PRODUCT MONOGRAPH

Pr LEVETIRACETAM

Levetiracetam

Tablets of 250 mg, 500 mg, and 750 mg

USP

Antiepileptic Agent

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[Pr] LEVETIRACETAM

levetiracetam

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablet 250 mg, 500 mg, and 750 mg	colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, macrogol, maize starch, polyvinyl alcohol - part hydrolysed, povidone, talc and titanium dioxide and coloring agents. The individual tablets contain the following coloring agents: 250 mg tablets: FD&C Blue # 2 500 mg tablets: Iron Oxide Yellow 750 mg tablets: FD&C Blue # 2, Iron Oxide Yellow and Iron Oxide Red

INDICATIONS AND CLINICAL USE

Adults

LEVETIRACETAM (Levetiracetam) are indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

Geriatrics (≥ 65 years of age):

There were insufficient numbers of elderly patients in controlled trials for epilepsy to adequately assess the efficacy or safety of levetiracetam in these patients. Only 9 of 672 patients treated with levetiracetam were 65 or over (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics, DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions, Geriatrics)**.

Pediatrics (< 18 years of age):

Safety and efficacy in patients below the age of 18 have not been studied (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics)**.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING SECTION** of the product monograph.

WARNINGS AND PRECAUTIONS

Neurologic

Somnolence and Fatigue

No studies on the effects on the ability to drive and use machines have been performed. 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 **ADVERSE REACTIONS**). Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

Dependence/Tolerance

As with all antiepileptic drugs, LEVETIRACETAM should be withdrawn gradually to minimize the potential of increased seizure frequency.

Psychiatric

Suicidal Ideation and Behavior

Suicidal ideation and behavior 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 behavior and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior 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 behavior 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

behavior 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 behavior 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.

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, 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

Levetiracetam can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms in cases reported in the postmarketing 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. Levetiracetam should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

Carcinogenesis and Mutagenesis

See **Product Monograph Part II: TOXICOLOGY, Carcinogenicity and Mutagenicity** for discussion on animal data.

Hematologic Abnormalities

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.

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 **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

Special Populations

Patients with Renal Impairment:

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 **ACTIONS AND CLINICAL PHARMACOLOGY, 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 **DOSAGE AND ADMINISTRATION**).

Pregnant Women:

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 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.

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.

Pregnancy Registry:

Pregnant patients taking 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/

Nursing Women:

Levetiracetam is excreted in breast milk. Therefore, there is a potential for serious adverse reactions from 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.

Pediatrics (< 18 years of age):

Safety and efficacy in patients below the age of 18 have not been studied.

Geriatrics (≥65 years of age):

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 61-88 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.

ADVERSE REACTIONS

Adverse Drug 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.

Clinical Trial Adverse Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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) behavioral/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 behavioral/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 1: 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%
Behavioral/ psychiatric symptoms		
Nonpsychotic[1]	14%	6%
Psychotic[2]	1%	0%
Coordination difficulties[3]	3%	2%

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

[1]"Non-psychotic behavioral/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 behavioral/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 2 for incidence rate of individual AEs contained within the categories.

Behavioral/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 2: 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%
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 3 lists the most common (>1%) adverse events that resulted in discontinuation or dose reduction.

Table 3: 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.

Post-Market Adverse Drug 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.

Nervous system disorders: encephalopathy, paraesthesia, choreoathetosis, dyskinesia, lethargy, gait disturbance

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.

Hepatic/Biliary/Pancreatic: abnormal liver function test, hepatitis, hepatic failure, pancreatitis (see **Hepatic Failure** section below)

Psychiatric: abnormal behavior, anger, panic attack, anxiety, confusional state, delirium, hallucination, psychotic disorders, (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Central Nervous System Adverse Events**) suicidal behavior (including completed suicide) (See **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.

Skin and subcutaneous tissue disorders: Toxic Epidermal Necrolysis, Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptom (DRESS), erythema multiforme, angioedema (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions)**, alopecia: in several alopecia cases, recovery was observed when levetiracetam was discontinued.

Immune System Disorders: Hypersensitivity reactions such as SJS, TEN, DRESS and anaphylactic reactions (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**).

