SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam Tablets USP 500 mg

2. QUALITATIVE AND QUANTITAVE COMPOSITION

Each Film coated tablet contains:

Levetiracetam USP 500 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM, DOSAGE AND THE ROUTE OF ADMINISTRATION

Tablets, 500mg, Oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Levetiracetam is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

4.2 Posology and method of administration

Posology

Partial onset seizures

The recommended dosing for monotherapy (from 16 years of age) and adjunctive therapy is the same; as outlined below.

All indications

Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of

treatment. However, a lower initial dose of 250 mg twice daily may be given based on physician assessment of seizure reduction versus potential side effects. This can be increased to 500 mg twice daily after two weeks.

Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 250 mg or 500 mg twice daily increases or decreases every two to four weeks.

Adolescents (12 to 17 years) weighing below 50 kg and children from 1 month of age

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to weight, age and dose. Refer to Paediatric population section for dosing adjustments based on weight.

Discontinuation

If Levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g*. in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

Special populations

Elderly (65 years and older)

Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Renal impairment" below).

Renal impairment

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighing 50 kg or more, the following formula:

$$\text{CLcr (ml/min)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ for women})$$

Then CLcr is adjusted for body surface area (BSA) as follows:

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m}^2\text{)}} \times 1.73$$

Dosing adjustment for adult and adolescent patients weighing more than 50 kg with impaired renal function

Group	Creatinine clearance(ml/min/1.73m^2)	Dose and frequency
Normal	≥ 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patien sunder going dialysis [(1)]	-	500 to 1,000 mg once daily [(2)]

[(1)] A 750 mg loading dose is recommended on the first day of treatment with Levetiracetam.

[(2)] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, Levetiracetam dose needs to be adjusted based on the renal function as Levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m^2 may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescent patients weighing less than 50 kg with impaired renal function

Group	Creatinine clearance (ml/min/1.73m^2)	Dose and frequency [1]	
		Infants 1 to less than (months	Infants 6 to 23 months children & adolescent weighing less than 50 kg
Normal	≥ 80	7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105ml/kg) twice daily	to 15 mg/kg (0.05 to 0.15ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10ml/kg) twice daily
End-stage rena disease patient undergoing dialysis		7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily (2) (4)	10 to 20 mg/kg (0.10 to 0.20ml/kg) once daily (3) (5)

[1] Levetiracetam oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

[2] A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with Levetiracetam.

[3] A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with Levetiracetam.

[4] Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.

[5] Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

Hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with

severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore, a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73m^2.

Paediatric population

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Levetiracetam oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Levetiracetam oral solution should be used.

Monotherapy

The safety and efficacy of Levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established.

No data available.

Adolescents (16 and 17 years of age) weighing 50 kg or more with partial onset seizures with or without secondary generalisation with newly diagnosed epilepsy.

Please refer to the above section on Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more

Add-on therapy for infants aged from 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg

Levetiracetam oral solution is the preferred formulation for use in infants and children under the age of 6 years.

For children 6 years and above, Levetiracetam oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets

The lowest effective dose should be used for all indications. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily.

Dose in children 50 kg or greater is the same as in adults for all indications.

Please refer to the above section on Adults (≥18 years) and adolescents (12 to 17 years) weighing 50

kg or more for all indications.

Add-on therapy for infants aged from 1 month to less than 6 months
The oral solution is the formulation to use in infants.

Method of administration
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of Levetiracetam may be experienced. The daily dose is administered in two equally divided doses.

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
Renal impairment
The administration of Levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section4.2).

Acute Kidney injury
The use of Levetiracetam has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months.

Blood cell counts
Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with Levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

Suicide
Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including Levetiracetam). A meta-analysis of randomized placebo-controlled

trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Abnormal and aggressive behaviours

Levetiracetam may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness. Patients treated with Levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes.

If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered. If discontinuation is considered, please refer to section 4.2.

Worsening of seizures

As with other types of antiepileptic drugs, Levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after Levetiracetam initiation or increase of the dose, and was reversible upon drug discontinuation or dose decrease. Patients should be advised to consult their physician immediately in case of aggravation of epilepsy.

Lack of efficacy or seizure worsening has been reported in patients with epilepsy associated with sodium voltage-gated channel alpha subunit 8 (SCN8A) mutations.

Electrocardiogram QT interval prolongation

Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Paediatric population

The tablet formulation is not adapted for use in infants and children under the age of 6 years.

Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

4.5 Interaction with other medicinal products and other forms of interaction.

Antiepileptic medicinal products

Pre-marketing data from clinical studies conducted in adults indicate that Levetiracetam did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Levetiracetam.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day Levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered Levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate.

