

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **PRO-LEVETIRACETAM – 250**

Pr **PRO-LEVETIRACETAM – 500**

Pr **PRO-LEVETIRACETAM – 750**

Levetiracetam Tablets

Tablets, 250 mg, 500 mg and 750 mg, Oral

USP

Antiepileptic

ATC Code: N03AX14

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Neurologic	07/2023
7 WARNINGS AND PRECAUTIONS, Cardiovascular	07/2023
7 WARNINGS AND PRECAUTIONS, Psychiatric	07/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PRO-LEVETIRACETAM (levetiracetam) is indicated as adjunctive therapy in the management of adult (> 18 years of age) patients with epilepsy who are not satisfactorily controlled by conventional therapy.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of levetiracetam in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see [7.1.3 Pediatrics](#) and [10.3 Pharmacokinetics, Special Populations and Conditions, 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 efficacy (see [7.1.4 Geriatrics](#), [4.2 Recommended Dose and Dosage Adjustment, Geriatrics](#) and [10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics](#)).

2 CONTRAINDICATIONS

PRO-LEVETIRACETAM 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](#).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

PRO-LEVETIRACETAM is given orally with or without food. After oral administration, the bitter taste of levetiracetam may be experienced.

4.2 Recommended Dose and Dosage Adjustment

Adults

Treatment should be initiated at a dose of 1000 mg/day, given as twice daily dosing (500 mg bid). Depending on 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.

In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice a day dosing, were shown to be effective. Although there was a tendency toward greater response rate with higher dose, 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.

Patients with Impaired Renal Function

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, PRO-LEVETIRACETAM 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 is needed.

CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

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

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

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

Table 1 - Dosing Adjustment for Patients with Impaired Renal Function

Group	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)	-	500 to 1000 mg once daily

(1) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

* or according to best clinical judgment

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/1.73m².

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see [1.1 Pediatrics](#) and [7.1.3 Pediatrics](#)).

Geriatrics (≥ 65 years of age)

Dose selection and titration should proceed cautiously in elderly patients, as renal function decreases with age.

4.4 Administration

The film-coated tablets must be taken orally, swallowed with liquid. The daily dose is administered in two equally divided doses.

4.5 Missed Dose

If the patient misses a dose by a few hours, they should be instructed to take PRO-LEVETIRACETAM as soon as they remember. If it is close to their next dose, they should be instructed to take their medication at the next regular time. Patients should not take two doses at the same time.

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 antidote for overdose with PRO-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 clinical status of the patient.

Standard hemodialysis procedures result in significant removal 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 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients
Oral	Film-coated tablet / 250 mg, 500 mg, 750 mg	Anhydrous citric acid, colloidal silicon dioxide, copovidone, ferric oxide red (750 mg only), ferric oxide yellow (500 mg and 750 mg), hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

PRO-LEVETIRACETAM 250 mg tablets: White, oval, biconvex, film-coated tablets, engraved “LEV” score “250” on one side, “APO” on the other side. Available in bottles of 100.

PRO-LEVETIRACETAM 500 mg tablets: Yellow, oval, biconvex, film-coated tablets, engraved “LEV” score “500” on one side, “APO” on the other side. Available in bottles of 100.

PRO-LEVETIRACETAM 750 mg tablets: Orange, oval, biconvex, film-coated tablets, engraved “LEV” score “750” on one side, “APO” on the other side. Available in bottles of 100.

7 WARNINGS AND PRECAUTIONS

General

As with all antiepileptic drugs, PRO-LEVETIRACETAM should be withdrawn gradually to minimize the potential of increased seizure frequency.

Carcinogenesis and Mutagenesis

See [16 NON-CLINICAL TOXICOLOGY, Carcinogenicity](#) and [16 NON-CLINICAL TOXICOLOGY, Genotoxicity](#) for 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. PRO-LEVETIRACETAM 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, Cardiac disorders](#)).

