescribing information available at www.torrentpharma.com]

PHARMACOLOGICAL PROPERTIES: 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. Although the exact role of this protein remains to be elucidated it has been shown to modulate exocytosis of neurotransmitters. Binding to SV2A is believed to be the primary mechanism for brivaracetam anticonvulsant activity.
INDICATION: As adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy
DOSAGE AND ADMINISTRATION: *Dosage:* The recommended starting dose is either 50 mg/day or 100 mg/day based on individual patient response and tolerability, the dose may be adjusted in the dose range of 50 mg/day to 200 mg/day. *Administration:* Brivaracetam film-coated tablets must be taken orally swallowed in whole with liquid and may be taken with or without food.
CONTRAINDICATION: Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.
WARNINGS & PRECAUTIONS: *Suicidal ideation and behavior:*Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs), including brivaracetam, in several indications. A meta-analysis of randomized placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for brivaracetam. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should any signs of suicidal ideation or behaviour emerge. *Hepatic impairment:* There are limited clinical data on the use of brivaracetam in patients with pre-existing hepatic impairment. Dose adjustments are recommended for patients with hepatic impairment.
DRUG INTERACTIONS: *Concomitant treatment with levetiracetam:*In the clinical studies, although the numbers were limited, there was no observed benefit of brivaracetam versus placebo in patients taking levetiracetam concurrently. No additional safety or tolerability concern was observed.*Interaction with alcohol:* In a reported pharmacokinetic and pharmacodynamic interaction study between brivaracetam 200 mg single dose and ethanol 0.6 g/L continuous infusion in healthy subjects, there was no pharmacokinetic interaction but brivaracetam approximately doubled the effect of alcohol on psychomotor function, attention and memory. Intake of brivaracetam with alcohol is not recommended. *Effects of other agents on the pharmacokinetics of brivaracetam:* In vitro data suggest that brivaracetam has a low interaction potential. The main disposition pathway of brivaracetam is by CYP-independent hydrolysis. A second disposition pathway involves hydroxylation mediated by CYP2C19. Brivaracetam plasma concentrations may increase when coadministered with CYP2C19 strong inhibitors (e.g. fluconazole, fluvoxamine), but the risk of a clinically relevant CYP2C19-mediated interaction is considered to be low. *Rifampicin:* In healthy subjects, coadministration with the strong enzyme inducer rifampicin (600 mg/day for 5 days), decreased brivaracetam area under the plasma concentration curve (AUC) by 45 %. Prescribers should consider adjusting the brivaracetam dose in patients starting or ending treatment with rifampicin. *Strong enzyme inducing AEDs* Brivaracetam plasma concentrations are decreased when coadministered with strong enzyme inducing AEDs (carbamazepine, phenobarbital, phenytoin) but no dose adjustment is required (see table 1). *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.*Effects of brivaracetam on other medicinal products:* Brivaracetam given 50 or 150 mg/day did not affect

the AUC of midazolam (metabolised by CYP3A4). The risk of clinically relevant CYP3A4 interactions is considered to be low. In reported vitro studies have shown that brivaracetam exhibits little or no inhibition of CYP450 isoforms except for CYP2C19. Brivaracetam may increase plasma concentrations of medicinal products metabolised by CYP2C19 (e.g. lanzoprazole, omeprazole, diazepam). When tested in vitro brivaracetam did not induce CYP1A1/2 but induced CYP3A4 and CYP2B6. No CYP3A4 induction was found in vivo (see midazolam above). CYP2B6 induction has not been investigated in vivo and brivaracetam may decrease plasma concentrations of medicinal products metabolised by CYP2B6 (e.g. efavirenz). In vitro interaction studies to determine the potential inhibitory effects on transporters concluded that there were no clinically relevant effects, except for OAT3. In vitro, Brivaracetam inhibits OAT3 with a half maximal inhibitory concentration 42-fold higher than the Cmax at the highest clinical dose. Brivaracetam 200mg/day may increase plasma concentrations of medicinal products transported by OAT3. *Antiepileptic drugs:* Potential interactions between brivaracetam (50 mg/day to 200 mg/day) and other AEDs were investigated in a pooled analysis of plasma drug concentrations from all phase 2-3 studies, in a population pharmacokinetic analysis of placebo-controlled phase 2-3 studies, and in dedicated drug-drug interaction studies (for the following AEDs: carbamazepine, lamotrigine, phenytoin and topiramate). The effect of the interactions on the plasma concentration is summarised in table 1 (increase is indicated as "↑" and decrease as "↓", area under the plasma concentration versus time curve as "AUC", maximum observed concentration as Cmax). Carbamazepine. Brivaracetam is a moderate reversible inhibitor of epoxide hydrolase resulting in an increased concentration of carbamazepine epoxide, an active metabolite of carbamazepine. In controlled studies, the carbamazepine epoxide plasma concentration increased by a mean of 37 %, 62 % and 98 % with little variability at brivaracetam doses of 50 mg/day, 100 mg/day and 200 mg/day respectively. No safety risks were observed. There was no additive effect of brivaracetam and valproate on the AUC of carbamazepine epoxide. *Oral contraceptives:* Co-administration of brivaracetam (100 mg/day) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) did not influence the pharmacokinetics of either substance. When brivaracetam was coadministered at a dose of 400 mg/day (twice the recommended maximum daily dose) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg), a reduction in estrogen and progestin AUCs of 27 % and 23 %, respectively, was observed without impact on suppression of ovulation. There was generally no change in the concentration-time profiles of the endogenous markers estradiol, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and sex hormone binding globulin (SHBG).

ADVERSE REACTIONS:*Very common: may affect more than 1 in 10 people:* feeling sleepy or dizzy*Common: may affect up to 1 in 10 people:*Flu,feeling very tired (fatigue),convulsion, a feeling of 'spinning' (vertigo),feeling and being sick, constipation,depression, anxiety, not being able to sleep (insomnia), irritability,infections of the nose and throat (such as the 'common cold'), cough, decreased appetite. *Uncommon: may affect up to 1 in 100 people:*allergic reactions,abnormal thinking and/or loss of touch with reality (psychotic disorder), being aggressive, nervous excitement (agitation) thoughts or attempts of harming or killing yourself: tell your doctor straight away a decrease in white blood cells (called 'neutropenia') - shown in blood tests. *Common: may affect up to 1 in 10 people:*restlessness and hyperactivity (psychomotor hyperactivity)

MARKETED BY:

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(Additional information is available on request)