PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrlevETIRAcetam Injection USP

Levetiracetam for Injection

Solution, 100 mg/mL, Intravenous

Concentrate – must be diluted before use

Antiepileptic Agent

SteriMax Inc.
2770 Portland Drive
Oakville, Ontario
L6H 6R4

Date of Initial Authorization:
May 13, 2022

Submission Control No: 255674

RECENT MAJOR LABEL CHANGES

None at the time of authorization.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

Levetiracetam Injection USP (levetiracetam for injection) is indicated as:

- adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.
- an alternative for patients when oral administration is temporarily not feasible.

1.1 Pediatrics

Pediatrics: Levetiracetam for injection is indicated in pediatric patients as adjunctive therapy in the treatment of:

- partial onset seizures with or without secondary generalization in adolescents, children and infants from 1 month of age with epilepsy.
- myoclonic seizures in adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- primary generalized tonic-clonic seizures in adolescents from 12 years of age with Idiopathic Generalized Epilepsy.
- an alternative for patients when oral administration is temporarily not feasible (see 4.2 Recommended Dose and Dosage Adjustment, Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7.1.4 Geriatrics; and 10.3 Pharmacokinetics, Geriatrics).

2. CONTRAINDICATIONS

Levetiracetam Injection USP is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- in patients who are hypersensitive to other pyrrolidine derivatives (see 7 WARNINGS AND PRECAUTIONS, Immune).

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Levetiracetam Injection USP is available in the form of an IV solution for injection.

4.2 Recommended Dose and Dosage Adjustment

Adults (> 18 years)

Add-on therapy in adults (>18 years) and adolescents (12 to 17 years) weighing 50 kg or more

Treatment should be initiated at a dose of 1000 mg/day, given as twice daily dosing (500 mg, b.i.d). Depending on the clinical response and tolerability, the daily dose may be increased every two weeks by increments of 1000 mg, to a maximum recommended daily dose of 3000 mg daily.

In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice daily oral dosing were shown to be effective. Although there was a tendency towards a greater response rate with higher doses, a consistent statistically significant increase in response with increased dose has not been shown. There are limited safety data from controlled clinical trials at doses higher than 3000 mg/day (approximately 40 patients), therefore these doses are not recommended.

Levetiracetam Injection USP IV Solution is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible. There is no experience with administration of intravenous levetiracetam for a period longer than 4 days.

Elderly Patients (65 years and older)
Dose selection and titration should proceed cautiously in elderly patients, as renal function decreases with age. Accordingly, adjustment of the dose is recommended in elderly patients with compromised renal function (see below).

Dosage Adjustments in Adult Patients with Impaired Renal Function

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, Levetiracetam Injection USP dosage should be reduced in patients with impaired renal function (see Table 1 below). Patients with end stage renal disease should receive supplemental doses following dialysis.

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). To estimate creatinine clearance (CLcr) in mL/min for adults and adolescents weighing 50 kg or more, use the following formula

$$CLcr = \frac{[140 - age\ (years)] \times weight(kg)}{72 \times serum\ creatinine\ (mg/dL)} (\times 0.85\ for\ female\ patients)$$

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

$$CLcr\ (mL/min/1.73\ m^2) = \frac{CLCr\ (mL/min)}{BSA\ Subject\ (m^2)} \times 1.73$$

Table 1: Dosing Adjustment for Adult and Adolescent Patients weighing more than 50 kg with Impaired Renal Function

Renal Function	Creatinine Clearance (mL/min/1.73 m^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] [2]	-	500 to 1000 mg once daily

[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.
*or according to best clinical judgement.

Dosage Adjustments in Adult Patients with Impaired Hepatic Function

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 m^2.

Pediatrics

Pediatric weight-based dosing for add-on therapy in children aged <12 years and adolescents (12-17 years) weighing <50 kg.

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

Add-on therapy in infants aged 1 month to <6 months

The initial therapeutic dose is 7 mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 21 mg/kg twice daily. Dose changes should not exceed increases or decreases of 7 mg/kg twice daily every 2 weeks. The lowest effective dose should be used.

Levetiracetam Injection USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible. There is no experience with administration of intravenous levetiracetam for a period longer than 4 days.

Table 2 Dose recommendations for infants aged 1 month to <6 months

Weight	Starting dose 7 mg/kg twice daily	Maximum dose 21 mg/kg twice daily
4 kg	28 mg (0.3 mL) twice daily	84 mg (0.85 mL) twice daily
5 kg	35 mg (0.35 mL) twice daily	105 mg (1.05 mL) twice daily
7 kg	49 mg (0.5 mL) twice daily	147 mg (1.5 mL) twice daily

Add-on therapy in infants aged 6 months to <4 years; children aged 4 to 11 years, and adolescents aged 12 to 17 years weighing less than 50 kg

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 increases or decreases of 10 mg/kg twice daily every 2 weeks. The lowest effective dose should be used. For adolescents aged 12 to 17 years weighing 50 kg or more, see adult dosing recommendations.

Table 3 Dose recommendations for infants aged 6 months to <4 years; children aged 4 to 11 years and adolescents (12 to 17 years) weighing <50 kg

Weight	Starting dose 10 mg/kg twice daily	Maximum dose 30 mg/kg twice daily
6 kg[1]	60 mg twice daily	180 mg twice daily
10 kg[1]	100 mg twice daily	300 mg twice daily
15 kg[1]	150 mg twice daily	450 mg twice daily
20 kg[1]	200 mg twice daily	600 mg 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.

Levetiracetam Injection USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible. There is no experience with administration of intravenous levetiracetam for a period longer than 4 days.

Dose Adjustment for Children with Renal Impairment

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). For young adolescents, children and infants, use the following formula (Schwartz formula):

$$CLCr(mL/min/1.73m^2) = \frac{Height\,(cm) \times ks}{Serum\,creatinine\,(mg/mL)}$$

ks = 0.45 in term infants < 1 years old.
ks = 0.55 in children < 13 years old; adolescent females.
ks = 0.7 in adolescent males.

Table 4 Dosing adjustment for infants, children and adolescent patients weighing less than 50 kg with impaired renal function.

Group	Creatinine clearance (mL/min/1.73 m²)	Dose and Frequency (1)	
		Infants aged 1 to < 6 months	Infants aged 6 to 23 months*; Children aged 2 to 11 years Adolescents aged 12 – 17 years weighing < 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 0.30 mL/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 0.20 mL/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 mL/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 mL/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 0.10 mL/kg) twice daily
End-Stage Renal Disease patients undergoing dialysis	-	7 to 14 mg/kg (0.07 to 0.14 mL/kg) once daily	10 to 20 mg/kg (0.10 to 0.20 mL/kg) once daily (a) (b)

*Infants aged 6 months to 23 months should receive levetiracetam oral solution.

IV Solution
(a) A 15 mg/kg (0.15 mL/kg) loading dose is recommended on the first day of treatment.
(b) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 mL/kg) supplemental dose is recommended.

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

Switching between IV and oral administration

Conversion to or from IV and oral administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

4.3 Reconstitution

Levetiracetam Injection USP is for single use only. Any unused solution should be discarded.

Levetiracetam Injection USP may be mixed with the following diluents and antiepileptic drugs and may be stored in propylene bottles and polyvinyl chloride (PVC) bags. The diluted solution should not be stored for more than 24 hours at a room temperature (15 - 30°C).

Diluents

- Sodium Chloride (0.9%) injection, USP
- Lactated Ringer's injection
- Dextrose 5% injection, USP

Other antiepileptics

- Lorazepam
- Diazepam
- Valproate Sodium

There are no data to support the physical compatibility of Levetiracetam Injection USP with antiepileptic drugs that are not listed above.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Product with particulate matter or discoloration should not be used.

4.4 Administration

Levetiracetam therapy can be initiated with either intravenous or oral administration.

One 5 mL vial of Levetiracetam Injection USP contains 500 mg levetiracetam (100 mg / mL).

Levetiracetam Injection USP is for intravenous (IV) use only. The recommended dose must be diluted in 100 mL of a compatible diluent and administered intravenously as a 15 -minute intravenous infusion. If a smaller volume is required (e.g. pediatric patients), the amount of diluent should be calculated to not exceed a maximum levetiracetam concentration of 15 mg per mL of diluted solution. Consideration should also be given to the total daily fluid intake of the patient.

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

See Table 5 for the recommended preparation and administration of Levetiracetam Injection USP to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg, or 3000 mg.

