Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

BRIVETAM 25mg film coated tablets.
BRIVETAM 50mg film coated tablets.

2. Qualitative and quantitative composition

Brivetam 25 mg film-coated tablets

Each film-coated tablet contains 25 mg brivaracetam.

Brivetam 50 mg film-coated tablets

Each film-coated tablet contains 50 mg brivaracetam.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Brivetam 25 mg film-coated tablets

Olive green coloured round shaped biconvex film coated tablets having both side plain.

Brivetam 50 mg film-coated tablets.

Yellow coloured caplet shaped Film coated tablets having one side break line and other side plain.

4. Clinical particulars

4.1 Therapeutic indications

Brivetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

4.2 Posology and method of administration

Posology

The physician should prescribe the most appropriate formulation and strength according to weight and dose. The recommended posology for adults, adolescents and children from 2 years of age is summarised in the following table. The dose should be administered in two equally divided doses, approximately 12 hours apart.

Recommended starting dose	**Recommended maintenance dose**	**Therapeutic dose range***
Adolescents and children weighing 50 kg or more, and adults		
50 mg/day (or 100 mg/day)**	100 mg/day	50 - 200 mg/day
Adolescents and children weighing from 20 kg to less than 50 kg		
1 mg/kg/day (up to 2 mg/kg/day)**	2 mg/kg/day	1 – 4 mg/kg/day
Children weighing from 10 kg to less than 20 kg		
1 mg/kg/day (up to 2.5 mg/kg/day)**	2.5 mg/kg/day	1 – 5 mg/kg/day

** Based on individual patient response, the dose may be adjusted within this effective dose range.*
*** Based on physician's assessment of need for seizure control*

Adults

The recommended starting dose is either 50 mg/day or 100 mg/day based on physician's assessment of required seizure reduction versus potential side effects. Based on individual patient response and tolerability, the dose may be adjusted in the effective dose range of 50 mg/day to 200 mg/day.

Adolescents and children weighing 50 kg or more
The recommended starting dose is 50 mg/day. Brivaracetam may also be initiated at 100 mg/day based on physician's assessment of need for seizure control. The recommended maintenance dose is 100 mg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 50 mg/day to 200 mg/day.
Adolescents and children weighing from 20 kg to less than 50 kg
the recommended starting dose is 1 mg/kg/day. Brivaracetam may also be initiated at doses up to 2 mg/kg/day based on physician's assessment of need for seizure control. The recommended maintenance dose is 2 mg/kg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 1 mg/kg/day to 4 mg/kg/day.

Children weighing from 10 kg to less than 20 kg

The recommended starting dose is 1 mg/kg/day. Brivaracetam may also be initiated at doses up to 2.5 mg/kg/day based on physician's assessment of need for seizure control. The recommended maintenance dose is 2.5 mg/kg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 1 mg/kg/day to 5 mg/kg/day.

Missed doses

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 brivaracetam has to be discontinued, it is recommended that the dose is reduced gradually by 50 mg/day on a weekly basis.

For patients below the age of 16 years, if 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 1 mg/kg/day (for patients with a body weight less than 50 kg) or 50 mg/day (for patients with body weight of 50 kg or more) is reached.

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

Special populations

Elderly (65 years of age and above)

No dose adjustment is needed in elderly patients (see section 5.2).

The clinical experience in patients ≥ 65 years is limited.

Renal impairment

No dose adjustment is needed in patients with impaired renal function (see section 5.2). Brivaracetam is not recommended in end-stage renal disease patients undergoing dialysis due to lack of data. Based on data in adults, no dose adjustment is necessary in paediatric patients with impaired renal function. No clinical data are available in paediatric patients with renal impairment.

Hepatic impairment

Exposure to brivaracetam was increased in adult patients with chronic liver disease. In patients with hepatic impairment, the following adjusted doses, administered in 2 divided doses, approximately 12 hours apart, are recommended for all stages of hepatic impairment (see sections 4.4 and 5.2). No clinical data are available in paediatric patients with hepatic impairment.

Age and body weight	**Recommended starting dose**	**Recommended maximum daily dose**
Adolescents and children weighing 50 kg or more, and adults	50 mg/day	150 mg/day
Adolescents and children weighing from 20 kg to less than 50 kg	1 mg/kg/day	3 mg/kg/day
Children weighing from 10 kg to less than 20 kg	1 mg/kg/day	4 mg/kg/day

Paediatric patients less than 2 years of age

The efficacy of brivaracetam in paediatric patients aged less than 2 years has not yet been established.
Currently available data are described in section 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

Method of administration

Brivaracetam film-coated tablets must be taken orally and swallowed in whole with liquid and may be taken with or without food (see section 5.2). Patients not being able to swallow tablets in whole or patients for whom the dose can not be met with the use of whole tablets should use Brivaracetam 10 mg/ml oral solution.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour
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 clinical studies 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. See also section 4.8, paediatric data.

