1. NAME OF THE MEDICINAL PRODUCT

Briviact oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg brivaracetam.

Excipient(s) with known effect
Each ml of oral solution contains 239.8 mg sorbitol (E420), 1 mg methyl parahydroxybenzoate (E218) and maximum 5.5 mg propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution
Slightly viscous, clear colourless to yellowish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Briviact is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 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. It is recommended to parent and care giver to administer Briviact oral solution with the measuring device (10 ml or 5 ml oral dosing syringe) provided in the carton box.

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. The dose should be administered in two equally divided doses, once in the morning and once in the evening. Based on individual patient response and tolerability, the dose may be adjusted in the dose range of 50 mg/day to 200 mg/day.

Children (from 4 years of age) and adolescents weighing 50 kg or more
The recommended starting dose is 50mg/day. Brivaracetam may also be initiated at 100 mg/day based on physician's assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening.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.

Children (from 4 years of age) and adolescents weighing less than 50 kg
The recommended starting dose is 1mg/kg/day. Brivaracetam may also be initiated at 2 mg/kg/day based on physician's assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening. 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.

The following table summarises the recommended posology for children from 4 years of age and adolescents.

	Children (≥4 years) and adolescents ≥50 kg Administered in 2 equally divided doses	Children (≥4 years) and adolescents <50 kg Administered in 2 equally divided doses
Therapeutic dose range	50 - 200 mg/day	1 - 4 mg/kg/day
Recommended starting dose	50 mg/day (or 100 mg/day)*	1 mg/kg/day (or 2 mg/kg/day)*
Recommended maintenance dose	100 mg/day	2 mg/kg/day

* Based on physician's assessment of need for seizure control.

The dose per intake for each patient should be calculated using the following formula:

Volume per administration (ml) = [weight (kg) x daily dose (mg/kg/day)] x 0.05

The table below provides examples of volumes of oral solution per intake depending on prescribed dose and body weight. The precise volume of oral solution is to be calculated according to the exact body weight of the child.

	Volumes of oral solution to be taken per administration			
Weight	*For a dose of 1 mg/kg/day* **0.05 ml/kg/intake** (corresponding to 0.5 mg/kg/intake)	*For a dose of 2 mg/kg/day* **0.1 ml/kg/intake** (corresponding to 1 mg/kg/intake)	*For a dose of 3 mg/kg/day* **0.15 ml/kg/intake** (corresponding to 1.5 mg/kg/intake)	*For a dose of 4 mg/kg/day* **0.2 ml/kg/intake** (corresponding to 2 mg/kg/intake)
10 kg	0.5 ml (5 mg)	1 ml (10 mg)	1.5 ml (15 mg)	2 ml (20 mg)
15 kg	0.75 ml (7.5 mg)	1.5 ml (15 mg)	2.25 ml (22.5 mg)	3 ml (30 mg)
20 kg	1 ml (10 mg)	2 ml (20 mg)	3 ml (30 mg)	4 ml (40 mg)
25 kg	1.25 ml (12.5 mg)	2.5 ml (25 mg)	3.75 ml (37.5 mg)	5 ml (50 mg)
30 kg	1.5 ml (15 mg)	3 ml (30 mg)	4.5 ml (45 mg)	6 ml (60 mg)
35 kg	1.75 ml (17.5 mg)	3.5 ml (35 mg)	5.25 ml (52.5 mg)	7 ml (70 mg)
40 kg	2 ml (20 mg)	4 ml (40 mg)	6 ml (60 mg)	8 ml (80 mg)
45 kg	2.25 ml (22.5 mg)	4.5 ml (45mg)	6.75 ml (67.5 mg)	9 ml (90 mg)
50 kg	2.5 ml (25 mg)	5 ml (50 mg)	7.5 ml (75 mg)	10 ml (100 mg)

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
If brivaracetam has to be discontinued it is recommended to withdraw it gradually by 50 mg/day on a weekly basis. 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.

Hepatic impairment
Exposure to brivaracetam was increased in adult patients with chronic liver disease. In adults, a 50 mg/day starting dose should be considered. In children and adolescents weighing 50 kg or greater, a 50 mg/day starting dose is recommended. A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment (see sections 4.4 and 5.2).
In children and adolescents weighing less than 50 kg, a 1 mg/kg/day starting dose is recommended. The maximum dose should not exceed 3 mg/kg/day. No clinical data are available in paediatric patients with hepatic impairment.