Table 5 Preparation and administration of Levetiracetam Injection USP

Dose	Withdrawal Volume	Volume of Diluent	Infusion Time	Frequency of Administration	Total Daily Dose
250 mg	2.5 mL (0.5 x of 5 mL vial)	100 mL	15-minutes	Twice daily	500 mg/day
500 mg	5 mL (1 x 5 mL vial)	100 mL	15-minutes	Twice daily	1000 mg/day

1000 mg	10 mL (2 x 5 mL vials)	100 mL	15-minutes	Twice daily	2000 mg/day
1500 mg	15 mL (3 x 5 mL vials)	100 mL	15-minutes	Twice daily	3000 mg/day

For example, to prepare a 1000 mg dose, dilute 10 mL of Levetiracetam Injection USP 100 mL of a compatible diluent and administer intravenously as a 15-minute infusion.

5. OVERDOSAGE

Symptoms
The highest reported levetiracetam overdose is approximately 10 times the therapeutic dose. In the majority of overdose cases, multiple drugs were involved. Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, and coma were observed with levetiracetam overdoses. The minimal lethal oral dose in rodents is at least 233 times the maximum clinically studied dose.

Treatment
There is no specific antidote for overdose with levetiracetam; treatment is symptomatic and may include hemodialysis. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status.

Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 6 Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous	100 mg/mL Solution	Glacial Acetic Acid (to adjust pH), Sodium acetate trihydrate, Sodium Chloride, Water for injection.

Levetiracetam Injection USP (500 mg / 5 mL) is available in a 10 mL glass vial with a rubber stopper, supplied as 10 vials per carton. The stopper is not made with natural rubber latex.

7. WARNINGS AND PRECAUTIONS

General

Levetiracetam Injection USP is contraindicated in patients who are hypersensitive to pyrrolidine

derivatives. Reactions have included anaphylaxis and angioedema (see 7 WARNINGS AND PRECAUTIONS, Immune).

Carcinogenesis and Mutagenesis

See section 16 NON-CLINICAL TOXICOLOGY for a discussion on animal data.

Cardiovascular

QT Prolongation
The effect of levetiracetam on the QTc interval was evaluated in a randomized, double- blind, placebo and positive-controlled, single-dose, four-way crossover study of levetiracetam(1000 mg or 5000 mg) in 52 healthy subjects. The maximum difference from placebo in the mean change from baseline QTc was 4.0 ms (90% CI: 0.0, 8.0) for levetiracetam 1000 mg treatment at 4 h after dosing and 4.1 ms (90% CI: 0.1, 8.1) for the levetiracetam 5000 mg (supratherapeutic) treatment at 1.5 h after dosing.

Rare cases of ECG QT interval prolongation have been observed during post-marketing surveillance in patients with and without a prior history of cardiac conditions. Levetiracetam Injection USP should be used with caution, particularly 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 (see 8.5 Post-Market Adverse Reactions).

Increase in Blood Pressure in Patients < 4 years of age.
In a randomized, placebo-controlled study in patients 1 month to < 4 years of age, a significantly higher risk of increased diastolic blood pressure was observed in levetiracetam-treated patients (17%), compared to the placebo-treated patients (2%). There was no overall difference in mean diastolic blood pressure between the treatment groups. This disparity between levetiracetam and placebo treatment groups was not observed in the studies of older children or in adults.

Monitor patients 1 month to < 4 years of age for increases in diastolic blood pressure.

Dependence/Tolerance

As with all antiepileptic drugs, Levetiracetam Injection USP should be withdrawn gradually to minimize the potential of increased seizure frequency.

Driving and Operating Machinery

Levetiracetam may cause somnolence and fatigue, as well as other central nervous system related symptoms (e.g., coordination difficulties). Therefore, patients are advised not to drive or operated machinery or other skilled tasks until it is established that their ability to perform such activities is not affected.

Hematologic

Cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration. Post-market reports include a fatality in a 4-month-old, with swelling of the limbs appearing 5 days after treatment initiation as first-line monotherapy treatment initiation. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (see 8.5 Post-Market Adverse Reactions).

Adults

Statistically significant decreases compared to placebo were seen in total mean RBC count, mean hemoglobin, and mean hematocrit in levetiracetam-treated patients in controlled trials. For hemoglobin values, the percentage of levetiracetam or placebo treated patients with possibly clinically significant abnormalities were less than 0.5% each. For hematocrit values, a total of 5.1% of levetiracetam treated versus 3.2% of placebo patients had at least one possibly significant decrease in hematocrit (≤ 37% in males and 32% in females).

For white blood cells (WBC), 2.9% of treated versus 2.3% of placebo patients had at least one possibly clinically significant decrease in WBC count (≤ 2.8 x 10^9/L), while 2.6% of treated vs. 1.7% of placebo patients had at least one possibly significant decrease in neutrophil count (≤ 1.0 x 10^9/L). Of the levetiracetam treated patients with a low neutrophil count, all but one rose towards or reached baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Pediatric Patients 4 Years to < 16 Years

Statistically significant decreases in WBC and neutrophil counts were seen in levetiracetam-treated patients as compared to placebo. The mean decreases from baseline in the levetiracetam-treated group were -0.4 x 10^9/L and -0.3 x 10^9/L, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in levetiracetam-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

In the controlled trial, more levetiracetam-treated patients had a possibly clinically significant abnormally low WBC value (3% of levetiracetam-treated patients versus 0% of placebo-treated patients), however, there was no apparent difference between treatment groups with respect to neutrophil count (5% of levetiracetam-treated patients versus 4.2% of placebo-treated patients). No patient was discontinued secondary to low WBC or neutrophil counts

In the controlled cognitive and neuropsychological safety study, 5 patients (8.6%) in the levetiracetam-treated group and two patients (6.1%) in the placebo-treated group had high eosinophil count values that were possibly clinically significant (≥ 10% or ≥ 0.7 x 10^9/L).

Hepatic/Biliary/Pancreatic

Reports of hepatitis and hepatic failure in patients taking levetiracetam, with and without other medications, have been received in post-market surveillance (see 8.5 Post-Market Adverse Reactions). For information on dosage adjustment in patients with severe hepatic impairment, see Dosage Adjustments in Adult Patients with Impaired Hepatic Function.

Immune

Hypersensitivity Reactions

Skin and Subcutaneous tissue disorders
Serious hypersensitivity reactions with dermatological involvement have been reported in both children and adults in association with levetiracetam use, including Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Such serious skin reactions may be life-threatening, and some patients have required hospitalization with very rare reports of fatal outcome. There is no way to tell if a mild rash will become a severe skin reaction. If any of these hypersensitivity reactions are suspected, and an alternative cause cannot be established, Levetiracetam Injection USP should be discontinued. Recurrence of the serious skin reactions following re-challenge with levetiracetam has been reported.

The median time to onset for reported cases of SJS and TEN was 12 days. The reporting rate of TEN and SJS associated with levetiracetam use, which is generally accepted to be an underestimate due to underreporting, is 9 cases/million patient years. This exceeds the background incidence rate estimates for these serious skin reactions in the general population; background estimates range between 0.5 to 6 cases per million-person years.

The time to onset of DRESS may be longer than for SJS and TEN, e.g. up to 6 weeks or more after treatment initiation. Typically, although not exclusively, DRESS initially presents with fever and rash, and then with other organ system involvement that may or may not include eosinophilia, lymphadenopathy, hepatitis, nephritis, and/or myocarditis. Because DRESS is variable in its expression, other organ system signs and symptoms not noted here may also occur. Organ involvement may be more severe than skin involvement.

Anaphylaxis and Angioedema
Levetiracetam can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms in cases reported in the post-marketing setting have included hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. In some reported cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, levetiracetam should be discontinued and the patient should seek immediate medical attention. Levetiracetam should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

Monitoring and Laboratory Tests

Levetiracetam can cause hematologic abnormalities, including decreases in white blood cell (WBC) and neutrophil counts, decreases in red blood cell (RBC) counts, hemoglobin, and hematocrit, and increases in eosinophil counts. (see 7 WARNINGS and PRECAUTIONS, Hematologic).

Reports of increases in liver function tests in patients taking levetiracetam, with and without other medications, have been received in post-market surveillance (see 8.5 Post-Market Adverse Reactions).

Neurologic

Coordination Difficulties
Levetiracetam may cause coordination difficulties. In controlled clinical studies in adult patients with partial onset seizure studies, 3.4% of adult levetiracetam-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo-treated patients. These events occurred most frequently within the first 4 weeks of treatment (see also Central Nervous System Adverse Reactions).

Seizure Worsening
A paradoxical reaction of worsening of seizure may be observed especially when starting treatment or at increase in dose.