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 operate machinery or other skilled tasks until it is established that their ability to perform such activities is not affected.

Hematologic

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 ($\leq 37\%$ 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 ($\leq 2.8 \times 10^9/L$), while 2.6% of treated vs. 1.7% of placebo patients had at least one possibly significant decrease in neutrophil count ($\leq 1.0 \times 10^9/L$). 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.

Cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration. Complete blood cell counts are advised in patients experiencing important

weakness, pyrexia, recurrent infections or coagulation disorders (see [8.5 Post-Market Adverse Reactions, Blood and lymphatic disorders](#)).

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 [4.2 Recommended Dose and Dosage Adjustment](#).

Immune

Hypersensitivity Reactions

- **Serious Dermatological Reactions**

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, PRO-LEVETIRACETAM 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**

PRO-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, the patient should seek immediate medical attention. PRO-LEVETIRACETAM should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

Neurologic

Somnolence and Fatigue

Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms (e.g. coordination difficulties), at the beginning of treatment or following a dose increase (see [8 ADVERSE REACTIONS](#)).

Seizure Worsening

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

Lack of efficacy or seizure worsening has also been reported in patients with epilepsy associated with sodium voltage-gated channel alpha subunit 8 (SCN8A) mutations. In the case of lack of efficacy or worsening seizures, use of PRO-LEVETIRACETAM should be re-evaluated.

Psychiatric

Suicidal Ideation and Behaviour

Suicidal 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 depression and/or 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 suicidal 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 suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 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 suicidal 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 suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this 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.

Psychiatric Reactions and Changes in Behaviour

PRO-LEVETIRACETAM may cause behavioural abnormalities and psychotic symptoms. Behavioural adverse reactions reported with levetiracetam include affect liability, aggression, agitation, anger, anxiety, apathy, depression, hostility, irritability, personality change, paranoia and obsessive-compulsive disorder (OCD). Closely monitor patients treated with PRO-LEVETIRACETAM for psychiatric signs and symptoms.

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, Special Populations and Conditions, 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 [4.2 Recommended Dose and Dosage Adjustment, Patients with Impaired Renal Function](#)).

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 [16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology](#))

- **Teratogenic Risk**

There is non-clinical evidence suggesting that levetiracetam is embryotoxic and teratogenic (see [16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology](#)). PRO-LEVETIRACETAM 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 PRO-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).

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. PRO-LEVETIRACETAM 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 PRO-LEVETIRACETAM 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 PRO-LEVETIRACETAM 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, and the as-yet uncharacterized risks to the infant.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of levetiracetam in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): 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 efficacy of levetiracetam in these patients (see also [4.2 Recommended Dose and Dosage Adjustment](#); and [10.3 Pharmacokinetics, Special Populations and Conditions](#)).

Renal function can be decreased in the elderly and levetiracetam is known to be substantially excreted by the kidney, 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 to 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 [4.2 Recommended Dose and Dosage Adjustment](#)).

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 and infection. 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

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Central Nervous System Adverse Events

Levetiracetam use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into the following categories: 1) somnolence and fatigue, 2) behavioural/psychiatric symptoms 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 four 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, irritability), approximately half of the patients reported these events within the first four weeks, with the remaining events occurring throughout the duration of the trials.

The following CNS adverse events were observed in controlled clinical trials.

Table 3 - 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 Event	Levetiracetam* + AED Therapy (n=672) (%)	Placebo + AED Therapy (n=351) (%)
Somnolence and fatigue		
Somnolence	15	10
Asthenia	14	10
Behavioural/psychiatric symptoms	14	6
Nonpsychotic ¹	1	0
Psychotic ²		
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 lability, euphoria, hostility, nervousness, neurosis, personality disorder and suicide attempt.

² "Psychotic behavioural/psychiatric symptoms" encompasses the following terms:

hallucinations, paranoid reaction, psychosis and psychotic depression.

