PRODUCT MONOGRAPH

Novo-Levetiracetam

Levetiracetam Tablets

750 mg

Antiepileptic

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PRODUCT MONOGRAPH
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Levetiracetam Tablets 750 mg
THERAPEUTIC CLASSIFICATION
Antiepileptic

ACTIONS 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

Summary

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.

Human Pharmacology

Pharmacokinetics

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 and Distribution

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

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 PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Special Populations

Elderly

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.

Pediatrics (6 to 12 years)

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.

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.

Renal Impairment

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

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

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

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 <70 mL/min (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

Clinical Trials

A Bioequivalence Study was conducted to compare the rate and extent of absorption of Levetiracetam from Teva Pharmaceuticals USA and Keppra from UCB Pharma Inc. Belgium for UCB Pharma Inc. USA; administered as a 1 x 750 mg tablet under fasting conditions in 22 healthy, adult subjects. The study design was a randomized, open-label, 2-way crossover, conducted under fasting conditions. Results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Levetiracetam (1 x 750 mg tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[◊]	Reference[†]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg x hr/mL)	170.938 173.932 (19.2%)	171.651 174.275 (17.9%)	100	96 – 103
AUC_I (mcg x hr/mL)	182.541 185.604 (19.1%)	182.404 184.636 (16.2%)	100	96 – 104
C_{max} (mcg/mL)	20.934 21.625 (26.4%)	22.699 23.501 (26.6%)	92	85 – 100
T_{max} [§] (hrs)	1.015 (59.7%)	0.781 (62.1%)		
$T_{½}$ [§] (hrs)	7.245 (17.5%)	6.959 (12.6%)		

◊ Test: Levetiracetam 750 mg Tablets (TEVA Pharmaceutical Industries, Ltd.)
† Reference: KEPPRA® 750 mg Tablets (Manufactured by UCB Pharma Inc. Belgium for UCB Pharma Inc. USA.). Purchased in the USA.
§ Expressed as the arithmetic mean (CV%) only

Clinical Efficacy

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 1.

Table 1: 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 2.

Table 2: 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 3 displays the efficacy results for Study N138.

Table 3: 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 4.

Table 4: 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%

INDICATIONS AND CLINICAL USE

Novo-Levetiracetam is indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in levetiracetam tablets.

WARNINGS

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.

See also PRECAUTIONS, Central Nervous System Adverse Events.

Withdrawal of Anti-Epileptic Drugs

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

PRECAUTIONS

General

Hematological Abnormalities

Minor but 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 ($\leq 2.8 \times 10^9$/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.

Central Nervous System Adverse Events (See WARNINGS)

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.

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

Table 5: 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 ADVERSE EVENTS, Table 6 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.

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, at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

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).

In patients with renal impairment Novo-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).

Pregnancy and Nursing

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. 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. The potential risk for humans is unknown. Novo-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

To facilitate monitoring of fetal outcomes of pregnant women exposed to levetiracetam, physicians should encourage patients to register, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

Nursing Mothers

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

Use in Pediatric Patients

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

Use in the Elderly

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.

There were insufficient numbers of elderly patients in controlled trials of epilepsy to adequately assess the efficacy or safety of levetiracetam in these patients. Nine of 672 patients treated with levetiracetam were 65 or over.

Drug Interactions

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. [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.

Clinical Pharmacokinetic Data

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.

Other Drug Interactions

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

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

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.

ADVERSE EVENTS

Commonly Observed

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.

Incidence of AEs in Controlled Clinical Trials

Table 6: 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		
Anmesia	2%	0%
Anxiety	2%	1%
Ataxia	3%	1%
Depression	4%	2%
Dizziness	9%	4%

Body System/ Adverse Event	Levetiracetam + AED Therapy (N = 672)	Placebo + AED Therapy (N=351)
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 7 lists the most common (>1%) adverse events that resulted in discontinuation or dose reduction."

Table 7: 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, hyperkinesias, memory impairment, myalgia, nasopharyngitis, pruritus, mood swings, and vision blurred.