Children less than 4 years
The safety and efficacy of brivaracetam in children aged less than 4 years have 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 oral solution can be diluted in water or juice shortly before swallowing and may be taken with or without food (see section 5.2). A nasogastric tube or a gastrostomy tube may be used when administering brivaracetam oral solution.

Briviact oral solution is provided with a 5 ml and a 10 ml oral dosing syringe with their adaptor.

Oral dosing syringe (5 ml graduated every 0.1 ml) with an adaptor, recommended for use by patients weighing less than 20 kg or needing a maximum of 50 mg (5 ml) brivaracetam per administration.
The 5 ml oral syringe must be used in patients weighing less than 20 kg to ensure accurate dosing as the 10 ml oral syringe does not allow accurate measurements of volumes <1 ml.
One full 5 ml oral dosing syringe corresponds to 50 mg of brivaracetam. The minimum extractible volume is 0.25 ml which is 2.5 mg of brivaracetam. As from the 0.1 ml graduation mark, each graduation corresponds to 0.1 ml which is 1 mg of brivaracetam. Additional graduations at 0.25 ml and 0.75 ml starting at 0.25 ml up to 5 ml are shown.

Oral dosing syringe (10 ml graduated every 0.25 ml) with an adaptor, recommended for use by patients weighing more than 20 kg or needing a dose between 50 mg and 100 mg (5 ml to 10 ml) brivaracetam per administration.
One full 10 ml oral dosing syringe corresponds to 100 mg of brivaracetam. The minimum extractible volume is 1 ml which is 10 mg of brivaracetam. As from the 1 ml graduation mark, each graduation corresponds to 0.25 ml which is 2.5 mg of brivaracetam.

Instructions for use are provided in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or other pyrrolidone derivatives 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 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. 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).

Excipients

Sodium content
Brivaracetam oral solution contains less than 1 mmol sodium (23mg) per ml, that is to say essentially 'sodium free'.

Fructose intolerance
This medicine contains 239.8 mg sorbitol (E420) in each ml. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Excipients which may cause intolerance
The oral solution contains methyl parahydroxybenzoate (E218), which may cause allergic reactions (possibly delayed).
Brivaracetam oral solution contains propylene glycol (E1520).

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 C_{max} 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 C_{max}).

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 % ↓ C_{max} 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] C_{max} 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 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).

4.6 Fertility, 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 (8.2 %) 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.

System organ class	Frequency	Adverse reactions from clinical trials
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 % (6/1,099) 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 % (3/1,099) 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 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 (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 %).

There are limited safety data from open-label studies in children from 1 month to <4 years of age. Limited data are available on neurodevelopment in children <4 years of age. 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

Symptoms

There is limited clinical experience with brivaracetam overdose in humans. Somnolence and dizziness have been reported in a healthy subject taking a single dose of 1,400 mg of brivaracetam.

Management of 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 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.
The efficacy outcomes are summarized in Table 2. Overall, brivaracetam was efficacious for the adjunctive treatment of partial onset seizures in patients 16 years of age and older between 50 mg/day and 200 mg/day.

Table 2: Key Efficacy Outcomes for Partial Onset Seizure Frequency per 28 Days

Study	**Placebo**	**Brivaracetam** * Statistically significant **(p-value)**		
		50 mg/day	**100 mg/day**	**200 mg/day**
Study N01253(1)				
	n= 96	n= 101		
50 % Responder rate	16.7	32.7* (p=0.008)	~	~
Percent reduction over placebo (%)	NA	22.0* (p=0.004)	~	~
Study N01252(1)				
	n = 100	n = 99	n = 100	
50 % Responder rate	20.0	27.3 (p=0.372)	36.0(2) (p=0.023)	~
Percent reduction over placebo (%)	NA	9.2 (p=0.274)	20.5(2) (p=0.010)	~
Study N01358				
	n = 259		n = 252	n = 249
50% Responder rate	21.6	~	38.9* (p<0.001)	37.8* (p<0.001)
Percent reduction over placebo (%)	NA	~	22.8* (p<0.001)	23.2* (p<0.001)