Psychiatric

Behavioural Abnormalities and Psychotic Symptoms
Levetiracetam Injection USP may cause behavioural abnormalities and psychotic symptoms. Patients treated with Levetiracetam Injection USP should be monitored for psychiatric signs and symptoms.
Behavioural and psychiatric adverse reactions were more common in children than in adults (see also Central Nervous System Adverse Reactions; and 8.2.1 Clinical Trial Adverse Reactions - Pediatrics).

Behavioural Abnormalities
In clinical studies, 13% of adult levetiracetam-treated patients and 38% pediatric (4 to 16 years of age) levetiracetam-treated patients compared to 6% and 19% of adult and pediatric placebo-treated patients experienced non-psychotic behavioural symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, irritability, nervousness, neurosis, and personality disorder).

Irritability was reported in 12% of the levetiracetam-treated patients compared to 0% of placebo-treated patients in clinical studies in pediatric patients 1 month to <4 years of age. Overall, for 11% of levetiracetam-treated pediatric patients, compared to 6% of placebo-treated patients, behavioural symptoms were reported at the time of decision to discontinue or reduce dosage. In a post-market case, a 5-year-old was discontinued from levetiracetam monotherapy after 3 weeks due to neuropsychiatric behaviours, including self-harm attempts.

Worsening of Aggressive Behaviour in Pediatrics
A randomized double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioural effects of levetiracetam as adjunctive therapy in pediatric patients (4 to 16 years of age). The results from an exploratory analysis indicated a worsening in levetiracetam-treated patients on aggressive behaviour (one of eight behaviour dimensions) as measured in the Achenbach Child Behaviour Checklist (CBCL/6 -18). Also, 1.6% of levetiracetam-treated patients experienced paranoia, and 3.1% experienced confusional state, compared to 0% of placebo-treated patients for both.

Psychotic Symptoms more Frequent in Pediatric Patients < 4 years
In clinical studies, 17% of levetiracetam-treated pediatric patients 1 month to <4 years of age, 2% of levetiracetam-treated pediatric patients 4 to 16 years of age, and 1% of levetiracetam-treated adult patients experienced psychotic symptoms, compared to 5%, 2%, and 0.2% of the corresponding age groups treated with placebo. Psychotic symptoms seen in both adults and children include hallucinations, psychosis, and psychotic depression.

Suicidal Behaviour and Ideation
Suicide ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicide ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo-controlled trials in which antiepileptic drugs were used for various indications has shown a small increased risk of suicide ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43,892 patients in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo-controlled clinical trials, and for the majority of epilepsy patients, treatment (antiepileptic drug or placebo was administered as adjunct to other antiepileptic agents (i.e. patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicide ideation and behaviour from the meta-analysis (0.43%) for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicide ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to t his population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Patients should be monitored for signs of depression and/or suicide 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 suicide ideation or behaviour change.

Renal

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, pharmacokinetic studies in renally-impaired patients indicate that apparent clearance is significantly reduced in subjects with renal impairment (see 10.3 Pharmacokinetics, Renal Insufficiency).

In patients with renal impairment, levetiracetam dosage should be appropriately reduced. Patients with end stage renal disease, i.e., those undergoing dialysis should be given supplemental doses after dialysis (see Dosage Adjustments in Adult Patients with Impaired Renal Function).

The use of levetiracetam has been very rarely associated with acute kidney injury, with a time onset ranging form a few days to several months.

Reproductive Health: Female and Male Potential

- **Fertility**

  The effect of this medication on human fertility is unknown. No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to

1800 mg/kg/day (see Reproductive and Developmental Toxicology)

- **Teratogenic Risk**

  There is non-clinical evidence suggesting that levetiracetam is embryotoxic and teratogenic (see Reproductive and Developmental Toxicology). Levetiracetam Injection USP should therefore be used during pregnancy only when the potential benefits outweigh the possible risks to the fetus (see 7.1.1 Pregnant Women).

7.1 Special Populations

7.1.1 Pregnant Women

Levetiracetam Blood Levels May Decrease During Pregnancy: As with other antiepileptic drugs, physiological changes during pregnancy may affect levetiracetam concentration. There have been reports of decreased levetiracetam concentration during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). It is recommended that clinical response should be monitored carefully in women receiving levetiracetam treatment during pregnancy, and determination of changes in plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy. In the event that medication is increased during pregnancy, the dose may need to be adjusted postpartum.

Anti-Epileptic Drugs and Risk to the Unborn Child: In reproductive toxicity studies in rats and rabbits, levetiracetam induced developmental toxicity at exposure levels similar to or greater than the human exposure. There was evidence of increased skeletal variations/minor anomalies, retarded growth, embryonic death, and increased pup mortality. In the rat, fetal abnormalities occurred in the absence of overt maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure.

There are no adequate and well-controlled studies on the use of levetiracetam in pregnant women. Levetiracetam and/or its metabolites cross the placental barrier in animal species and in humans.

Information about the potential risk for humans is limited. Pregnancy registry data indicate that the risk of having a child with a birth defect is greater for women on antiepileptic polytherapy, including levetiracetam as a component, than for women not treated with antiepileptic drugs. Levetiracetam Injection USP should not be used during pregnancy unless potential benefits to mother and fetus are considered to outweigh potential risks to both. Discontinuation of antiepileptic treatments may result in disease worsening, which can be harmful to the mother and the fetus.

Pregnancy Registry: Pregnant patients taking Levetiracetam Injection USP should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the following website: http://www.aedpregnancyregistry.org/

7.1.2 Breast-feeding

Levetiracetam is excreted in breast milk. Therefore, there is a potential for serious adverse reactions from Levetiracetam Injection USP in nursing infants. A decision should be made

whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Available data in children did not suggest an impact on growth and puberty. However, long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown (see also 8.2.1 Clinical Trial Adverse Reactions - Pediatrics).

7.1.4 Geriatrics

There were 347 patients treated with levetiracetam in clinical trials that were 65 or over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly patients in controlled trials for epilepsy to adequately assess the effectiveness of levetiracetam in these patients (see also Elderly Patients (65 years and older); and 10.3 Pharmacokinetics, Geriatrics).

Renal function can be decreased in the elderly and levetiracetam is known to be substantially excreted by the kidney. Therefore, the risk of adverse reactions to the drug may be greater in patients with impaired renal function. A pharmacokinetic study in 16 elderly subjects (age 61-88 years) showed a decrease in clearance by about 40% with oral administration of both single dose and 10 days of multiple twice-daily dosing. This decrease is most likely due to the expected decrease in renal function in these elderly subjects. Care should therefore be taken in dose selection for elderly patients, and it may be useful to monitor renal function (see Elderly Patients (65 years and older)).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In well-controlled clinical studies, the most frequently reported adverse events associated with the use of levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, dizziness, infection; and most notably in pediatrics, altered mood and behaviour, as well as decreased appetite. Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first four weeks of treatment with levetiracetam.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults
The partial onset seizure data below are representative of the adverse event findings from other seizure types.

Central Nervous System Adverse Reactions

Levetiracetam use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into 3 main categories: 1) somnolence and fatigue 2) behavioural/psychiatric, and 3) coordination difficulties.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. Somnolence/asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment, and usually resolved while patients remained on treatment. In the case of behavioural/psychiatric symptoms (including such adverse events as aggression, agitation, anger, anxiety, emotional lability, hostility, and irritability), approximately half of the patients reported these events within the first 4 weeks, with the remaining events occurring throughout the duration of the trials. See Table 7 for the incidence rate of individual adverse events contained within each category.

Behavioural/psychiatric symptoms (including agitation, emotional lability, hostility, anxiety, etc.) have been reported approximately equally in patients with and without a psychiatric history.

Table 7 Total combined incidence rate for each of the three categories of CNS adverse events in placebo-controlled add-on clinical trials.

Category of CNS Adverse Events	Levetiracetam* + Anti-epileptic Therapy (n=672)	Placebo + Antiepileptic Therapy (N=351)
Somnolence and Fatigue		
Somnolence	15%	10%
Fatigue	14%	10%
Behavioural / Psychological Symptoms		
Non-psychotic (1)	14%	6%
Psychotic (2)	1%	0%
Coordination Difficulties		
Coordination Difficulties (3)	3%	2%

*Reflects levetiracetam doses of 1000 mg, 2000 mg, 3000 mg, and 4000 mg per day.

(1) "Non-psychotic behavioural/psychiatric symptoms" encompasses the following terms: agitation, antisocial reaction, anxiety, apathy, depersonalization, depression, emotional l ability, euphoria, hostility, euphoria, hostility, nervousness, n eurosis, personality disorder, and suicide attempt.

(2) "Psychotic behavioural/psychiatric symptoms" encompasses the following terms: hallucination, paranoid reaction, psychosis, and psychotic depression.