However, data suggested a 20% higher Levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite but not of Levetiracetam. Nevertheless, the concentration of this metabolite remain slow.

Methotrexate

Concomitant administration of Levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and Levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.

Oral contraceptives and other pharmacokinetics interactions

Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of Levetiracetam.

Laxatives

There have been isolated reports of decreased Levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral Levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking Levetiracetam.

Food and alcohol

The extent of absorption of Levetiracetam was not altered by food, but the rate of absorption was slightly reduced.

No data on the interaction of Levetiracetam with alcohol are available.

4.6 Pregnancy and lactation

Women of child bearing potential

Specialist advice should be given to women who are of childbearing potential. Treatment with Levetiracetam should be reviewed when a woman is planning to become pregnant. As with all antiepileptic medicines, sudden discontinuation of Levetiracetam should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple antiepileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated anti-epileptics.

Pregnancy

A large amount of post-marketing data on pregnant women exposed to Levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the 1st trimester) do not suggest an increase in the risk for major congenital malformations. Only limited evidence is available on the neurodevelopment of children exposed to Levetiracetam monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays.

Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended.

Physiological changes during pregnancy may affect Levetiracetam concentration. Decrease in Levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (upto 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with Levetiracetam should be ensured.

Breastfeeding

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if Levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

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

Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The adverse reaction profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3,416 patients treated with Levetiracetam. These data are supplemented with the use of Levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The safety profile of Levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

MedDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Infections & infestations	Nasopharyngitis			Infection	
Blood & lymphatic system disorders			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis	
Immune system disorders				Drug reaction with eosinophilia and systemic symptoms(DRESS)[(1)], Hypersensitivity (including angioedema and anaphylaxis	
Metabolism & nutrition disorders		Anorexia	Weight decreased, weight increase	Hyponatraemia	
Psychiatric disorders		Depression, hostility/ aggression, anxiety, insomnia, nervousness/ irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal, delirium	Obsessive compulsive disorder [(2)]
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness,	Amnesia, memory impairment, coordination abnormal/ataxia,	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance,	

		lethargy, tremor	paraesthesia, disturbance inattention	encephalopathy, seizures aggravated, Neuroleptic malignant syndrome(3)	
Eye disorders			Diplopia, vision blurred		
Ear and labyrinth disorders		Vertigo			
Cardiac disorders				Electrocardiogram QT prolonged	
Respiratory, thoracic and mediastinal disorders		Cough			
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis	
Hepatobiliary disorders			Liver function test abnormal	Hepatic failure, hepatitis	
Renal and Urinary Disorders				Acute Kidney injury	
Skin and subcutaneous tissue disorders		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme	

Musculoskeletal and connective tissue disorders			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased[3]	
General disorders and administration site conditions		Asthenia/fatigue			
Injury, poisoning and procedural complications			Injury		

[1] See Description of selected adverse reactions.

[2] Very rare cases of development of obsessive-compulsive disorders (OCD) in patients with underlying history of OCDor psychiatric disorders have been observed in post-marketing surveillance.

[3] Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Description of selected adverse reactions

Multi-organ hypersensitivity reactions

Multi-organ hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported rarely in patients treated with Levetiracetam. Clinical manifestations may develop 2 to 8weeks after starting treatment. These reactions are variable in expression, but typically present with fever, rash, facial oedema, lymphadenopathies, hematologic abnormalities and can be associated with involvement of different organ systems, mostly the liver. If multi-organ hypersensitivity reaction is suspected, Levetiracetam should be discontinued.

The risk of anorexia is higher when Levetiracetam is co-administered with Topiramate.

In several cases of alopecia, recovery was observed when Levetiracetam was discontinued.

Bone marrow suppression was identified in some of the cases of pancytopenia.

Cases of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with Levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with Levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with Levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with Levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of Levetiracetam.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for Levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction profile of Levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of Levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%),

mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Levetiracetam was not different (non-inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioral and emotional functioning indicated a worsening in Levetiracetam treated patients on aggressive behavior as measured in a standardized and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However, subjects who took Levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioral and emotional functioning; in particular measures of aggressive behavior were not worse than baseline.

4.9 Overdose

Symptoms

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Levetiracetam overdoses.

Management of overdose

After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for Levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyzer extraction efficiency is 60 % for Levetiracetam and 74 % for the primary metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-epileptics, other anti-epileptics, ATC code: N03AX14.

The active substance, Levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

The mechanism of action of Levetiracetam still remains to be fully elucidated. *In vitro* and *in vivo* experiments suggest that Levetiracetam does not alter basic cell characteristics and normal neurotransmission.