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 (see section 4.2).

Sodium content

Brivaracetam film-coated tablets contain less than 1 mmol sodium (23mg) per tablet,that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Formal interaction studies have only been performed in adults.

Pharmacodynamic 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 (see section 5.1).

Interaction with alcohol

In a 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.

Pharmacokinetic interactions

Effects of other medicinal products 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 (see section 5.2).

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. Limited clinical data are available implying that coadministration of cannabidiol may increase the plasma exposure of brivaracetam, possibly through CYP2C19 inhibition, but the clinical relevance is uncertain.

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 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 drugdrug 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).

Table 1: Pharmacokinetic interactions between brivaracetam and other AEDs

AED coadministered	**Influence of AED on brivaracetam plasma concentration**	**Influence of brivaracetam on AED plasma concentration**
Carbamazepine	AUC 29 % ↓ Cmax 13 % ↓ No dose adjustment required	Carbamazepine - None Carbamazepine-epoxide ↑ (See below) No dose adjustment required.
Clobazam	No data available	None
Clonazepam	No data available	None
Lacosamide	No data available	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None (monohydroxy derivative, MHD)
Phenobarbital	AUC 19 % ↓ No dose adjustment required	None
Phenytoin	AUC 21 % ↓ No dose adjustment required	None [a] AUC 20% ↑ [a] Cmax 20% ↑
Pregabalin	No data available	None
Topiramate	None	None
Valproic acid	None	None
Zonisamide	No data available	None

[a] based on a study involving the administration of a supratherapeutic dose of 400 mg/day brivaracetam.

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 clinical 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 oestrogen 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).

4.6 Pregnancy and Lactation

Women of childbearing potential

Physicians should discuss family planning and contraception with women of childbearing potential taking brivaracetam (see Pregnancy).

If a woman decides to become pregnant, the use of brivaracetam should be carefully re- evaluated.

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

For all anti-epileptic drugs, it has been shown that in the offspring of treated women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3 % in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the underlying condition is responsible has not been

elucidated. Discontinuation of anti-epileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Risk related to brivaracetam

There is a limited amount of data from the use of brivaracetam in pregnant women. There is no data on placental transfer in humans, but brivaracetam was shown to readily cross the placenta in rats (see section 5.3). The potential risk for humans is unknown. Animal studies did not detect any teratogenic potential of brivaracetam (see section 5.3).

In clinical studies, brivaracetam was used as adjunctive therapy and when it was used with carbamazepine, it induced a dose-related increase in the concentration of the active metabolite, carbamazepine-epoxide (see section 4.5). There is insufficient data to determine the clinical significance of this effect in pregnancy.

As a precautionary measure, brivaracetam should not be used during pregnancy unless clinically necessary i.e. (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

It is unknown whether brivaracetam is excreted in human breast milk. Studies in rats have shown excretion of brivaracetam in breast milk (see section 5.3). 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. In case of co-administration of brivaracetam and carbamazepine, the amount of carbamazepine-epoxide excreted in breast milk could increase. There is insufficient data to determine the clinical significance.

Fertility

No human data on the effect of brivaracetam on fertility are available. In rats, there was no effect on fertility with brivaracetam (see section 5.3).

4.7 Effects on ability to drive and use machines

Brivaracetam has minor or moderate influence on the ability to drive and use machines.

Due to possible differences in individual sensitivity some patients might experience somnolence, dizziness, and other central nervous system (CNS) related symptoms. Patients should be advised not to drive a car or to operate other potentially hazardous machines until they are

familiar with the effects of brivaracetam on their ability to perform such activities.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions (>10 %) with brivaracetam treatment were: somnolence (14.3 %) and dizziness (11.0 %). They were usually mild to moderate in intensity. Somnolence and fatigue were reported at a higher incidence with increasing dose.

The discontinuation rate due to adverse reactions was 3.5 %, 3.4 % and 4.0 % for patients randomized to brivaracetam at respectively the dose of 50 mg/day, 100 mg/day and 200 mg/day and 1.7 % for patients randomized to placebo. The adverse reactions most frequently resulting in discontinuation of brivaracetam therapy were dizziness (0.8 %) and convulsion (0.8 %).