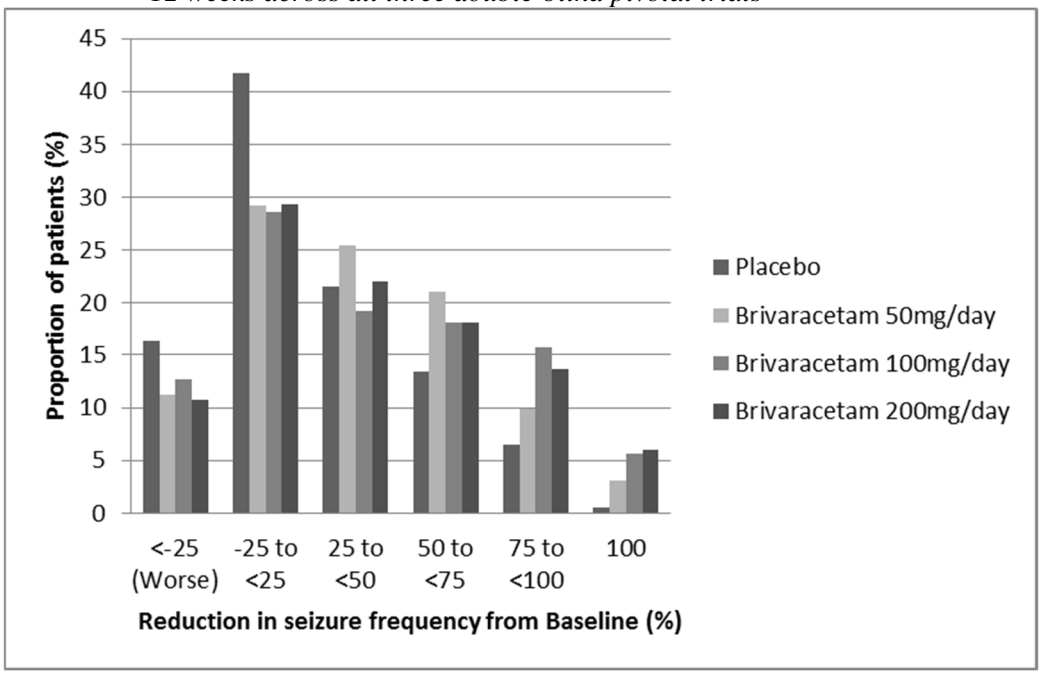
n = randomised patients who received at least 1 dose of study medication
~ Dose not studied
* Statistically significant
(1) Approximately 20 % of the patients were on concomitant levetiracetam
(2) The primary outcome for N01252 did not achieve statistical significance based on the sequential testing procedure . The 100 mg/day dose was nominally significant.

In clinical studies, a reduction in seizure frequency over placebo was higher with the dose of 100 mg/day than with 50 mg/day. Apart from dose-dependent increases in incidences of somnolence and fatigue brivaracetam 50 mg/day and 100 mg/day had a similar safety profile including CNS-related AEs and with long-term use.

Figure 1 shows the percentage of patients (excluding patients with concomitant levetiracetam) by category of reduction from baseline in POS frequency per 28 days in all 3 studies. Patients with more than a 25 % increase in POS are shown at left as “worse”. Patients with an improvement in percent reduction in baseline POS frequency are shown in the 4 right-most categories. The percentages of

patients with at least a 50 % reduction in seizure frequency were 20.3 %, 34.2 %, 39.5 %, and 37.8 % for placebo, 50 mg/day, 100 mg/day, and 200 mg/day, respectively.

Figure 1: Proportion of patients by category of seizure response for brivaracetam and placebo over 12 weeks across all three double-blind pivotal trials



In a pooled analysis of the three pivotal trials, no differences in efficacy (measured as 50 % responder rate) was observed within the dose range of 50 mg/day to 200 mg/day when brivaracetam is combined with inducing or non-inducing AEDs. In clinical studies 2.5 % (4/161), 5.1 % (17/332) and 4.0% (10/249) of the patients on brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively became seizure free during the 12-week treatment period compared with 0.5 % (2/418) on placebo.

Improvement in the median percent reduction in seizure frequency per 28 days has been observed in patients with type IC seizure (secondary generalized tonic-clonic seizures) at baseline treated with brivaracetam (66.6 % (n=62), 61.2 % (n=100) and 82.1 % (n=75) of the patients on brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively as compared to placebo 33.3 % (n=115)).

The efficacy of brivaracetam in monotherapy has not been established. Brivaracetam is not recommended for use in monotherapy.

Treatment with levetiracetam

In two phase 3 randomised placebo-controlled studies, levetiracetam was administered as concomitant AED in about 20 % of the patients. Although the number of subjects is limited, there was no observed benefit of brivaracetam versus placebo in patients taking levetiracetam concurrently which may reflect competition at the SV2A binding site. No additional safety or tolerability concerns were observed.