(3) "Coordination difficulties" encompasses the following terms: ataxia, abnormal gait, incoordination .

There was no clear dose relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. In a controlled study including a dose of 4000 mg, administered without titration, the incidence rate of somnolence during the first 4 weeks of treatment for patient receiving the high dose was 42%, compared to 21% for patients receiving 2000 mg/day.

Table 8 Incidence (%) of treatment-emergent adverse events in placebo-controlled add-onstudies by body system. Adverse events occurred in at least 1% of levetiracetam-treated patients and occurred more frequently than in placebo-treated patients (Studies N051, N052, N132, and N138).

Adverse Event	Levetiracetam (N=769)	Placebo (N=439)
Body as a Whole		
Asthenia	14%	10%
Infection	13%	7%
Digestive System		
Tooth disorder	2%	1%
Hemic and Lymphatic System		
Ecchymosis	2%	1%
Nervous System		
Amnesia	2%	0%
Anxiety	2%	1%
Ataxia	3%	1%
Depression	4%	2%
Dizziness	9%	4%
Emotional lability	2%	0%
Hostility	2%	1%
Nervousness	4%	2%
Personality disorder	1%	0%
Somnolence	15%	10%
Thinking abnormal	2%	1%
Vertigo	3%	1%
Respiratory System		
Pharyngitis	6%	4%
Rhinitis	4%	3%
Sinusitis	2%	1%

Lack of dose-related incidence of adverse events within therapeutic range
Based on the data from the controlled clinical trials, there was no evidence of dose relationship within the recommended dose range of 1000 to 3000 mg/day.

Discontinuation or dose reduction in well controlled clinical studies
In well controlled clinical studies, 14.3% of patients receiving levetiracetam and 11.7% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. Table 9 lists the most common (>1%) adverse events that resulted in discontinuation or dose reduction.

Table 9 Adverse events that most commonly resulted in discontinuation or dose reduction in placebo-controlled studies in patients with epilepsy.

Adverse Event	Levetiracetam (N=672)	Placebo (N=351)
Asthenia	9 (1.3%)	3 (0.9%)
Headache	8 (1.2%)	2 (0.6%)
Convulsion	16 (2.4%)	10 (2.8%)
Dizziness	11 (1.6%)	0
Somnolence	31 (4.6%)	6 (1.7%)
Rash	0	5 (1.4%)

The overall adverse event experience profile of levetiracetam was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse event experience reports by age and race.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

In patients aged 1 month to <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 to 16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open-labels extension studies; 223 of which were treated with levetiracetam in placebo-controlled studies. In both these pediatric 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.

Adverse reaction profile

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications.

Safety results in pediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychological adverse reactions, as well as anorexia / decreased appetite, which were more common in children than in adults (see Behavioural Abnormalities and Psychotic Symptoms).

The risk of anorexia is found to be higher when levetiracetam is co-administrated with topiramate.

Children aged 4 to 16 years

For the most frequent adverse reactions in children and adolescents aged 4 to 16 years, see Table 10.

Table 10 Adverse Reactions* occurring in ≥2%of patients in Pooled Placebo-Controlled,Add-On Studies in Pediatric Patients Ages 4 to 16 Years Experiencing Partial Onset Seizures

Adverse Event	Levetiracetam (N=165)	Placebo (N=131)
Headache	19%	15%
Nasopharyngitis	15%	12%
Vomiting	15%	12%
Somnolence	13%	9%
Fatigue	11%	5%
Aggression	10%	5%
Abdominal Pain Upper	9%	8%
Cough	9%	5%
Nasal Congestion	9%	2%
Decreased Appetite	8%	2%
Abnormal Behaviour	7%	4%
Dizziness	7%	5%
Irritability	7%	1%
Pharyngolaryngeal Pain	7%	4%
Diarrhea	6%	2%
Lethargy	6%	5%
Insomnia	5%	3%
Agitation	4%	1%
Anorexia	4%	3%
Head Injury	4%	0%
Constipation	3%	1%
Contusion	3%	1%
Depression	3%	1%
Fall	3%	2%
Influenza	3%	1%
Mood Altered	3%	1%
Affect Lability	2%	1%
Anxiety	2%	1%

Adverse Event	Levetiracetam (N=165)	Placebo (N=131)
Arthralgia	2%	0%
Confusional State	2%	0%
Conjunctivitis	2%	0%
Ear Pain	2%	1%
Gastroenteritis	2%	0%
Joint Sprain	2%	1%
Mood Swings	2%	1%
Neck Pain	2%	1%
Rhinitis	2%	0%
Sedation	2%	1%

*Adverse reactions that occurred in ≥2% of levetiracetam-treated patients and more frequently than in placebo-treated patients.

In the controlled pooled pediatric clinical studies in patients 4 -16 years of age, 7% of patients receiving levetiracetam and 9% receiving placebo discontinued as a result of an adverse reaction.

Children 1 month to <4 years

Because of the short exposure period in this 7-day study, incidences of adverse reactions are expected to be less than in other pediatric studies in older patients. Therefore, other controlled pediatric data above, should be considered to apply to this group.

Table 11 Adverse Reactions* occurring in ≥5% of patients in a 7-day Placebo-Controlled, Add-On Study in Pediatric Patients Ages 1 Month to < 4 Years Experiencing Partial Onset Seizures

Adverse Event	Levetiracetam (N=60)	Placebo (N=56)
Somnolence	13%	2%
Irritability	12%	0%

*Individual adverse reactions that occurred in ≥5% of levetiracetam-treated patients and were numerically more common than in placebo-treated patients.

8.3 Less Common Clinical Trial Adverse Reactions

Eye disorders: blurred vision, diplopia

Gastrointestinal disorders: nausea; dyspepsia

Hepatic/Biliary/Pancreatic: abnormal liver function test

Injury, Poisoning, and procedural complication: injury

Musculoskeletal and connective tissue disorder: myalgia, muscular weakness

Psychiatric disorders: suicide attempt, suicide ideation

Nervous system disorders: memory impairment, paraesthesia, disturbances in attention, hyperkinesia, balance disorder; tremor

Skin and subcutaneous tissue disorders: eczema, pruritis erythema multiforme, rash, peripheral nerve symptoms; alopecia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Levetiracetam can cause hematologic abnormalities, including decreases in white blood cell (WBC) and neutrophil counts, decreases in red blood cell (RBC) counts, hemoglobin, and hematocrit, and increases in eosinophil counts (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Increased Blood Pressure: Children aged 1 month to < 4 years should be monitored for increases in diastolic blood pressure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

8.5 Post-Market Adverse Reactions

In post-marketing experience, nervous system and psychiatric disorders have most frequently been reported. In addition to adverse reactions during clinical studies, and listed above, the following adverse reactions have been reported in post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic disorders: agranulocytosis, leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some cases), thrombocytopenia (see 7 WARNINGS AND PRECAUTIONS, Immune).

Cardiac disorders: electrocardiogram QT prolonged

Hepatic/Biliary/Pancreatic: Reports of increases in liver function tests, hepatitis, hepatic failure, and pancreatitis in patients taking levetiracetam, with and without other medications, have been received.

Immune system disorders: Hypersensitivity reactions such as SJS, TEN, DRESS and anaphylactic reactions (see 7 WARNINGS AND PRECAUTIONS, Immune).

Infections and infestations: Infection

Metabolism and nutrition disorders: weight decreased, cases of hypokalemia and hypomagnesaemia have been associated with the use of levetiracetam; hyponatremia

Musculoskeletal and connective tissue disorders: muscular weakness, rhabdomyolysis and/or blood creatine phosphokinase increase has been reported in diverse patient populations,

however, a higher prevalence of these reports in Japanese patients may signal an elevated risk.

Nervous system disorders: paraesthesia, lethargy, choreoathetosis, dyskinesia, hyperkinesia , increase in seizure frequency.

Psychiatric: anger, panic attack, anxiety, confusional state, hallucination, psychotic disorders (including self-harm attempts by a 5 year-old on levetiracetam monotherapy (see Behavioural Abnormalities and Psychotic Symptoms**)**, suicidal behaviour (including completed suicide); personality disorder; thinking abnormal (see Suicidal Behaviour and Ideation)

Renal and urinary disorders: Cases of acute kidney injury (including acute renal failure, nephritis)

Reproductive Health: Fetal toxicity associated with concomitant use of levetiracetam and other antiepileptic drugs has been reported in pregnancy registries (see 7.1.1 Pregnant Women)**.**

Skin and subcutaneous tissue disorders: alopecia (in several cases, recovery was observed when levetiracetam was discontinued), erythema multiforme, angioedema; toxic epidermal necrosis; Stevens-Johnson syndrome

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In Vitro Studies on Metabolic Interaction Potential

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (paracetamol UGT i.e. UCT1A6, ethinyl estradiol UGT i.e. UGT1A1 and *p*-nitrophenol UGT i.e. UGT [p16.2]) and epoxide hydrolase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. In human hepatocytes in culture, levetiracetam did not cause enzyme induction.

Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; therefore, clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Thus, *in vitro* data, in combination with the pharmacokinetic characteristics of the drug, indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions.

9.3 Drug-Behavioural Interactions

The effect of lifestyle choices (e.g., smoking, alcohol consumption) on the use of levetiracetam has not been established.

9.4 Drug-Drug Interactions

Adults

The drugs listed in the table below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 12 Established or Potential Drug-Drug Interactions.

Proper/Common name	Source of Evidence	Effect	Clinical comment
phenytoin, valproate	Pharmacokinetic study	Levetiracetam was co-administered with either phenytoin or valproate at doses of 3000 mg/day and 1000 mg/day (500 mg BID), respectively. No clinically significant interactions were observed.	
Oral contraceptives ethinyl estradiol and levonorgesterol	Pharmacokinetic study	No clinically significant pharmacokinetic interactions were observed in healthy subjects between levetiracetam (500 mg BID) and the oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgesterol and levetiracetam (500 mg BID).	Given that the pharmacokinetic interactions study did not include using levetiracetam as adjunctive therapy nor did it cover the recommended dosage range, physicians should therefore advise their female patients to be alert to any irregular vaginal bleeding or spotting, and to immediately report to them any occurrences.
Digoxin	Pharmacokinetic study	Co-administration of levetiracetam (1000 mg BID) and digoxin (0.25 mg/day) did not influence the pharmacokinetics of either drug, nor the pharmacodynamics (ECG) of digoxin.	

Proper/Common name	Source of Evidence	Effect	Clinical comment
Warfarin	Pharmacokinetic study	Co-administration of levetiracetam (1000 mg BID) and R and S warfarin (2.5 mg, 5 mg, or 7.5 mg daily) did not influence the pharmacokinetics either drug Prothrombin time was not affected by levetiracetam.	
Probenecid (a renal tubular secretion blocking agent)	Pharmacokinetic study	Probenacid at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg BID C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid and the renal clearance of the metabolite ucb L057 was decreased by 60%. This alteration is likely related to competitive inhibition of tubular secretion of ucb L057. The effect of levetiracetam on probenacid was not studied.	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Other Antiepileptic Drugs (AEDs)

Potential drug interactions between levetiracetam and other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data suggest that levetiracetam may not significantly influence the plasma concentrations of these other AEDs, and that the other AEDs may not significantly influence the plasma concentrations of levetiracetam.

Potentially Lethal Methotrexate Blood Levels

Concomitant administration of levetiracetam and methotrexate has been rarely 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.

Carbamazepine

Based on post-market experience, concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity (e.g. nystagmus, nausea, vomiting).

Topiramate

Based on an analysis of clinical trial data, the risk of anorexia is higher when levetiracetam is co-administered with topiramate.

Laxative

Based on reports of decreased efficacy of oral levetiracetam when administered concomitantly with the osmotic laxative macrogol (polyethylene glycol). Therefore, macrogol (polyethylene glycol) should not be taken orally for one hour before and for one hour after taking Levetiracetam Injection USP.

Antacid

No data on the influence of antacids on the absorption of levetiracetam is available.

Pediatrics

As in adults, there is no evidence of clinically significant medicinal product interactions in pediatric 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.

9.5 Drug-Food Interactions

Levetiracetam is rapidly and almost completely absorbed after oral administration. The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Levetiracetam is a drug of the pyrrolidine class chemically unrelated to existing antiepileptic drugs (AEDs). As with other drugs in this class, the mechanism of action of levetiracetam in man is not known.

10.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetics of levetiracetam have included healthy volunteers, adult and pediatric patients with epilepsy, elderly subjects, and subjects with renal and hepatic impairment. Results of these studies indicate that levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. Food does not affect the extent of absorption of levetiracetam, although the rate is decreased. Levetiracetam is not protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of the dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacodynamic activity and are renally excreted. Plasma half-life of levetiracetam across studies is 6-8 hours. Plasma half-life is increased in subjects with renal impairment, and in the elderly primarily due to impaired renal clearance.

Based on its pharmacokinetic characteristics, levetiracetam is unlikely to produce or to be subject to metabolic interactions.

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 body weight. Therefore, there is no need for plasma level monitoring of levetiracetam.

The pharmacokinetics of levetiracetam have been characterized in single- and multiple-dose PK studies, with doses up to 5000 mg; these studies included healthy volunteers (N=98), patients with epilepsy (N=58 adult patients and N=24 pediatric patients), elderly subjects (N=16) and subjects with renal and hepatic impairment (N=36 and 16, respectively).

Absorption

Levetiracetam is rapidly and almost completely absorbed after oral administration. The oral bioavailability of levetiracetam tablets is 100%. Plasma peak concentrations (C_{max}) are achieved at 1.3 hours after dosing. The extent of absorption is independent of both dose and the presence of food, but the latter delays T_{max} by 1.5 hours and decreases C_{max} by 20%. The pharmacokinetics of levetiracetam are linear over the dose range of 500 – 5000 mg. Steady-state is achieved after two days of a twice daily administration schedule. Mean peak concentrations (C_{max}) are 31 and 43 µg/mL, respectively, following a single 1000 mg dose, and a repeated 1000 mg twice daily dose.

Distribution

Neither levetiracetam nor its primary metabolite is significantly bound to plasma proteins (<10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 L/kg, a value that

is close to the total body water volume. No tissue distribution data for humans are available.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose). The production of this metabolite is not dependent on any liver cytochrome P450 isoenzymes and is mediated by serine esterase(s) in various tissues, including blood cells. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hours and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The primary metabolite, ucb L057, is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function (see 7 WARNINGS AND PRECAUTIONS, Renal; and Dosage Adjustments in Adult Patients with Impaired Renal Function).

Special Populations and Conditions

Pediatrics

Children (4 to 12 years)

Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after single dose (20 mg/kg). The half-life of levetiracetam was 6.0 hours. The body weight adjusted apparent clearance of levetiracetam was approximately 40% higher than in adults.

A repeat dose pharmacokinetic study was conducted in pediatric patients (age 4-12 years) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses with a T_{max} of about 1 hour and a $t_{1/2}$ of 5 hours across the three dosing levels. The pharmacokinetics of levetiracetam in children was linear between 20 to 60 mg/kg/day. The apparent body clearance was 1.1 mL/min/kg. The potential interaction of levetiracetam with other AEDs was also evaluated in these patients. The apparent body clearance was 1.1 mL/min/kg. Levetiracetam had no significant effect on the plasma concentrations of carbamazepine, valproic acid, topiramate or lamotrigine. However, there was about a 22% increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED (e.g. carbamazepine).

Infants and Children (1 month to 4 years)

Following single dose administration (20 mg/kg) of a 10% oral solution to children with epilepsy (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).

Population Pharmacokinetic Analysis

Population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age showed that body weight was significantly correlated to the clearance of levetiracetam in pediatric patients; 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.

IV Solution: A population pharmacokinetic analysis for the intravenous formulation was conducted in 49 patients (1 month to <16 years of age) weighing 3 -79 kg. Patients received levetiracetam as a 15-minute IV infusion at doses between 14 mg/kg/day and 60 mg/kg twice daily. Plasma concentrations and model derived steady-state exposure AUC (0-12) were within the range of the exposure observed in pediatric patients receiving equivalent doses of the oral solution.

Geriatrics

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects, ranging in age from 61 to 88 years, with 11 of the 16 patients aged 75 years of age or over with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of 500 mg twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was increased about 40% (10 to 11 hours) when compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Sex

Levetiracetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearances adjusted for bodyweight were comparable.

Pregnancy and Breast-feeding

Levetiracetam levels may decrease during pregnancy.