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

Fetal toxicity associated with concomitant use of levetiracetam and other antiepileptic drugs has been reported in pregnancy registries.

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.

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 pharmacokinetic 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.

Alcohol

No data on the interaction of levetiracetam with alcohol is available.

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 levonorgesterol, 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.

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.

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.

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). $C^{SS}{}_{max}$ 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 probenecid was not studied.

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.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been reported.

DOSAGE AND ADMINISTRATION

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.

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

Patients with Impaired Renal Function

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, levetiracetam dosage should be reduced in patients with impaired renal function (see Table 4 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.

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

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

Then CL_{cr} is adjusted for body surface area (BSA) as follows:

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

Table 4: Dosing Adjustment For Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min/1.73m^2)	Dosage and Frequency
Normal	≥80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe*	<30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis (1)	-	500 to 1000 mg once daily

(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 / 1.73m^2.

Elderly Patients

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

Missed Dose

If the patient misses a dose by a few hours, they should be instructed to take 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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 a least 233 times the maximum clinically studied dose.

Treatment

There is no 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 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.

ACTION AND CLINICAL PHARMACOLOGY

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 **PHARMACOLOGY, Preclinical Studies**, for experimental *in vitro* and *in vivo* data in animals).

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 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 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.

Excretion:

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 **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Special Populations and Conditions

Pediatrics:

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

Geriatrics:

Pharmacokinetics of levetiracetam were evaluated in 16 elderly patients, ranging in age from 61-88 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.

Gender:

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.

Race:

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 mL / min / 1.73 m^2 (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency:

Single dose pharmacokinetics were performed in 20 subjects with renal impairment (N=7 mild/CL_{cr} of 50-79 mL / min; N=8 moderate/CL_{cr} of 30-49 mL / min; N=5 severe/CL_{cr}<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 **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store between 15-30°C (59-86°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

LEVETIRACETAM 250 mg are blue coloured, oblong shaped, biconvex, scored film coated tablet, debossed with “LT” and “1” on either side of scoreline and plain on other side. They are supplied in bottles of 120 tablets.

LEVETIRACETAM 500 mg are yellow coloured, oblong shaped, biconvex, scored film coated tablet, debossed with “LT” and “2” on either side of scoreline and plain on other side. They are supplied in bottles of 120 tablets.

LEVETIRACETAM 750 mg are orange coloured, oblong shaped, biconvex, scored film coated tablet, debossed with “LT” and “3” on either side of scoreline and plain on other side. They are supplied in bottles of 120 tablets.

Composition:

LEVETIRACETAM are available in 3 strengths, namely 250 mg, 500 mg, and 750 mg. Each tablet contains the labeled amount of levetiracetam as the active (medicinal) ingredient.

The following inactive ingredients are common to all tablet strengths: colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, maize starch, and povidone.

In addition, all tablet strengths contain macrogol, polyvinyl alcohol - part hydrolysed, talc and titanium dioxide.

Colorants are present in the tablets as follows:

250 mg tablets: FD&C Blue # 2
500 mg tablets: Iron Oxide Yellow
750 mg tablets: FD&C Blue # 2, Iron Oxide Yellow and Iron Oxide Red

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

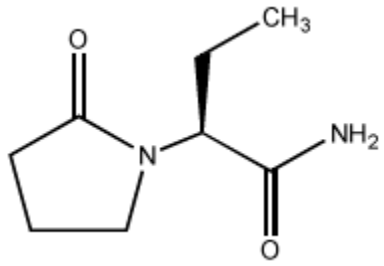
Proper name: levetiracetam

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

Molecular formula: $C_8H_{14}N_2O_2$

Molecular Weight: 170.21

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: Δ log P (log $P_{octanol}$ – log $P_{cyclohexane}$) was calculated at pH 7.4 using phosphate buffered saline and at pH 1.0 using KCl/HCl. The Δ log P at pH 7.4 is 3.65 and at pH 1.0 is 3.10.