Tabulated list of adverse reactions

In the table below, adverse reactions, which were identified based on review of the three placebo-controlled, fixed-dose studies safety database in subjects ≥ 16 years of age, are listed by System Organ Class and frequency.

The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reactions from clinical studies**
Infections and infestations	Common	Influenza
Blood and lymphatic system disorders	Uncommon	Neutropenia
Immune system disorders	Uncommon	Type I hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Depression, anxiety, insomnia, irritability
	Uncommon	Suicidal ideation, psychotic disorder, aggression, agitation
Nervous system disorders	Very common	Dizziness, somnolence
	Common	Convulsion, vertigo

Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory tract infections, cough
Gastrointestinal disorders	Common	Nausea, vomiting, constipation
General disorders and administration site conditions	Common	Fatigue

Description of selected adverse reactions

Neutropenia has been reported in 0.5 % (6/1099) brivaracetam patients and 0 % (0/459) placebo patients. Four of these subjects had decreased neutrophil counts at baseline, and experienced additional decrease in neutrophil counts after initiation of brivaracetam treatment. None of the 6 cases of neutropenia were severe, required any specific treatment or led to discontinuation of brivaracetam and none had associated infections.

Suicidal ideation has been reported in 0.3 % (3/1099) brivaracetam patients and 0.7 % (3/459) placebo patients. In the short-term clinical studies of brivaracetam in epilepsy patients, there were no cases of completed suicide and suicide attempt, however both have been reported in open-label extension studies (see section 4.4).

Reactions suggestive of immediate (Type I) hypersensitivity have been reported in a small number of brivaracetam patients (9/3022) during clinical development.

Paediatric population

The safety profile of brivaracetam observed in children from 1 month of age was consistent with the safety profile observed in adults. In the open label, uncontrolled, long-term studies suicidal ideation was reported in 4.7 % of paediatric patients assessed from 6 years onwards (more common in adolescents) compared with 2.4 % of adults and behavioural disorders were reported in 24.8 % of paediatric patients compared with 15.1 % of adults. The majority of events were mild or moderate in intensity, were non-serious, and did not lead to discontinuation of study drug. An additional adverse reaction reported in children was psychomotor hyperactivity (4.7 %).

No specific pattern of adverse event (AE) was identified in children from 1 month to < 4 years of age when compared to older paediatric age groups. No significant safety information was identified indicating the increasing incidence of a particular AE in this age group. As data available in children younger than 2 years of age is limited, brivaracetam is not indicated in this age range. No clinical data are available in neonates.

Elderly

Of the 130 elderly subjects enrolled in the brivaracetam phase 2/3 development program (44 with epilepsy), 100 were 65-74 years of age and 30 were 75-84 years of age. The safety profile in elderly patients appears to be similar to that observed in younger adult patients.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

There is no specific antidote for overdose with brivaracetam. Treatment of an overdose should include general supportive measures. Since less than 10 % of brivaracetam is excreted in urine, haemodialysis is not expected to significantly enhance brivaracetam clearance (see section 5.2).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX23

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. 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.

Clinical efficacy and safety

The efficacy of brivaracetam for the adjunctive therapy of partial onset seizures (POS) was established in 3 randomized, double-blind, placebo-controlled, fixed-dose, multi-center clinical studies in subjects 16 years of age and older. The daily dose of brivaracetam ranged from 5 to 200 mg/day across these studies. All studies had an 8-week baseline period followed by a 12-week treatment period with no up-titration. 1,558 patients received study drug of which 1,099 received brivaracetam. Study enrollment criteria required that patients have uncontrolled POS despite treatment with either 1 or 2 concomitant AEDs. Patients were required to have at least 8 POS during the baseline period. The primary

endpoints in the phase 3 studies were the percent reduction in POS frequency over placebo and the 50 % responder rate based on 50 % reduction in POS frequency from baseline.

The most commonly taken AEDs at the time of study entry were carbamazepine (40.6 %), lamotrigine (25.2 %), valproate (20.5 %), oxcarbazepine (16.0 %), topiramate (13.5 %), phenytoin (10.2 %) and levetiracetam (9.8 %). The median baseline seizure frequency across the 3 studies was 9 seizures per 28 days. Patients had a mean duration of epilepsy of approximately 23 years.

5.2 Pharmacokinetic properties

Brivaracetam film-coated tablets, oral solution and solution for intravenous injection show the same AUC,while the maximum plasma concentration is slightly higher after intravenous administration. Brivaracetam exhibits linear and time-independent pharmacokinetics with low intra- and inter- subject variability, and features complete absorption, very low protein binding, renal excretion following extensive biotransformation, and pharmacologically inactive metabolites.