³”Coordination difficulties” encompasses the following terms: ataxia, abnormal gait, incoordination.

See [Table 4](#) for incidence rate of individual AEs contained within the categories.

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

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. In a controlled study including a dose of 4000 mg, administered without titration, the incidence rate of somnolence during the first four weeks of treatment for patients receiving the high dose was 42%, compared to 21% for patients receiving 2000 mg/day.

Table 4 - Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Studies by Body System. (Adverse events occurred in at least 1% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients.) (Studies N051, N052, N132 and N138)

Body System / Adverse Event	Levetiracetam + AED Therapy (n = 672) (%)	Placebo + AED Therapy (n = 351) (%)
Body as a Whole		
Asthenia	14	10
Infection*	13	7
Digestive System		
Tooth disorders	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 disorders	1	0
Somnolence	15	10
Thinking abnormal	2	1
Vertigo	3	1

Body System / Adverse Event	Levetiracetam + AED Therapy (n = 672) (%)	Placebo + AED Therapy (n = 351) (%)
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	2	1

* In levetiracetam-treated patients, the majority of “Infection” events (93%) were coded to reported terms of “common cold” or “infection upper respiratory”.

Other events reported by 1% or more of patients treated with levetiracetam but as or more frequent in the placebo group were: abdominal pain, accidental injury, amblyopia, anorexia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, cough increased, diarrhea, diplopia, drug level increased, dysmenorrhea, dyspepsia, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, headache, insomnia, nausea, otitis media, pain, paresthesia, rash, tremor, urinary tract infection, vomiting and weight gain.

Additional Events Observed in Placebo Controlled Trials

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 5 lists the most common (>1%) adverse events that resulted in discontinuation or dose reduction.

Table 5 - Adverse Events that Most Commonly Resulted in Discontinuation or Dose Reduction in Placebo-Controlled Studies in Patients with Epilepsy

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

The following adverse events were seen in well-controlled studies of levetiracetam for indications in epilepsy other than those approved in this labeling: balance disorder, disturbance in attention, eczema, hyperkinesia, memory impairment, myalgia, nasopharyngitis, pruritus, mood swings, and vision blurred, aggression, agitation, depression, and irritability.

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

PRO-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](#) and [7 WARNINGS AND PRECAUTIONS, Immune](#)).

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. Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and lymphatic disorders: agranulocytosis, leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of these cases), thrombocytopenia (see [7 WARNINGS AND PRECAUTIONS, Hematologic](#)).

Cardiac disorders: electrocardiogram QT prolonged.

Hepatic/Biliary/Pancreatic: Reports of abnormal 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](#)).

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

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: encephalopathy, paraesthesia, choreoathetosis, dyskinesia, lethargy, gait disturbance, increase in seizure frequency, neuroleptic malignant syndrome (NMS) with higher prevalence in Japanese patients.

Psychiatric: abnormal behaviour, anger, panic attack, anxiety, confusional state, delirium, hallucination, psychotic disorders, paranoia (see [8.2 Clinical Trial Adverse Reactions, Central Nervous System Adverse Events](#)), suicidal behaviour (including completed suicide), and obsessive-compulsive disorder (OCD) (see [7 WARNINGS AND PRECAUTIONS, Psychiatric](#)).

Renal and urinary disorders: Cases of acute kidney injury (including acute renal failure, nephritis) have been reported in patients treated with levetiracetam.

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: Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptom (DRESS), erythema multiforme, angioedema (see [7 WARNINGS AND PRECAUTIONS, Immune](#)), alopecia: in several alopecia cases, recovery was observed when levetiracetam was discontinued.

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

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.

For two of these AEDs - phenytoin and valproate - formal PK interaction studies with levetiracetam were performed. Levetiracetam was co-administered with either phenytoin or valproate at doses of 3000 mg/day and 1000 mg/day respectively. No clinically significant interactions were observed.

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

Antacids

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

Digoxin

Levetiracetam (1000 mg bid) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Methotrexate

Concomitant administration of levetiracetam and methotrexate has been very 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.