Melting Range: 115-119°C

CLINICAL TRIALS

Comparative bioavailability studies

Study 281-09 was a double blind, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of 1 x 750 mg LEVETIRACETAM (Laboratoire Riva Inc.) and Keppra® (UCB Pharma Inc.) conducted in normal, healthy, adult, human subjects under fasting conditions. Data from 24 subjects who completed the study are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Levetiracetam (1 x 750 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval
AUC_T (mcg.h / mL)	199.08 200.67 (12.9%)	202.63 204.16 (12.4%)	98.2%	96.92 – 99.59 %
AUC_I (mcg.h / mL)	205.26 206.68 (12.0%)	208.97 210.47 (12.1%)	98.2%	97.20 – 99.26%
C_{max} (mcg / mL)	23.94 24.79 (28.2%)	24.07 24.56 (20.5%)	99.5%	91.36 – 108.28%
T_{max} (h)§	0.50 (0.33 – 2.00)	0.50 (0.33 – 3.00)		
$T_{½}$ (h)€	7.59 (9.1%)	7.56 (9.3%)		

* LEVETIRACETAM 750 mg – (Laboratoire Riva Inc.)
† Keppra® Tablets 750 mg (Levetiracetam 750 mg) - Manufactured for UCB Canada Inc.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Study demographics and trial design

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 12-14 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 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 5.

Table 5: 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 6.

Table 6: 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 7 displays the efficacy results for Study N138.

Table 7: 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
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 8.

Table 8: 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%

DETAILED PHARMACOLOGY

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 μM 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-asparate) 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}H] ucb 30889). [^{3}H]LEV and [^{3}H]ucb 30889 are structurally related radioligands. [^{3}H]ucb 30889 was preferentially used in binding studies, as it displayed a ten-fold higher affinity than [^{3}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}H]ucb 30889 can be displaced by unlabeled LEV. Experimental data indicate that this binding site labeled by [^{3}H]ucb 30889 appears to be the synaptic vesicle protein SV2A. [^{3}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}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}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}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.

TOXICOLOGY

General Toxicity

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

Reproductive 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. 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 / 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.

Carcinogenesis and Mutagenesis

Carcinogenesis

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 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.

Mutagenesis

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.

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Product Monograph for Keppra® (UCB Pharma Inc.) Date of Revision: September 20, 2018. Control No. 217699.

PART III: CONSUMER INFORMATION

Pr LEVETIRACETAM
(Levetiracetam Tablets)

This leaflet is part III of a three-part "Product Monograph" published when LEVETIRACETAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LEVETIRACETAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

LEVETIRACETAM is a prescription medicine used to help reduce the number of seizures when taken together with other seizure medicines, in adults 18 years and older.

What it does:

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

When it should not be used:

Do not take LEVETIRACETAM if you are allergic to levetiracetam or any of the other ingredients in LEVETIRACETAM listed in the "nonmedicinal ingredients" section below.

What the medicinal ingredient is:

levetiracetam

What the nonmedicinal ingredients are:

LEVETIRACETAM nonmedicinal ingredients: colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, macrogol, maize starch, polyvinyl alcohol - part hydrolysed, povidone, talc and titanium dioxide and coloring agents.

The individual tablets contain the following coloring agents:

250 mg tablets: FD&C Blue # 2
500 mg tablets: Iron Oxide Yellow
750 mg tablets: FD&C Blue # 2, Iron Oxide Yellow and Iron Oxide Red

What dosage forms it comes in:

LEVETIRACETAM are available as tablets containing 250 mg, 500 mg, or 750 mg levetiracetam.

WARNINGS AND PRECAUTIONS

Because LEVETIRACETAM can affect your mental alertness and coordination, it is very important not to perform any potentially hazardous tasks such as driving a car or operating machinery until you know how LEVETIRACETAM affects you.

A small number of people may have thoughts of suicide (harming or killing themselves) when taking antiepileptic drugs such as LEVETIRACETAM.

If at any time you have these thoughts, immediately contact your doctor. **Do not discontinue 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. Serious skin reactions known as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported with levetiracetam. Although very rare, severe forms of these reactions may lead to death. Seek immediate medical attention if you develop any combination of:

- 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.