Absorption

Brivaracetam is rapidly and completely absorbed after oral administration and the absolute bioavailablity is approximately 100 %. The median tmax for tablets taken without food is 1 hour (tmax range is 0.25 to 3 h).

Coadministration with a high-fat meal slowed down the absorption rate (median tmax 3 h) and decreased the maximum plasma concentration (37 % lower) of brivaracetam, while the extent of absorption remained unchanged.

Distribution

Brivaracetam is weakly bound (≤ 20 %) to plasma proteins. The volume of distribution is 0.5 L/kg, a value close to that of the total body water. Due to its lipophylicity (Log P) brivaracetam has high cell membrane permeability.

Biotransformation

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid (approximately 60 % the elimination), and secondarily by hydroxylation on the propyl side chain (approximately 30 % the elimination). The hydrolysis of the amide moiety leading to the carboxylic acid metabolite (34 % of the dose in urine) is supported by hepatic and extra-hepatic amidase. *In vitro*, the hydroxylation of brivaracetam is mediated primarily by CYP2C19. Both

metabolites, are further metabolised forming a common hydroxylated acid formed predominantly by hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). *In vivo*, in human subjects possessing ineffective mutations of CYP2C19, production of the hydroxy metabolite is decreased 10-fold while brivaracetam itself is increased by 22 % or 42 % in individuals with one or both mutated alleles. The three metabolites are not 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. Less than 1 % of the dose is excreted in faeces and less than 10 % of brivaracetam is excreted unchanged in urine. The terminal plasma half-life (t1/2) is approximately 9 hours. The total plasma clearance in patients was estimated to 3.6 L/h.

Linearity

Pharmacokinetics is dose-proportional from 10 to at least 600 mg.

Interactions with medicinal products

Brivaracetam is cleared by multiple pathways including renal excretion, non-CYP-mediated hydrolysis and CYP-mediated oxidations. *In vitro*, brivaracetam is not a substrate of human P-glycoprotein (P-gp), multidrug resistance proteins (MRP) 1 and 2, and likely not organic anion transporter polypeptide 1B1 (OATP1B1) and OATP1B3. In vitro assays showed that brivaracetam disposition should not be significantly affected by CYP (eg. CYP1A, CYP2C8, CYP2C9, CYP2D6 and CYP3A4) inhibitors. In vitro, brivaracetam was not an inhibitor of the CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4, or the transporters P-gp, BCRP, BSEP MRP2, MATE-K, MATE-1, OATP1B1, OATP1B3, OAT1 and OCT1 at clinically relevant concentrations. In vitro, brivaracetam did not induce CYP1A2.

Pharmacokinetics in special patient groups

Elderly (65 years of age and above)

In a study in elderly subjects (65 to79 years old; with creatinine clearance 53 to 98 ml/min/1.73 m^2) receiving brivaracetam 400 mg/day in bid administration, 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 similar (0.76 ml/min/kg) to young healthy male subjects (0.83 ml/min/kg) (see section 4.2).
Renal impairment

A study in subjects with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m² and not requiring dialysis) revealed that the plasma AUC of brivaracetam was moderately increased (+21 %) relative to healthy controls, while the AUC of the acid, hydroxy and hydroxyacid metabolites were increased 3-, 4-, and 21-fold, respectively. The renal clearance of these non active metabolites was decreased 10-fold. The hydroxyacid metabolite did not reveal any safety concerns in non clinical studies. Brivaracetam has not been studied in patients undergoing hemodialysis (see section 4.2).

Hepatic impairment

A pharmacokinetic study in subjects with hepatic cirrhosis (Child-Pugh classes A, B, and C) showed similar increases in exposure to brivaracetam irrespective of disease severity (50 %, 57 % and 59 %), relative to matched healthy controls. (see section 4.2).

Body weight

A 40 % decrease in steady-state plasma concentration has been estimated across a body weight range from 46 kg to 115 kg. However, this is not considered to be a clinically relevant difference.

Gender

There are no clinically relevant differences in the pharmacokinetics of brivaracetam by gender.

Race

The pharmacokinetics of brivaracetam was not significantly affected by race (Caucasian, Asian) in a population pharmacokinetic modeling from epilepsy patients. The number of patients with other ethnic background was limited.

Pharmacokinetic/pharmacodynamics relationship

The EC50 (brivaracetam plasma concentration corresponding to 50 % of the maximum effect) was estimated to be 0.57 mg/L. This plasma concentration is slightly above the median exposure obtained after brivaracetam doses of 50 mg/day. Further seizure frequency reduction is obtained by increasing the dose to 100 mg/day and reaches a plateau at 200 mg/day.