Oral Contraceptives

A pharmacokinetic clinical interaction study has been performed in healthy subjects between the oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, and the lowest therapeutic dose of levetiracetam (500 mg bid). No clinically significant

pharmacokinetic interactions were observed.

However, pharmacokinetic interaction studies using levetiracetam as adjunctive therapy and covering the recommended dosage range have not been conducted. Therefore, physicians should advise their female patients to be alert to any irregular vaginal bleeding or spotting, and to immediately report to them any occurrences.

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam (1000 mg bid). $C_{\text{max}}^{\text{SS}}$ 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 probenecid was not studied.

Warfarin

Levetiracetam (1000 mg bid) did not influence the pharmacokinetics of R and S warfarin (2.5 mg, 5 mg or 7.5 mg daily). Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

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 studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

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 (see [10.1 Mechanism of Action, Preclinical Studies](#) below for experimental *in vitro* and *in vivo* data in animals).

Preclinical Studies

The pharmacological activity of levetiracetam has been assessed in a variety of animal models of acute seizures and chronic epilepsy. Many studies included standard antiepileptic drugs (AEDs) as comparative agents.

Levetiracetam displayed protection against seizures in animal models of chronic epilepsy involving genetic and kindled animals with spontaneous, recurrent seizures. This contrasts to a lack of anticonvulsant activity in two primary screening tests for AEDs, the maximal electroshock (MES) test, and the maximal pentylenetetrazol (PTZ) test. In general, levetiracetam is devoid of any activity against single seizures induced by maximal stimulation with different chemoconvulsants and only shows a minor anticonvulsant action upon submaximal stimulation and in threshold tests. An exception is the antiseizure protection observed against secondarily generalized activity from focal seizures induced by the chemoconvulsants pilocarpine and kainic acid. The predictive value of these animal models for mechanism of action is uncertain.

In vitro studies show that levetiracetam, at concentrations of up to 10 μ M did not appear to result in significant ligand displacement at known receptor sites such as benzodiazepine, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate) reuptake sites or second messenger systems. It is unclear whether binding to any of these sites would occur at higher levetiracetam concentrations. Levetiracetam does not appear to modulate neuronal voltage-gated sodium and T-type calcium currents. Levetiracetam partially inhibits N-type calcium currents in neuronal cells.

A binding site for levetiracetam (LEV), that appears to be saturable, has been demonstrated in rat brain [K_d of 62 ± 20 nM and B_{max} of 4.5 ± 0.1 pmol/mg protein] and spinal cord [K_d of 52 ± 14 nM and B_{max} of 1.6 ± 0.1 pmol/mg protein], using a tritiated derivative of levetiracetam ($[^3\text{H}]$ ucb 30889). $[^3\text{H}]$ LEV and $[^3\text{H}]$ ucb 30889 are structurally related radioligands. $[^3\text{H}]$ ucb 30889 was preferentially used in binding studies, as it displayed a ten-fold higher affinity than $[^3\text{H}]$ LEV for their binding sites. In the rat, both radioligands were shown to label the same binding sites. These sites have the same tissue distribution and are almost exclusively restricted to the brain. All sites, in the rat, labeled by $[^3\text{H}]$ ucb 30889 can be displaced by unlabeled LEV. Experimental data indicate that this binding site labeled by $[^3\text{H}]$ ucb 30889 appears to be the synaptic vesicle protein SV2A. $[^3\text{H}]$ ucb 30889 was also suggested to bind to SV2A in human brain [K_d of 53 ± 7 nM and B_{max} of 3.6 ± 0.7 pmol/mg protein] and in CHO cells expressing the human recombinant protein. Measurement of $[^3\text{H}]$ ucb 30889 binding to brain membranes from SV2A knockout mice was 79 ± 9 DPM/assay vs. 933 ± 65 DPM/assay in brain membranes from wild type mice. $[^3\text{H}]$ ucb 30889 binds to SV2A but not to the related isoforms SV2B and SV2C, expressed in fibroblasts. In Chinese hamster ovary (CHO) cells and tissue from the human cerebral cortex, the binding curves in competition experiments did not reveal the existence of the multiple SV2A binding sites that are observed with $[^3\text{H}]$ ucb 30889. This indicates that LEV is

non-selective or poorly selective with respect to the different SV2A binding sites.