Ethnic origin

Formal pharmacokinetic studies of the effects of race have not been conducted. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Hepatic Insufficiency

A single dose pharmacokinetic study was performed in 16 subjects with hepatic impairment (N=5 mild/Child-Pugh Grade A; N=6 moderate/Grade B; N=5 severe/Grade C vs 5 healthy controls). For the mild and moderate subgroups neither mean nor individual pharmacokinetic values were clinically different from those of controls. In patients with severe hepatic impairment, mean apparent body clearance was 50% that of normal subjects, with decreased renal clearance accounting for most of the decrease. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <60 mL/min/1.73 m^2 (see Dosage Adjustments in Adult Patients with Impaired Hepatic Function; and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Renal Insufficiency

Single dose pharmacokinetics were performed in 20 subjects with renal impairment (N=7 mild/CLcr of 50-79 mL/min; N=8 moderate/CLcr of 30-49 mL/min; N=5 severe/CLcr<30 mL/min), and N=11 matching healthy volunteers. Clearance of levetiracetam is correlated with creatinine clearance and levetiracetam pharmacokinetics following repeat administration were well predicted from single dose data. The apparent body clearance of the parent drug levetiracetam is reduced in patients with impaired renal function by approximately 40% in the mild group, 50% in the moderate group, and 60% in the severe renal impairment group. For the primary metabolite ucb L057, the decrease in clearance values from baseline was greater than that seen for the parent drug in all subject groups.

In anuric (end stage renal disease) patients, the apparent body clearance was approximately 30% compared to that of normal subjects. Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see Dosage Adjustments in Adult Patients with Impaired Renal Function; and 7 WARNINGS AND PRECAUTIONS, Renal).

11 STORAGE, STABILITY AND DISPOSAL

Levetiracetam Injection USP is a clear, colourless transparent solution. Check colour and consistency of Levetiracetam Injection USP prior to use. Do not use product if solution shows haziness, particulate matter, discolouration, leakage, if the vial is damaged, or if the seal is broken.

Un-diluted Levetiracetam Injection USP
Store in the original container to protect from light. Store concentrate at 15 - 30°C. This medicinal product is single use only; any unused solution should be discarded. Do not freeze.

Diluted Levetiracetam Injection USP
Dilution should be used immediately. Once diluted, Levetiracetam Injection USP is stable after dilution for 24 hours at 15 - 30°C in Polypropylene bottles and PVC Flexible bags.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

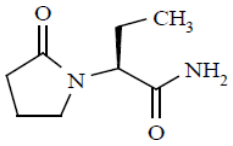
Drug Substance

Proper name: levetiracetam

Chemical name: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

Molecular formula and molecular mass: $C_8H_{14}N_2O_2$ and 170.21 g/mol

Structural formula:



Physicochemical properties:

Physical Form: A white to off-white powder.

Solubility: It is very soluble in water, soluble in acetonitrile and practically insoluble in hexane.

pKa and pH values: The pKa of levetiracetam cannot be determined due to the absence of ioniziable groups. The pH of the IV solution is between 5.0 – 6.0.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Partial onset seizures (adults and pediatrics aged 1 month to 16 years)

Adults

Trial Design and Demographics

Table 13 Summary of patient demographics for clinical trials in Partial Onset Seizures in Adults with Epilepsy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age ±SD (years)	Sex
N132	Double-blind, randomized, placebo-controlled, parallel group, multicenter safety and efficacy trial	LEV: 1000 mg/day (500 mg, bid), LEV: 3000 mg/day (1000 mg, bid) Oral 4-week up-titration 14-week evaluation	Placebo: 95 LEV (1000 mg/day): 98 LEV (3000 mg/day): 101	Placebo: 38 ± 11 LEV 1000 mg/day: 38 ± 11 LEV 3000 mg/day: 38 ± 11	178 M 116 F
N051	Multicentre, double-blind, randomized, placebo-controlled safety and efficacy trial	LEV: 1000 mg/day (500 mg, bid), LEV: 2000 mg/day (1000 mg, bid) Oral 4-week titration 12-week evaluation	Placebo: 112 LEV (1000 mg/day): 106 LEV (2000 mg/day): 106	Placebo: 37 ± 12 LEV1000 mg/day: 36 ± 10 LEV 2000 mg/day: 37 ± 12	157 M 167 F
N138	Multicentre, double-blind, placebo-controlled, parallel group, responder-selected study	LEV: 3000 mg/day (1500 mg, bid) Oral 18-week Add-on: 4-week up-titration 14-week evaluation Monotherapy 12-week monotherapy	Placebo: 105 LEV (3000 mg/day): 181	Placebo: 36 ± 12 LEV: 37 ± 12	137 M 149 F

Study Results

The efficacy of levetiracetam as adjunctive therapy (added to other antiepileptic drugs) in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in a total of 904 adult patients who had a history of partial onset seizures with or without secondary generalization.

General Methodology

Patient Population

Patients in these three studies had refractory partial onset seizure for a minimum of 1 (or 2) year(s) prior to enrollment. They had previously taken a minimum number of classical AEDs (either one or two), and at the time of the study were taking a stable dose regimen of at least one AED. During the baseline period, it was required that patients experienced a minimum of 12 partial onset seizures over 12 weeks (Study N132) or 4 partial onset seizures during each 4-week period (Study N051) or 2 partial onset seizures per 4-week period (Study N138).

Dosing Schedule

After a prospective baseline period of approximately 12 weeks, patents were randomized to placebo, or levetiracetam at 1000 mg, 2000 mg, or 3000 mg/day (depending on the study), given as twice daily doses. In all trials, there was a 2 or 4-week titration period, followed by a 12-14-week maintenance period.

Measure of Efficacy

The primary measure of efficacy was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomized treatment period (titration + maintenance). Secondary efficacy parameters include the 50% and 100% responder rate in partial onset seizure frequency over the entire randomized treatment period. Efficacy results are based on the ITT population with the exception of a few patients lacking evaluable seizure frequency data.

The above trial description applies to all three studies below. Thus, for each trial, only partial distinguishing information is stated below.

Study N132

Study N132 was a parallel-group study conducted in the United States comparing placebo, levetiracetam 1000 mg/day, and levetiracetam 3000 mg/day in 95, 98, and 101 randomized patients, respectively. The efficacy for study N132 is display in Table 14.

Table 14 Median percent reduction from baseline in weekly frequency of Partial Onset Seizures in Study N132

	AED + Placebo	AEDs + Levetiracetam 1000 mg/day	AEDs + Levetiracetam 3000 mg/day
N	95	97	101
Median Baseline Seizure Frequency	1.77	2.53	2.08
Percent reduction in partial seizure frequency from baseline	6.9%	36.9%	38.1%

*P<0.001 versus placebo

Study N051

Study N051 was a cross-over study conducted in Europe comparing placebo, levetiracetam 1000 mg/day, and levetiracetam 2000 mg/day in 112, 106, and 106 randomized patients, respectively.

The first period of the study (Period A) was designed to be analyzed as a parallel-group study. The efficacy results for Period A are displayed in Table 15.

Table 15 Median percent reduction from baseline in weekly frequency of Partial Onset Seizures in study N051 Period A

	AED + Placebo	AEDs + Levetiracetam 1000 mg/day	AEDs + Levetiracetam 2000 mg/day
N	111	106	105
Median Baseline Seizure Frequency	2.46	2.82	2.59
Percent reduction in partial seizure frequency from baseline	1.1%	20.7%	24.4%

*P<0.001 versus placebo

Study N138

Study N138 was a parallel-group study conducted in Europe comparing placebo and levetiracetam 3000 mg/day in 105 and 181 randomized patients, respectively. Table 16 display the efficacy result for Study N138.

Table 16 Median percent reduction from baseline in weekly frequency of Partial Onset Seizures in study N138

	AED + Placebo	AEDs + Levetiracetam 3000 mg/day
N	104	180
Median Baseline Seizure Frequency	1.78	1.67
Percent reduction in partial seizure frequency from baseline	7.3%	36.8%

Responder Rates

Each patient is categorized according to their efficacy data: percent reduction from baseline in weekly frequency of partial onset seizures, calculated over the entire randomized treatment period. The percentage of patients who remained on levetiracetam for at least 21 days and achieved ≥50% reduction, or a 100% reduction (seizure free) within each of the three pivotal studies is presented in Table 17.

Table 17 Partial onset responder rate of the entire treatment period by randomized dose.