BEFORE you use LEVETIRACETAM talk to your doctor or pharmacist if:

- you have any health problems, including ones you have had in the past;
- you have kidney disease;
- you have ever shown unusual sensitivity (rash or any other signs of allergy) to any other antiepileptic drugs;
- you are taking any medication, including ones you can get without a prescription;
- you have recurrent infections or blood coagulation disorders;
- you are pregnant or thinking about becoming pregnant. Taking more than one antiepileptic medication during pregnancy increases the risk of birth defects. You and your doctor will have to decide if LEVETIRACETAM is right for you while you are pregnant. If you use LEVETIRACETAM while you are pregnant, ask your healthcare provider about joining the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free). Women who are pregnant and planning to take LEVETIRACETAM should call the pregnancy registry to enable collection of valuable data about LEVETIRACETAM use in pregnancy;
- you are breastfeeding. LEVETIRACETAM is known to pass into breast milk and may harm your baby. You and your doctor should decide whether you

should take LEVETIRACETAM or breastfeed, but not both.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you take including prescription or non-prescription medicines, vitamins or herbal supplements. LEVETIRACETAM and other medicines may affect each other.

If you are a female patient taking an oral contraceptive, watch for irregular menstruation or spotting and immediately report such occurrences to you doctor as this may be an indication that the oral contraceptive many not be working properly and you may get pregnant.

Tell your doctor if you are taking a drug called methotrexate, used to treat certain types of cancer, severe psoriasis, and rheumatoid arthritis. Taking LEVETIRACETAM and methotrexate together can be harmful.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:

LEVETIRACETAM are taken orally twice a day, once in the morning and once in the evening, at about the same time each day. The treatment with LEVETIRACETAM usually starts with a dose of 1000 mg given half (500 mg) in the morning and half (500 mg) in the evening. After two weeks your dose may be increased. The typical daily maintenance dose is between 1000 mg and 3000 mg.

Your doctor may use a different dose if you have problems with your kidneys.

LEVETIRACETAM can be taken with or without food. After administration, the bitter taste of levetiracetam may be experienced.

If your doctor decides to stop your treatment with LEVETIRACETAM, he/she will decrease the dose step by step. This is to prevent your symptoms from coming back again or becoming worse.

It is very important that you take LEVETIRACETAM exactly as your doctor has instructed. Do not stop taking it abruptly. Never change the dose yourself. Do not stop taking LEVETIRACETAM or any other seizure medicine unless your healthcare provider told you to. Stopping a seizure medicine all at once can cause seizures that will not stop (status epilepticus), a very serious problem.

Tell your healthcare provider if your seizures get worse or if you have any new types of seizures.

Remember: This medicine has been prescribed only for you. Do not give it to anybody else. If you require any further information or advice, please consult your doctor or pharmacist.

Overdose:

In case of drug overdose, contact a health care practitioner, 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 go on as usual. **Do not take two doses at the same time**.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most frequently observed side effects are:

- sleepiness
- weakness
- infection (such as a common cold)
- dizziness

Other side effects include:

- mood and behaviour changes such as anxiety, irritability or anger, depression, nervousness, personality disorder, and hostility
- lack of coordination
- vertigo (sensation of rotation)
- abnormal thinking
- loss of memory (amnesia)
- bruising
- toothache
- sore throat, runny nose, stuffed nose/head (sinusitis)

Some people may experience extreme sleepiness and tiredness and difficulty coordinating muscles normally.

Hair loss (alopecia) has been reported; in several cases when levetiracetam was discontinued, the hair grew back.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Seek Emergency Medical Attention**
		Only if severe	**In all cases**	
Uncommon	Thoughts of suicide or hurting yourself			✓
Rare	**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.			✓
	Serious skin reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms): 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.			✓
	Extreme sleepiness and tiredness and/or difficulty coordinating muscles normally.		✓	
	Mood and behaviour changes such as anxiety, irritability or anger, depression.		✓	
	Rhabdomyolysis: muscle pain or weakness, dark urine			✓

This is not a complete list of side effects. For any unexpected effects while taking LEVETIRACETAM, contact your doctor or pharmacist.

HOW TO STORE IT

Store tablets between 15–30ºC. Keep out of reach and sight of children.

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.

MORE INFORMATION

If you want more information about LEVETIRACETAM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling the sponsor Laboratoire Riva Inc. at 1-800-363-7988.

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