The clinical relevance of these data to humans is unknown.

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 to 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 to 5000 mg. Steady-state is achieved after two days of a twice daily administration schedule. Mean peak concentrations (C_{max}) are 31 and 43 mcg/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 pharmacologically inactive 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. 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 evidence for enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hours and was unaffected by dose, route of administration 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 renal clearance is 0.6 mL/min/kg. Approximately 93% of the dose was excreted within 48 hours. 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 and clearance is thus reduced in patients with impaired renal function (see [7 WARNINGS AND PRECAUTIONS, Renal](#) and [4.2 Recommended Dose and Dosage Adjustment, Patients with Impaired Renal Function](#)).

Special Populations and Conditions

- **Pediatrics (6 to 12 years of age):** Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6 to 12 years) after a single dose. The apparent clearance of levetiracetam adjusted to body weight was approximately 40% higher than in epileptic adults.
- **Geriatrics (61 to 88 years of age):** Pharmacokinetics of levetiracetam were evaluated in

16 elderly patients, 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 bid 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 body weight were comparable.
- **Ethnic origin:** Formal pharmacokinetic studies of the effects of race have not been conducted. Because levetiracetam is primarily renally excreted and there are no known important racial differences in creatinine clearance, significant 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 $<60 \text{ mL/min}/1.73 \text{ m}^2$ (see [7 WARNINGS AND PRECAUTIONS](#) and [4 DOSAGE AND ADMINISTRATION](#)).
- **Renal Insufficiency:** Single dose pharmacokinetics were performed in 20 subjects with renal impairment (N=7 mild/ CL_{cr} of 50 to 79 mL/min; N=8 moderate/ CL_{cr} of 30 to 49 mL/min; N=5 severe/ $CL_{cr} <30 \text{ mL/min}$), 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 [7 WARNINGS AND PRECAUTIONS](#) and [4 DOSAGE AND ADMINISTRATION](#)).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C-30°C.

12 SPECIAL HANDLING INSTRUCTIONS

No Special Handling Instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

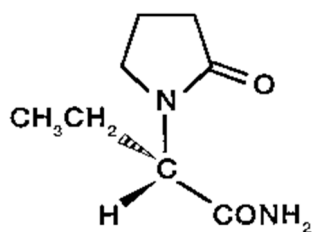
Drug Substance

Proper name: levetiracetam

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

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

Structural formula:



Physicochemical properties:

Physical Form: a white to off-white crystalline powder with a faint odor and a bitter taste.

Solubility: It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane.

pKa and pH values: The pKa of levetiracetam is <-2 and cannot be determined with accuracy due to the chemical instability of the protonated form.

The protonation of levetiracetam starts at H_0 values between -1 and -2.

Partition co-efficient: $\Delta \log P$ ($\log P_{\text{octanol}} - \log P_{\text{cyclohexane}}$) was calculated at pH 7.4 using phosphate buffered saline and at pH 1.0 using KCl/HCl. The $\Delta \log P$ at pH 7.4 is 3.65 and at pH 1.0 is 3.10.