In a third study, a pre-specified analysis demonstrated efficacy over placebo for 100 mg/day and 200 mg/day in patients with prior exposure to levetiracetam. The lower efficacy observed in these patients compared to the leveticacetam-naïve patients was likely due to the higher number of prior AEDs used and higher baseline seizure frequency.

Elderly (65 years of age and above)
The three pivotal double-blind placebo-controlled studies included 38 elderly patients aged between 65 and 80 years. Although data are limited, the efficacy was comparable to younger subjects.

Open label extension studies
Across all studies, 81.7 % of the patients who completed randomized studies were enrolled in the long-term open-label extension studies. From entry into the randomized studies,5.3 % of the subjects exposed to brivaracetam for 6 months (n=1,500) were seizure free compared to 4.6 % and 3.7 % for subjects exposed for 12 months (n=1,188) and 24 months (n=847), respectively. However, as a high proportion of subjects (26%) discontinued from the open-label studies due to lack of efficacy, a selection bias may have occurred, as the subjects who stayed in the study responded better than those who have terminated prematurely.
In patients who were followed up in the open-label extension studies for up to 8 years, the safety profile was similar to that observed in the short-term, placebo-controlled studies.

Paediatric population

In children aged 4 years and older, partial onset seizures have a similar clinical expression to those in adolescents and adults. Experience with epilepsy medicines suggests that the results of efficacy studies performed in adults can be extrapolated to children down to the age of 4 years provided the paediatric dose adaptations are established and safety has been demonstrated (see sections 5.2 and 4.8). Doses in patients from 4 years of age were defined by weight-based dose adaptations which have been established to achieve similar plasma concentrations to the ones observed in adults taking efficacious doses (section 5.2).

A long-term, uncontrolled, open-label safety study included children (from 4 years to less than 16 years) who continued treatment after completing the PK study (see section 5.2) and children directly enrolled into the safety study. Children who directly enrolled received a brivaracetam starting dose of 1 mg/kg/day and depending on response and tolerability, the dose was increased up to 5 mg/kg/day by doubling the dose at weekly intervals. No child received a dose greater than 200 mg/day. For children weighing 50 kg or greater the brivaracetam starting dose was 50 mg/day and depending on response and tolerability, the dose was increased up to a maximum of 200 mg/day by weekly increments of 50 mg/day.

From the pooled open-label safety and PK studies in adjunctive therapy, 149 children have received brivaracetam, of whom 116 have been treated for ≥6 months, 107 for ≥12 months, 58 for ≥24 months, and 28 for ≥36 months.

The efficacy and tolerability of brivaracetam in paediatric patients less than 4 years of age have not been established (see section 4.2). Brivaracetam was evaluated in these patients in a short term open-label pharmacokinetic study and an ongoing open-label extension study, in 16 subjects from 1 month to <4 years of age (see section 5.2).

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 t_{max} for tablets taken without food is 1 hour (t_{max} range is 0.25 to 3 h).
Coadministration with a high-fat meal slowed down the absorption rate (median t_{max} 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, 2C8, 2C9, 2D6 and 3A4) inhibitors.

In vitro, brivaracetam was not an inhibitor of the CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 3A4, 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 m²) 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 indicated that the dose of 2.0 mg/kg twice a day provides the same steady-state average plasma concentration as in adults receiving 100 mg twice daily. The estimated plasma clearance was 1.61 L/h, 2.18 L/h and 3.19 L/h for children 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). 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 C_{max}, 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

Sorbitol liquid (E420)
Glycerol (E422)
Sucralose
Raspberry flavour (propylene glycol (E1520) 90 % - 98 %)
Carmellose sodium
Sodium citrate
Methyl parahydroxybenzoate (E218)
Citric acid anhydrous (for pH-adjustment)
Purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiery date of the product is indicated on the packaging materials.
After first opening: 5 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. It is recommended to store the product at room temperature.

6.5 Nature and contents of container

300 ml amber glass bottle (type III) with a white child resistant closure (polypropylene) in a box also containing a 5 ml and 10 ml graduated oral dosing syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product, neat or diluted, or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. REGISTRATION HOLDER

NEOPHARM LTD,
6 Hashiloach St.,
POB 7063,
Petach Tiqva 4951439,
Israel.

9. REGISTRATION NUMBER

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