Percent Reduction	AED + Placebo	AEDs + Levetiracetam 1000 mg/day	AEDs + Levetiracetam 2000 mg/day	AEDs + Levetiracetam 3000 mg/day
Study N132				
N	95	97	-	101
≥50%	7%	36%	-	40%
seizure free (100%)	0%	3%	-	6%
Study N051				
N	111	106	105	-
≥50%	6%	21%	34%	-
seizure free (100%)	1%	2%	3%	-
Study N138				
N	104	-	-	180
≥50%	14%	-	-	39%
seizure free (100%)	0%	-	-	7%

Pediatrics

Trial Design and Demographics

Table 18 Summary of patient demographics for clinical trials in Partial Onset Seizures in Pediatric Patients 4 Years to 16 Years with Epilepsy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range) (years)	Sex
N159	Randomized, double-blind, placebo-controlled, multicentre trial	LEV initial dose: 20 mg/kg/day (10 mg/kg, bid) Dose adjusted by 20 mg/kg/day every 2 weeks to a target dose of 60 mg/kg/day Oral 4-week up titration 10-week evaluation	Placebo: 97 LEV: 101	Placebo: 9.7 (3-17) years LEV: 10.4 (4 – 17) years	100 M 98 F

LEV: levetiracetam.:

Table 19 Summary of patient demographics for clinical trials in Partial Onset Seizures in Pediatric Patients 1 Month to <4 Years with Epilepsy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age ±SD (months)	Sex
N1009	Double-blind, randomized, placebo-controlled, multicenter trial	Age 1 month to < 6 months: LEV initial dose: 20 mg/kg/day titrated to 40 mg/kg/day Age 6 months to < 4 years: LEV initial dose: 25 mg/kg/day titrated to 50 mg/kg/day Oral 5-day treatment 1 day up-titration 4 days stable-dose treatment	Placebo: 56 LEV: 60	Placebo: 23.5 ± 12.1 LEV: 23.4 ± 13.4	57 M 59 F

LEV: levetiracetam.

Study Results

Children 4 to 16 years

In pediatric 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). Table 20 displays the efficacy result.

Table 20 Responder rate in children aged 4 to 16 years with partial onset seizures following adjunctive treatment with levetiracetam.

	Levetiracetam 60 mg/kg/day N=101	PBO N=97
≥50% reduction in seizure frequency per week	44.6%	19.6%

**with continued long-term treatment

In the open-label follow-up, 11.4% of the patients were seizure-free for at least 6 months, and 7.2% were seizure-free for at least 1 year.

Infants & Children 1 month to <4 years

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 1 month to less than 6 months, and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old were used in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percentage 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. Table 21 displays the efficacy result.

Table 21 Responder rate in children aged 1 month to <4 years with partial onset seizures following adjunctive treatment with levetiracetam.

	Levetiracetam 40 mg/kg/day or 50 mg/kg/day N=60	PBO N=56
≥50% reduction in seizure frequency per week	43.6%	19.6%

The results are consistent across age groups. In the open-label follow-up, 8.6% of the patients were seizure-free for at least 6 months and 7.8% were seizure-free for at least 1 year.

Thirty-five 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.

Myoclonic seizures (adults and adolescents)

Trial Design and Demographics

Table 22 Summary of patient demographics for clinical trials in Myoclonic Seizures in Patients ≥ 12 Years of Age with Juvenile Myoclonic Epilepsy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age ±SD (years)	Sex
N166	Randomized, double-blind, placebo-controlled, multicenter trial	LEV: initial dose: 1000 mg/day (500 mg, bid) titrated to target 3000 mg/day over 4 weeks Oral 12-week evaluation	Placebo: 60 LEV: 61	Placebo: 26.8 ± 9.5 LEV: 25 ± 7.4	44 M 77 F

LEV: levetiracetam.

Study Results

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 12 years 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. Efficacy result is presented in Table 23.

Table 23 Responder rate in adults and adolescents aged 12 years and older with myoclonic seizures following adjunctive treatment with levetiracetam.

	Levetiracetam 3000 mg/day N=61	PBO N=60
≥50% reduction in seizure frequency per week	58.3%	23.3%

In the open-label follow-up, 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 .

Primary generalized tonic-clonic seizures (adults and adolescents)

Trial Design and Demographics

Table 24 Summary of patient demographics for clinical trials in Primary Generalized Tonic-Clonic Seizures in Patients ≥ 6 Years of Age

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age ±SD (years)	Sex
N1057	Multicentre, randomized, double-blind, placebo-controlled, parallel group study	Adults: 3000 mg/day Children*: 60 mg/kg/day Oral 4-week up-titration 20-week evaluation	Placebo: 84 LEV: 80	Placebo: 30.6 ± 12.1 LEV: 26.9 ± 11.2	73 M 91 F

LEV: levetiracetam. *includes adolescents up to <16 years of age and weighing <50 kg.

Study Results

Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized 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 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses. Efficacy result is presented in Table 25.

Table 25 Responder rate in adults and adolescents aged 12 years and older with primary generalized tonic-clonic seizures following adjunctive treatment with levetiracetam.

	Levetiracetam 3000 mg/day or 60 mg/kg/day N=80	PBO N=81
≥50% reduction in seizure frequency per week	72.2%	45.2%

In the open-label follow-up, 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.

Regarding the IV formulation:

All clinical studies supporting the efficacy of levetiracetam utilized the oral formulation. The finding of efficacy of levetiracetam injection is based on the results of studies using an oral

formulation of levetiracetam, and on the demonstration of comparative bioavailability of the oral and parenteral formulations (see 10.3 Pharmacokinetics, Special Populations and Conditions).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General

Toxicology

The general toxicity of levetiracetam was evaluated after oral administration in acute (mouse, rat, dog and monkey), subacute and chronic (two to 52 weeks or longer in the mouse, rat and dog) studies. Acute (mouse, rat and dog) and two-week (rat and dog) toxicity studies were also conducted using iv administration.

The single-dose studies in mice, rats and dogs indicate a low acute toxicity potential. Lethality was only reached after iv dosing in these studies; although in a subsequent study in mice (micronucleus test), lethality was reached at 10000 mg/kg orally. Oral administration is associated with only transient clinical signs (emesis, salivation, tremors, decreased motor activity, ataxia, tachypnea and side lying). In dogs, emesis is a dose-limiting effect.

Repeat administration of levetiracetam is well tolerated. Mortality is observed only following iv administration of 900 mg/kg in rats. In general, clinical signs are minimal across studies and species with the most consistent observations being neuromuscular effects, salivation, and emesis in dogs. In the rodent only, treatment-related changes in the liver and kidney were reported. In the liver, a reversible increase in liver weight and hypertrophy of centrilobular hepatocytes was observed in both sexes in rats and mice. Centrilobular vacuolation associated with lipid deposition occurred in male rats and in mice. Kidney pathology consisting of hyaline droplet nephropathy, exacerbation of chronic progressive nephropathy and associated changes was observed in male rats.

These changes are considered to be a male rat-specific pathology associated with α2-microglobulin accumulation in the proximal tubules that is not toxicologically relevant to man. There was no target organ identified in the dog. No lethality, organ failure or other irreversible toxicity was observed after long-term oral treatment up to 1800 mg/kg/day in the rat, 960 mg/kg/day in the mouse and 1200 mg/kg/day in the dog.

Studies in neonatal or juvenile animals do not indicate any greater potential for toxicity compared to adult animals. Investigations involving oral administration of up to 2 weeks of ucb L057, the major human metabolite, indicate a low potential for toxicity in rats and dogs.

Carcinogenicity

Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. There was no evidence of carcinogenicity. Two studies have been conducted in mice. In one study, mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m^2 or exposure basis). In a second study, mice received levetiracetam by oral gavage for 2 years at dose levels

of 1000, 2000 and 4000 mg/kg/day. Due to poor survival at the highest dose of 4 000 mg/kg/day in this study, the high dose was reduced to 3000 mg/kg/day (equivalent to 12 times the MRHD). In neither study was evidence of carcinogenicity seen.

Genotoxicity

Levetiracetam was not mutagenic in the Ames test or in mammalian cells in vitro in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an in vitro analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an in vivo mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or the in vitro mouse lymphoma assay.

Reproductive and Developmental Toxicology

No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day.

Administration to rats before mating and throughout pregnancy and lactation was associated with slightly retarded fetal growth and skeletal ossification *in utero* and slight increase in pup mortality between birth and day 8 postpartum at 1800 mg/kg/day and slightly retarded skeletal ossification at 350 mg/kg/day.

When female rats were administered levetiracetam orally up to 1800 mg/kg/day from day 15 of pregnancy to weaning (day 21 postpartum), no effects were observed on litter parameters, pup survival and development. The dose of 1800 mg/kg/day corresponds to 30 -fold the upper recommended daily dose in man on a mg/kg/day basis or 6-fold when calculated on a mg/m^2 body surface area basis.

In pregnant rats treated at 400, 1200 and 3600 mg/kg/day from day 6 to 15 of pregnancy, the no adverse effect level for embryo-fetal survival, growth and development is 1200 mg/kg/day. There was a slight increase in the proportion of fetuses with supernumerary ribs (thoracolumbar border) and a marginal reduction in skeletal ossification at 3600 mg/kg/day. The NOAEL was 3600 mg/kg/day for pregnant female rats (12 times the maximum recommended human dose [MRHD] on a mg/m^2 basis).