Melting Range: 115 °C to 119 °C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 6 - Summary of Patient Demographics for Clinical Trials in Epilepsy

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
N132	Phase III, multicentre, randomized, add-on, double-blind, placebo-controlled, parallel-group	Levetiracetam: 1000 mg/day, 3000 mg/day Placebo Oral Up to 38 weeks <u>Baseline:</u> 12 weeks <u>Titration:</u> 6 weeks <u>Evaluation:</u> 12 weeks <u>Withdrawal:</u> 8 weeks	294	38 (16 - 70)	178 M 116 F
N051	Phase III, double-blind, two-period and three-treatment crossover, placebo-controlled, randomized, add-on, multicentre	Levetiracetam: 1000 mg/day, 2000 mg/day Placebo Oral Up to 48 weeks <u>Baseline:</u> 12 weeks <u>Transition period A:</u> 4 weeks <u>Evaluation period A:</u> 12 weeks <u>Transition period B:</u> 4 weeks <u>Evaluation period B:</u> 12 weeks	324	37 (14 - 69)	157 M 167 F

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
		<u>Withdrawal</u> : 2 weeks			
N138	Phase III, unbalanced, multicentre, double-blind, parallel-group, placebo-controlled, responder-selected	Levetiracetam: 3000 mg/day Placebo Oral Part I: Efficacy under add-on treatment Up to 30 weeks <u>Baseline</u> : 12 weeks <u>Up-titration</u> : 4 weeks <u>Evaluation period A</u> : 12 weeks <u>Add-on evaluation</u> : 12 weeks <u>Responder selection</u> : 2 weeks <u>Withdrawal</u> : 6 weeks Part II: Efficacy under monotherapy Up to 24 weeks <u>Therapy shift</u> : 12 weeks <u>Monotherapy</u> : 12 weeks <u>Withdrawal</u> : 6 weeks	286	36 (17 - 70)	138 M 148 F

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 seizures 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 Schedules

After a prospective baseline period of approximately 12 weeks, patients 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- to 14-week maintenance period.

Study Results

- **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 primary 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 displayed in Table 7.

Table 7 - Median Percent Reduction from Baseline in Weekly Frequency of Partial Onset Seizures in Study N132

	AEDs + 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 crossover 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 8.

Table 8 - Median Percent Reduction from Baseline in Weekly Frequency of Partial Onset Seizures in Study N051 Period A

	AEDs + 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 9 displays the efficacy results for Study N138.

Table 9 - Median Percent Reduction from Baseline in Weekly Frequency of Partial Onset Seizures in Study N138

	AEDs + Placebo	AEDs + Levetiracetam 3000 mg/day
N	104	180

	AEDs + Placebo	AEDs + Levetiracetam 3000 mg/day
Median baseline seizure frequency	1.78	1.67
Percent reduction in partial seizure frequency from baseline	7.3%	36.8%*

*P<0.001 versus placebo

- **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 10.

Table 10 - Partial Onset Responder Rate over the Entire Treatment Period by Randomized Dose

Percent Reduction	AEDs + 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%

14.2 Comparative Bioavailability Studies

A blinded, randomized, two-treatment, two-period, single oral dose (1 x 750 mg), crossover comparative bioavailability study of PRO-LEVETIRACETAM tablets, 750 mg (Pro Doc Ltée) and KEPBRA® tablets, 750 mg (Lundbeck Canada Inc.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 15 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Levetiracetam (1 x 750 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (mcg·h/mL)	190 191 (9)	192 193 (11)	98.8	96.1 – 101.5
AUC _I (mcg·h/mL)	197 198 (10)	199 201 (12)	98.8	96.1 – 101.6
C _{max} (mcg/mL)	21.0 21.8 (29)	20.8 21.3 (21)	100.9	92.4 – 110.2
T _{max} ³ (h)	0.52 (36)	0.71 (48)		
T _½ ³ (h)	7.33 (11)	7.29 (11)		

¹ PRO-LEVETIRACETAM (levetiracetam) tablets, 750 mg (Pro Doc Ltée)

² KEPPRA® (levetiracetam) tablets, 750 mg (Lundbeck Canada Inc.)

³ Expressed as the arithmetic mean (CV %) only

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 intravenous (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 α 2-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 for up to 2 weeks of ucb L057, the major human metabolite, indicate a low potential for toxicity in rats and dogs.

