

Summary of Product Characteristics

1. Name of the Medical Product

Levetiracetam Symgens 500 mg/100 mL Solution for Injection

2. Quality and Quantitative Composition

Each ml contains 100 mg levetiracetam.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

A clear, colorless solution filled in a 100-mL bag. Free from visible particles.

4. Clinical Particulars

4.1 Therapeutic indication

Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalization 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 and children from 4 years of age with epilepsy; myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy; primary generalized tonic-clonic seizures in adults, adolescents and children from 6 years of age with idiopathic generalised epilepsy.

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

4.2 Posology and method of administration

Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

Levetiracetam concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion (see Cautions for Usage).

There is no experience with administration of intravenous levetiracetam for longer period than 4 days.

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

Adults: Monotherapy: Adults and adolescents from 16 years of age: The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after 2 weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1,500 mg twice daily.

Add-on therapy: 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.

Depending upon the clinical response and tolerance, the daily dose can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

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

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 previously mentioned cases levetiracetam oral solution should be used.

Monotherapy: The initial therapeutic dose is 10 mg/kg twice daily.

Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increments or decrements of 10 mg/kg twice daily

every two weeks. The lowest effective dose should be used.

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

Dose recommendations for children and adolescents: (See Table 1.)

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
15 kg ⁽¹⁾	150 mg (1.5 mL) twice daily	450 mg (4.5 mL) twice daily
20 kg ⁽²⁾	200 mg (2 mL) twice daily	600 mg (6 mL) twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg ⁽²⁾	500 mg twice daily	1500 mg twice daily

(1) Children 25 kg or less should preferably start the treatment with levetiracetam 100 mg/mL oral solution
(2) Dose in children and adolescents 50 kg or more is the same as in adults.

Adequate presentation must be used to ensure the accuracy of the dosing.

Elderly: Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal impairment: The daily dose must be individualised according to renal function (see Precautions).

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, using the following formula: (See Equation 1 and Table 2.)

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

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

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

Table 2. Dosing adjustment for adult and adolescent patients weighing more than 50kg with impaired renal function.

Group	Creatinine clearance (mL/min/1.73m ²)	Dosage and frequency
Normal	>80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	<30	250 to 500 mg twice daily
End-stage renal disease patients Undergoing dialysis ⁽¹⁾	-	500 to 1000 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 m² may be estimated from serum creatinine (mg/dl) determination using, for young adolescents and children using the following formula (Schwartz formula): See Equation 2 and Table 3.

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

Ks=0.55 in Children to less than 13 years and in adolescent female; ks =0.7 in adolescent male.

Table 3. Dosing adjustment for children and adolescent patients weighing less than 50kg with impaired renal function.

Group	Creatinine clearance (mL/min/1.73m ²)	Dosage and frequency ⁽¹⁾ children and adolescent weighing less than 50kg
Normal	>80	10 to 30 mg/kg (0.10 to 0.30 mL/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0.10 to 0.20 mL/kg) twice daily
Moderate	30-49	5 to 15 mg/kg (0.05 to 0.15 mL/kg) twice daily
Severe	<30	250 to 500 mg/kg (0.05 to 0.10 mL/kg) twice daily
End-stage renal disease patients Undergoing dialysis	-	500 to 1000 mg/kg (0.10 to 0.20 mL/kg) once daily ^{(*)(**)}

(1) Levetiracetam oral solution should be used for dose under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achieved by taking multiple tablet and for patients unable to swallow tablets.

(*) A 15 mg/kg (0.15mL/kg) loading dose is recommended on the first day of treatment with levetiracetam.

(**) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.1 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/1.73 m².

4.3 Contraindication

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients.

4.4 Special warning and precautions for use

Warnings

This medicine may cause drowsiness therefore should not drive or operate machinery and should not drink alcohol or anything that is mixed with alcohol while using this medicine.

This medicine may cause abnormalities of blood cell.

This medicine is contraindicated in pregnancy because it may cause teratogenic effects on the fetus.

The medicine should be used with caution in liver and renal disease.

Special Precautions

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

Renal or hepatic 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.

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.

Depression and/or suicidal ideation: 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.

Ability to Perform Tasks that Require Judgement, Motor or Cognitive Skills: 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.

Use in Children: 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 interactions

Antiepileptic drugs: Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam did not influence the serum concentrations of existing antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic drugs 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 remains low.

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, digoxin and warfarin: Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg 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

Fertility: No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

Women of childbearing 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 antiepileptics.

Pregnancy: A large amount of postmarketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the first 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 (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured.

Lactation: 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.

4.7 Effects on ability to drive and use machine

This medicine may cause drowsiness therefore should not drive or operate machinery and should not drink alcohol or anything that is mixed with alcohol while using this medicine.

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

Clinical trial data and post marketing data: *Summary of the safety profile:* The adverse event profile presented as follows 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 most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Adverse drug reactions (ADRs) are listed as follows by MedDRA system organ class by frequency.

Frequency are defined as: Very common $\geq 1/10$; Common $\geq 1/100$ to $< 1/10$; Uncommon $\geq 1/1,000$ to $< 1/100$; Rare $\geq 1/10,000$ to $< 1/1,000$; Very rare $< 1/10,000$; Not known (cannot be estimated from the available data).

Infections and infestations: Very common: nasopharyngitis.

Rare: infection.

Blood and lymphatic system disorders: Uncommon: thrombocytopenia, leucopenia.

Rare: pancytopenia, neutropenia, agranulocytosis.

Immune system disorders: Rare: drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis).

Metabolism and nutrition disorders: Common: anorexia.

Uncommon: weight decreased, weight increase.