In vitro studies show that Levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca2+ from intraneuronal stores. In addition it partially reverses the reductions in GABA-and glycine-gated currents induced by zinc and β-carbolines. Furthermore, Levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between Levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamics effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalized seizures without having a pro-convulsants effect. The primary metabolite is inactive.

In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photo paroxysmal response) has confirmed the broad spectrum pharmacological profile of Levetiracetam.

Clinical efficacy and safety

Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy.

In adults, Levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled

studies at 1000 mg, 2000mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%, 31.6% and 41.3% for patients on 1000, 2000 or 3000 mg Levetiracetam respectively and of 12.6% for patients on placebo.

Paediatric population

In paediatric patients (4 to 16 years of age), Levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received Levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing).

44.6% of the Levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

In paediatric patients (1 month to less than 4 years of age), Levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was use in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percent of patients with ≥50% reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6% of the Levetiracetam treated patients and 19.6% of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6% of the patients were seizure-free for at least 6 months and 7.8% were seizure-free for at least 1 year.

35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control

clinical studies of which only 13 were aged < 6 months.

Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16years of age with newly diagnosed epilepsy.

Efficacy of Levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or Levetiracetam 1000 - 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response.

Six-month seizure freedom was achieved in 73.0% of Levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on Levetiracetam and on carbamazepine CR respectively).

In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to Levetiracetam adjunctive therapy (36 adult patients out of 69).

Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.

In this study, Levetiracetam, dose was 3000 mg/day given in 2 divided doses.

58.3% of the Levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which

included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, Levetiracetam dose was 3000mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses.

72.2% of the Levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and inpatients with epilepsy.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of Levetiracetam expressed as mg/kg bodyweight. Therefore there is no need for plasma level monitoring of Levetiracetam.

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

Adults and adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %.

Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of at twice daily administration schedule.

Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively.

The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.

Neither Levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %).

The volume of distribution of Levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Biotransformation

Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P_{450} isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose).

Other unidentified components accounted only for 0.6 % of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either Levetiracetam or its primary metabolite.

In vitro, Levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 AND UGT1A6) and epoxide hydroxylase activities. In addition, Levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

In human hepatocytes in culture, Levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4. The in vitro data and in vivo interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, the interaction of Levetiracetam with other substances, or *vice versa,* is unlikely.

Elimination

The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion *via* faeces accounted for only 0.3 % of the dose.

The cumulative urinary excretion of Levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.

The renal clearance of Levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that Levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

Elderly

In the elderly, the half-life is increased by about 40 % (10 to 11 hours). This is related to the decrease in renal function in this population (see section 4.2).

Renal impairment

The apparent body clearance of both Levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of Levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2).

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively.

The fractional removal of Levetiracetam was 51 % during a typical 4-hour dialysis session.

Hepatic impairment

In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of Levetiracetam. In most subjects with severe hepatic impairment, the clearance of Levetiracetam was reduced by more than 50 % due to a concomitant renal impairment (see section 4.2).

Paediatric population

Children (4 to 12 years)

Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half-life of Levetiracetam was 6.0 hours. The apparent body weight adjusted clearance was approximately 30 % higher than in epileptic adults.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years), Levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 ml/min/kg.

Infants and children (1 month to 4 years)

Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), Levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96 ml/min/kg).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of Levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical

use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800mg/kg/day (x 6 the MRHD on a mg/m2 or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryo mortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m2 basis) and 1200 mg/kg/day for fetuses.

Four embryo - foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m2 basis).

A peri- and post-natal development study was performed in rats with Levetiracetam doses of 70, 350 and 1800mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the

F1 offspring up to weaning (x 6 the MRHD on a mg/m2 basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6 – 17 the MRHD on a mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch USP, Povidone USP (K-30), Purified Water, Microcrystalline Cellulose USP (PLAIN), Croscarmellose Sodium USP (PRIMELLOSE), Colloidal Silicon Dioxide USP (AEROSIL-200), Magnesium Stearate USP, Hypromellose (HPMC 15 CPs), Talc, Titanium

Dioxide, Polyethylene Glycol (PEG 6000), Indigo Carmine Lake, Isopropyl Alcohol, Methylene Chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Keep away from reach of children

6.5 Nature and contents of container

Alu-Alu Pack of 10 tablets

6.6 Special precautions for disposal and other handling

There is no special requirement for disposal.

6.7 Inscription in a list of poisonous substances
List I

7. Marketing Authorization Holder

Address of applicant
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