Paediatric population
In a pharmacokinetic study with a 3-week evaluation period and weekly fixed 3-step up- titration using the brivaracetam oral solution, 99 subjects aged 1 month to < 16 years were evaluated. Brivaracetam was

administered at weekly increasing doses of approximately 1 mg/kg/day, 2 mg/kg/day, and 4 mg/kg/day. All doses were adjusted by body weight, and did not exceed a maximum of 50 mg/day, 100 mg/day, and 200 mg/day. At the end of the evaluation period, subjects may have been eligible for entry into a long-term follow-up study continuing on their last received dose (see section 4.8). Plasma concentrations were shown to be dose-proportional in all age groups. Population pharmacokinetics modeling was performed based on sparse plasma concentration data collected in the 3-week PK study and the ongoing long-term follow-up study. 232 paediatric patients with epilepsy, aged 2 months to 17 years, were included in the analysis. The analysis indicated that doses of 5.0 (body weights 10-20 kg) and 4.0 mg/kg/day (body weights 20-50 kg) provide the same steady-state average plasma concentration as in adults receiving 200 mg/day. The estimated plasma clearance was 0.96 L/h, 1.61 L/h, 2.18 L/h and 3.19 L/h for children weighing 10 kg, 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). Currently, no clinical data are available in neonates.

5.3 Preclinical safety data

In safety pharmacology studies, the predominant effects were CNS related (mainly transient CNS depression and decreased spontaneous locomotor activity) seen at multiples (greater than 50 fold) of the pharmacologically active dose of brivaracetam, 2 mg/kg. Learning and memory function were not affected.

Findings not observed in clinical studies, but seen in the repeated-dose toxicology dog studies at exposure similar to the clinical plasma AUC, were hepatotoxic effects (mainly porphyria). However, toxicological data accumulated on brivaracetam and on a structurally- related compound indicate that the dog liver changes have developed through mechanisms not relevant for humans. No adverse liver changes were seen in rats and monkeys following chronic administration of brivaracetam at 5- and 42-fold the clinical AUC exposure. In monkeys, CNS signs (prostrate, loss of balance, clumsy movements) occurred at 64 fold the clinical Cmax, these effects being less apparent over time.

Genotoxicity studies have not detected any mutagenic or clastogenic activity. Carcinogenicity studies did not indicate any oncogenic potential in rats, whereas increased incidences of hepatocellular tumors in male mice are considered to result of a non- genotoxic, mode of action linked to a phenobarbitone-like liver enzyme induction, which is a known rodent specific phenomenon.

Brivaracetam did not affect male or female fertility and has demonstrated no teratogenic potential in either rat or rabbit.

Embryotoxicity was observed in rabbits at a maternal toxic dose of brivaracetam with an exposure level 8-fold the clinical AUC exposure at the maximum recommended dose. In rats, brivaracetam was shown to readily cross the placenta and to be excreted in milk of lactating rats with concentrations similar to maternal plasma levels.

Brivaracetam did not show any dependence potential in rats.

Juvenile animals studies
In juvenile rats, brivaracetam exposure levels 6- to 15-fold the clinical AUC exposure at the maximum recommended dose induced developmental adverse effects (i.e. mortality, clinical signs, decreased body weight and lower brain weight). There were no adverse effects on CNS function, neuropathological and brain histopathological examination. In juvenile dogs, the brivaracetam-induced changes at the exposure level 6- fold the clinical AUC were similar to those observed in adult animals. There were no adverse effects in any of the standard developmental or maturation endpoints.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline cellulose, Dibasic calcium phosphate, Isopropyl alcohol, Purified Talc, Colloidal silicon dioxide, Microcrystalline cellulose N102, Povidone K 30, Easy coat Iron oxide yellow AFC, Easy coat Iron oxide Black & Purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

2 years

6.4 Special Precautions for storage

Store below 30° C. Protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and Content of container

Brivacetam Tablets are packaged in Alu-Alu blisters. Pack size of 10 tablets packed in printed carton along with insert.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing Authorization Holder

Tiba healthcare Ltd.
PO BOX- 243-00623,
Nairobi, Kenya.

8. Marketing Authorization Number

BRIVETAM 25MG TABLET
CTD11096

BRIVETAM 50MG TABLET
CTD11098

9. Date of first authorization/renewal of the authorization

09/07/2024

10. Date of revision of the text

10/5/2025