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.

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/m² 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 4000 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.

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/m² 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. This dose was toxic for the mothers. This dose represents 60-fold the upper recommended dose in man on a mg/kg/day basis, or 12-fold on a mg/m² 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/m² 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

1. KEPPRA® (tablets, 250 mg, 500 mg, and 750 mg), submission control 268666, Product Monograph, UCB Canada Inc. (MAR 07, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **PRO-LEVETIRACETAM – 250**

Pr **PRO-LEVETIRACETAM – 500**

Pr **PRO-LEVETIRACETAM – 750**

Levetiracetam Tablets

Read this carefully before you start taking **PRO-LEVETIRACETAM** and each time you get a refill. 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 **PRO-LEVETIRACETAM**.

What is **PRO-LEVETIRACETAM** used for?

PRO-LEVETIRACETAM is used in adults to help reduce the number of seizures. It is to be used with other seizure medicines.

How does **PRO-LEVETIRACETAM** work?

PRO-LEVETIRACETAM belongs to the family of medicines called antiepileptics for treating epilepsy. The exact way that **PRO-LEVETIRACETAM** works to treat seizures is not known.

What are the ingredients in **PRO-LEVETIRACETAM**?

Medicinal ingredients: levetiracetam

Non-medicinal ingredients: anhydrous citric acid, colloidal silicon dioxide, copovidone, ferric oxide red (750 mg only), ferric oxide yellow (500 mg and 750 mg), hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

PRO-LEVETIRACETAM comes in the following dosage forms:

Film-coated tablets: 250 mg, 500 mg and 750 mg.

Do not use **PRO-LEVETIRACETAM** if:

- you are allergic to levetiracetam or to any of the other ingredients in **PRO-LEVETIRACETAM** (see [What are the ingredients in PRO-LEVETIRACETAM?](#)).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PRO-LEVETIRACETAM. Talk about any health conditions or problems you

may have, including if you:

- have any health problems, including ones you have had in the past
- have kidney disease
- have had to ever shown unusual sensitivity (rash or any other signs of allergy) to any other antiepileptic drugs
- have recurrent infections or blood coagulation disorders
- have or have had a history of any heart problems or problems with the way your heart beats
- take any medicines that affect the heart or how it beats
- are pregnant or thinking about becoming pregnant. Taking more than one antiepileptic medication during pregnancy increases the risk of birth defects.
 - You and your healthcare professional will have to decide if PRO-LEVETIRACETAM is right for you while you are pregnant
 - If you use PRO-LEVETIRACETAM while you are pregnant, ask your healthcare provider about joining the North American Antiepileptic Drug Pregnancy Registry by calling 1-888-233-2334 (toll free). Women who are pregnant and planning to take PRO-LEVETIRACETAM should call the pregnancy registry. It will enable the collection of valuable data about PRO-LEVETIRACETAM use in pregnancy
- are breastfeeding or planning to breastfeed. PRO-LEVETIRACETAM is known to pass into breast milk and may harm your baby. You and your healthcare professional should decide whether you should take PRO-LEVETIRACETAM or breastfeed, but not both
- are 65 years of age or older
- have severe liver problems
- are of Japanese descent
- have seizures associated with a particular genetic mutation called SCN8A mutation. Ask your healthcare professional if you are unsure

Other warnings you should know about:

Driving and Operating Machinery: PRO-LEVETIRACETAM may affect your coordination and make you feel sleepy and tired. You should not drive or operate machinery until you know how PRO-LEVETIRACETAM affects you.

Changes in behaviour: You should pay attention to any mental changes, especially sudden changes in your mood, behaviours, thoughts, or feelings. Call your healthcare professional **right away**, if you 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 PRO-LEVETIRACETAM. If at any time you have these thoughts, get medical help right away. **Do NOT** stop PRO-LEVETIRACETAM on your own.