In pregnant rabbits, the no-adverse effect level for embryo-fetal survival, growth and development was 200 mg/kg/day, a dose producing adverse effects in the mothers. At the highest dose of 1800 mg/kg/day, a 2.5-fold increase in fetal abnormalities was observed together with marked maternal toxicity. This was not seen in two other studies. The dose of 1800 mg/kg/day corresponds to 30-fold the upper recommended dose in man on a mg/kg/day basis or 11-fold when calculated on a mg/m^2 basis.

In a study in pregnant mice, levetiracetam administered at 3000 mg/kg/day from day 6 to 15 of pregnancy produced a slight retardation of growth and skeletal ossification and no effect on survival and morphological development. Plasma levetiracetam concentrations at approximate peak time were 20-fold higher than peak concentrations measured in man after 3000 mg/day.

17 SUPPORTING PRODUCT MONOGRAPHS

pdp-levETIRAcetam (Levetiracetam Oral Solution 100 mg/mL, Levetiracetam for injection 100 mg/mL), submission control # 250898, Product Monograph, PENDOPHRARM, Division of Pharmascience Inc. (December 15, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrlevETIRAcetam Injection USP

Levetiracetam for Injection

Read this carefully before you or your child receives **Levetiracetam Injection USP** because it contains important information for you and your child. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Levetiracetam Injection USP.**

What is Levetiracetam Injection USP used for?

Levetiracetam Injection USP is used to help reduce the number of your seizures, or your child's seizures when taken together with other seizure medications.

Levetiracetam Injection USP may be given for several days when you or your child are unable to take seizure medications by mouth.

How does Levetiracetam Injection USP work?

Levetiracetam Injection USP belongs to the family of medicines called antiepileptics. The exact way that Levetiracetam Injection USP works to treat seizures is not known.

What are the ingredients in Levetiracetam Injection USP?

Medicinal ingredients: Levetiracetam

Non-medicinal ingredients: Glacial Acetic Acid (to adjust pH), Sodium acetate trihydrate, Sodium Chloride, Water for injection.

Levetiracetam Injection USP comes in the following dosage forms:

IV Solution for Injection: 100 mg/mL

Do not use Levetiracetam Injection USP if:

- you or your child are allergic to levetiracetam; or to any of the other ingredients in Levetiracetam Injection USP (see **What are the ingredients in Levetiracetam Injection USP?**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given, or your child is given Levetiracetam Injection USP. Talk about any health conditions or problems you or your child may have, including if you (or your child):

- have or have had a history of any heart problems or problems with the way your heart beats. You may develop these even if you've never had a heart problem before;
- take any medicines that affect the heart or how it beats;
- take certain medicines that can cause an electrolyte imbalance;
- have any health problems, including ones you or your child have had in the past;

- have kidney disease;
- have had an allergic reaction such as swelling of the face, lips, eyes, tongue, and throat; trouble swallowing or breathing, and hives (anaphylaxis or angioedema) to other antiepileptic medicines in the past;
- are taking any medication, including ones you can get without a prescription;
- have recurrent infections or blood coagulation disorders;
- are pregnant or thinking about becoming pregnant. Taking more than one antiepileptic medication during pregnancy increases the risk of your baby having birth defects.
    - You and your doctor will have to decide if Levetiracetam Injection USP is right for you whileyou are pregnant.
    - If you decide to take Levetiracetam Injection USP while you are pregnant, ask your healthcare provider about joining the North American Antiepileptic Drug Pregnancy Registry. You can join by calling the toll-free number (888) 233-2334. Women who are pregnant and planning to take Levetiracetam Injection USP should join the pregnancy registry. It will enable the collection of valuable data about Levetiracetam Injection USP use in pregnancy;
- are breast-feeding or planning to breast-feed. Levetiracetam is known to pass into breast milk and may harm your baby. You and your doctor should decide whether you should take Levetiracetam Injection USP or breast-feed, but not both.

Other warnings you should know about:

Changes in behaviour: You should pay attention to any mental changes, especially sudden changes in you or your child's mood, behaviours, thoughts, or feelings. These changes are seen more commonly in children than in adults.

Call your doctor or your child's doctor **right away,** if you or your child have any changes in behaviour that are new, worse, or worry you. These changes could include:

- feeling depressed, nervous, or anxious
- feeling angry, agitated or hostile
- in some people, psychotic symptoms, such as hallucinations (seeing or hearing things that are not really there), delusions (false or strange thoughts or beliefs), and unusual behaviour.

A small number of people may have thoughts of suicide (harming or killing themselves) when taking antiepileptic drugs such as Levetiracetam Injection USP. If at any time you or your child have these thoughts, get medical help **right away. Do NOT** stop Levetiracetam Injection USP on your own.

Trouble with coordination and driving and operating machinery: Levetiracetam Injection USP may affect your or your child's coordination. It may also make you or your child feel sleepy and tired. It is more likely to happen at the beginning of your or your child's treatment or after an increasein the dose. You should not drive or operate machinery until you know how Levetiracetam Injection USP affects you.

Severe Allergic Reaction Involving the Skin and Other Organs: There is no way to tell if a mild skin rash will become a severe reaction. The following serious skin reactions have been reported with levetiracetam:

- Stevens-Johnson Syndrome (SJS)
- Toxic Epidermal Necrolysis (TEN);
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Although very rare, severe forms of these reactions may lead to death.

Get medical help **right away** if you develop any combination of the following:

- a rash or any serious skin reaction such as blistering or peeling of the lips, eyes or mouth;
- fever;
- swollen glands;
- joint pain;
- problems related to the liver, kidneys, heart, lungs or other organs;
- a serious allergic reaction (anaphylaxis or angioedema) such as swelling of the face, lips, eyes, tongue, and throat; trouble swallowing or breathing, and hives.

Tell your healthcare professional about all the medicines you or your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Levetiracetam Injection USP:

- other antiepileptic medicines (such as carbamazepine, topiramate);
- Oral contraceptives (used for birth control);
- Methotrexate (used to treat certain types of cancer and arthritis).

How Levetiracetam Injection USP is given to you or your child:

Levetiracetam Injection USP will be given to you or your child:

- by a doctor or nurse;
- as an infusion into a vein (intravenous infusion);
- twice a day for several days.

Usual dose:

Your doctor will decide how much Levetiracetam Injection USP you or your child will need. The dose you or your child will be given will depend on your or your child's age, weight and medical history.

Stopping treatment: If your doctor decides to stop your or your child's treatment with Levetiracetam Injection USP, he/she will decrease the dose slowly. This is to prevent your or your child's symptoms from coming back again or becoming worse.

Overdose:

If you think you or your child has been given too much Levetiracetam Injection USP, your doctor or nurse will take appropriate treatment and monitoring measures.

What are possible side effects from using Levetiracetam Injection USP?

These are not all the possible side-effects you or your child may have when given Levetiracetam Injection USP. If you or your child experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- Feeling sleepy and tired / feeling tired. This side effect generally occurs in the first few weeks of treatment and may improve over time; however, it may return if you are taking Levetiracetam Injection USP for a long period of time.
- Headache
- Lack or loss of strength
- Feeling irritated
- Infection
- Bruising
- Feeling dizzy
- Sore throat
- Runny and stuffy nose
- Vomiting
- Abdominal pain
- Diarrhea

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Nasal congestion, infection	✓		
Convulsions, worsening seizures, balance disorder, dizziness, lethargy		✓	
Decreased appetite	✓		
UNCOMMON			
Mood and Behaviour changes: aggression, agitation, anger, anxiety, apathy, depression, hostility, mood swings, personality disorder, Nervousness / irritability Psychotic symptoms such as hallucinations (seeing or hearing things that are not really there), delusions (false or strange thoughts or beliefs)		✓	
RARE			
Worsening seizures			✓
Thoughts of suicide or hurting yourself			✓
Severe Allergic Reactions: swelling of the face, eyes, or tongue, difficulty swallowing, wheezing, hives and generalized itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconsciousness			✓

Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skins and /or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches, or swollen glands			✓
Toxic Epidermal Necrolysis (TEN) (severe skin reaction): redness, blistering and/or peeling of large areas of the skin.			✓
Extreme sleepiness and tiredness and/or difficulty coordinating, and weakness		✓	
Rhabdomyolysis (breakdown of damaged muscle): muscle spasms, weakness, red-brown (tea-coloured) urine.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Levetiracetam Injection USP will be stored by your doctor. Keep out of reach and sight of children.

If you want more information about Levetiracetam Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sterimaxinc.com, or by calling 1-800-881-3550.

This leaflet was prepared by SteriMax Inc.

Last Revised: May 13, 2022