Rare: hyponatraemia.

Psychiatric disorders: Common: depression, hostility/aggression, anxiety, insomnia, nervousness/irritability.

Uncommon: suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation.

Rare: completed suicide, personality disorder, thinking abnormal.

Nervous system disorders: Very common: somnolence, headache.

Common: convulsion, balance disorder, dizziness, lethargy, tremor.

Uncommon: amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention.

Rare: choreoathetosis, dyskinesia, hyperkinesia, gait disturbance.

Eye disorders: Uncommon: diplopia, vision blurred.

Ear and labyrinth disorders: Common: vertigo.

Respiratory, thoracic and mediastinal disorders: Common: cough

Gastrointestinal disorders: Common: abdominal pain, diarrhoea, dyspepsia, vomiting, nausea.

Rare: pancreatitis.

Hepatobiliary disorders: Uncommon: liver function test abnormal.

Rare: hepatic failure, hepatitis.

Renal and urinary disorders: Rare: acute kidney injury.

Skin and subcutaneous tissue disorders: Common: rash.

Uncommon: alopecia, eczema, pruritus.

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme.

Musculoskeletal and connective tissue disorders: Uncommon: muscular weakness, myalgia.

Rare: rhabdomyolysis and blood creatine phosphokinase increased*.

General disorders and administration site conditions: Common: asthenia/fatigue.

Injury, poisoning and procedural complications: Uncommon: injury.

* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Description of selected adverse reactions: The risk of anorexia is higher when levetiracetam is coadministered 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.

Paediatric population: 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.

The adverse event 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.

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

behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised 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 behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

4.9 Overdose

Symptoms and signs: Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses.

Treatment: There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacodynamics: Mechanism of action: 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.

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 Ca^{2+} 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 release. 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 drug.

Pharmacodynamic effects: Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having pro-convulsant effect. The primary metabolite is inactive.

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

5.2 Pharmacokinetic Properties

Pharmacokinetics: 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. The time independent pharmacokinetic profile of levetiracetam was also confirmed following 1,500 mg intravenous infusion for 4 days with twice daily dosing.

There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients 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).

The pharmacokinetic profile has been characterized following oral administration. A single dose of 1500 mg levetiracetam diluted in 100 ml of a compatible diluent and infused

intravenously over 15 minutes is bioequivalent to 1,500 mg levetiracetam oral intake, given as three 500 mg tablets.

The intravenous administration of doses up to 4,000 mg diluted in 100 ml of 0.9 % sodium chloride infused over 15 minutes and doses up to 2,500 mg diluted in 100 ml of 0.9 % sodium chloride infused over 5 minutes was evaluated. The pharmacokinetic and safety profiles did not identify any safety concerns.

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 a twice daily administration schedule. Peak concentrations (C_{max}) are typically 31 and 43 $\mu\text{g/ml}$ following a single 1000 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.

Peak plasma concentration (C_{max}) observed in 17 subjects following a single intravenous dose of 1500 mg infused over 15 minutes was $51 \pm 19 \mu\text{g/mL}$ (arithmetic average \pm standard deviation).

Metabolism: 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 P450 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 P450 isoforms (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.

Special patient populations: Children (4 to 12 years): Following single 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.

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.

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.

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.

5.3 Preclinical Safety data

Toxicology: Non-clinical Information: Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity.

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 effects on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in fetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality 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-fetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in fetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/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 1800 mg/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/m² basis).

Environmental risk assessment (ERA): The use of levetiracetam in accordance with the product information is not likely to result in an unacceptable environmental impact (see Cautions for Usage).

6. Pharmaceutical Particulars

6.1 List of excipient

Sodium Chloride

Sodium Acetate trihydrate
Glacial Acetic Acid
Water for Injection

6.2 Incompatibilities

Incompatibilities and Use and handling: Levetiracetam, 100 mg/ml concentrate for solution for infusion: Table 4 presents the recommended preparation and administration of levetiracetam concentrate to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg, or 3000 mg in two divided doses. (See Table 4.)

Dose	Withdrawal volume	Volume of diluent	Infusion time	Frequency of administration	Total daily dose
250mg	2.5 mL (half 5 mL vial)	100mL	15 minutes	Twice daily	500 mg/day
500mg	5 mL (one 5 mL vial)	100mL	15 minutes	Twice daily	1000 mg/day
1000mg	10 mL (two 5 mL vial)	100mL	15 minutes	Twice daily	2000 mg/day
1500mg	15 mL (one 5 mL vial)	100mL	15 minutes	Twice daily	3000 mg/day

This medicinal product is for single use only, any unused solution should be discarded. This medicinal product must not be mixed with other medicinal products except those mentioned as follows. Levetiracetam concentrate was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in infusion bags at controlled room temperature 15-25°C.
Diluents: Sodium chloride (0.9%) injection; Lactated Ringer's injection; Dextrose 5% injection. Product with particulate matter or discoloration should not be used. Any unused drug or waste material should be disposed of in accordance with local requirements.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C; excursions permitted to 15-30°C; Do not keep in refrigerator

6.5 Nature and contents of container

100-mL Polyolefin/ Styrene-block copolymer based bags sealed with medium modified polypropylene ports and caps and wrapped in aluminum foil pouches.

7. Marketing Authorization Holder

Symgens Co.,Ltd.
1/102 Soi Ngam Wong Wan 43 Yeak 2-1 (Chinnakhet 1/21) Thung Song Hong, Laksi, Bangkok 10210, Thailand

8. Marketing Authorization Numbers

1C ____/____ (NG)

9. Date of Authorization

Date of authorization:

10. Date of revision of the text

XX/XXXX/XXXX