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 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
- allergic reactions (anaphylaxis or angioedema) such as swelling of the face, lips, eyes, tongue, and throat, trouble swallowing or breathing, and hives

Worsening Seizures: Your seizures may get worse:

- when you begin your treatment with PRO-LEVETIRACETAM, or your dose is increased;
- if you take PRO-LEVETIRACETAM to treat seizures associated with a particular genetic mutation (i.e., SCN8A mutation). PRO-LEVETIRACETAM may also be ineffective in treating these seizures.

Tell your healthcare professional if you notice your seizures remain present. If they get worse, tell your healthcare professional **right away**.

See the "[Serious side effects and what to do about them](#)" table, below, for more information on these and other serious side effects.

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

The following may interact with PRO-LEVETIRACETAM:

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

How to take PRO-LEVETIRACETAM:

- Take PRO-LEVETIRACETAM exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take PRO-LEVETIRACETAM in the morning and in the evening at about the same time each day.
- PRO-LEVETIRACETAM can be taken with or without food.
- Swallow the tablets with water.
- After taking PRO-LEVETIRACETAM you may have a bitter taste in your mouth.

Remember: This medicine has been prescribed only for you. Do not give it to anybody else.

Usual dose:

- The usual starting dose of PRO-LEVETIRACETAM is 500 mg twice a day, once in the morning and once in the evening.
- Based on your response and your tolerability, your healthcare professional may increase your daily dose.
- Your healthcare professional may prescribe you a different dose if you have problems with your kidneys.

Stopping treatment: If your healthcare professional decides to stop your treatment with PRO-LEVETIRACETAM, they will decrease the dose slowly. This is to help prevent your symptoms from coming back again or becoming worse.

- **Do NOT** stop taking PRO-LEVETIRACETAM unless your healthcare professional has told you to. Stopping a seizure medicine suddenly can cause you to have seizures that will not stop (status epilepticus). This can be very serious.
- Never change the dose yourself

Overdose:

If you think you, or a person you are caring for, have taken too much PRO-LEVETIRACETAM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take it as soon as you remember, and then go on as usual. However, if it is almost time for your next dose, skip the dose you forgot and continue with your next scheduled dose. **Do not take two doses at the same time.**

What are possible side effects from using PRO-LEVETIRACETAM?

These are not all the possible side effects you may have when taking PRO-LEVETIRACETAM. If you experience any side effects not listed here, tell your healthcare professional.

The most frequently observed side effects are:

- sleepiness
- lack or loss of strength
- infection (such as a common cold)
- dizziness

Other side effects include:

- vertigo (sensation of rotation)
- loss of memory (amnesia)
- bruising
- toothache
- sore throat, runny nose, stuffed nose/head (sinusitis)
- hair loss (alopecia)
- headache

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Thoughts of suicide or hurting yourself			✓
RARE			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Extreme sleepiness and tiredness and/or difficulty coordinating muscles normally		✓	
Mood and Behaviour changes: aggression, agitation, anger, anxiety, apathy (lack of enthusiasm), depression, hostility, mood swings, personality disorder, nervousness / irritability, repeated unwanted thoughts or sensations or the urge to do something over and over again		✓	
Serious skin reactions (Stevens - Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)): any combination of itchy skin rash, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark urine			✓
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			✓
Worsening seizures			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN FREQUENCY			
Psychotic symptoms: hallucination (seeing or hearing things that are not really there), delusions (false or strange thoughts or beliefs), paranoia (intense feeling of distrust, fear of persecution) and unusual behaviour		✓	
Rhabdomyolysis: (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine			✓
Neuroleptic Malignant Syndrome (more common in people of Japanese descent): pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			✓
Liver disorder: nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark 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:

Store tablets between 15°C-30°C.

Keep out of reach and sight of children.

If you want more information about PRO-LEVETIRACETAM:

- 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 (<http://www.apotex.ca/products>), or by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or medinfo@prodoc.qc.ca.

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