Post-Marketing Experience

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: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of these cases), thrombocytopenia.

Metabolism and nutrition disorders: weight loss

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

Psychiatric: suicidal behavior (including completed suicide)

Skin: alopecia

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.

SYMPTOMS AND TREATMENT OF OVERDOSE

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 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.

DOSAGE AND ADMINISTRATION

General

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, reduced doses are recommended for patients with renal impairment.

Novo-Levetiracetam is given orally with or without food.

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

Novo-Levetiracetam dosage should be reduced in patients with impaired renal function (see Table 8 below). Patients with end stage renal disease should receive supplemental doses following dialysis. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

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

Table 8: Dosing adjustment for patients with impaired renal function

Group	**Creatinine Clearance (mL/min)**	**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 judgement

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 < 70 mL/min.

Elderly Patients

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

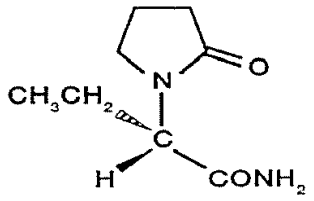
PHARMACEUTICAL INFORMATION

Drug Substance

U.S.A.N: levetiracetam

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

Structural Formula:



Molecular Formula: $C_8H_{14}N_2O_2$

Molecular Weight: 170.21

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 $_{cyctohexane}$) 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

Composition: Novo-Levetiracetam tablets contain the labeled amount of levetiracetam. Inactive ingredients include croscarmellose sodium, magnesium stearate, povidone, purified water, starch and coloring agents.

The individual tablets contain the following coloring agents:

750 mg tablets: Iron Oxide Yellow
FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake
Iron Oxide Red.

Stability and Storage Recommendations

Store between 15-30°C (59-86°F)

AVAILABILITY OF DOSAGE FORMS

Novo-Levetiracetam tablets, 750 mg are orange, oblong-shaped, biconvex film-coated tablets, engraved with 93 on one side, and 7287 on the other side. They are supplied in bottles of 120 tablets and 500 tablets.

INFORMATION FOR THE CONSUMER (PATIENT)

Novo-Levetiracetam
Levetiracetam Tablets 750 mg
Antiepileptic

Information For The Patient

Please read this information carefully before you start to take your medicine, even if you have taken this medicine before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. For further information or advice, please ask your doctor or pharmacist.

What Is Novo-Levetiracetam?

- Novo-Levetiracetam belongs to the family of medicines called antiepileptics for treating epilepsy.

- Novo-Levetiracetam has been prescribed for you by your doctor to reduce your number of seizures. It is taken with other seizure medications to help control seizures.

Important Points You Must Tell Your Doctor Before Taking Novo-Levetiracetam

- About all your medical conditions, especially if you have any kidney disease.

- If you are pregnant or thinking about becoming pregnant, or if you are breast-feeding.

- Any other medicines (prescription and nonprescription) you are taking.

How to Take Novo-Levetiracetam

- It is very important that you take Novo-Levetiracetam exactly as your doctor has instructed.

- Never change the dose yourself.

- Do not stop taking it abruptly.

- Novo-Levetiracetam tablets are taken orally twice a day (typically morning and evening). Novo-Levetiracetam can be taken with or without food.

- 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.

- Consult your doctor before taking any other medicines (prescription or nonprescription).

Precautions When Taking Novo-Levetiracetam

Contact your doctor immediately if you experience any severe, unusual or allergic reactions.

- When taking Novo-Levetiracetam, it is very important not to perform any potentially hazardous tasks such as driving a car or operating dangerous machinery until you are sure this medication does not affect your mental alertness or physical coordination.

- A very small number of people may have thoughts of suicide.

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

Side Effects

- The most frequently observed side effects are somnolence (sleepiness), asthenia (weakness), infection (such as common cold) and dizziness. Other side effects include abnormal thinking, amnesia (loss of memory), anxiety, ataxia (lack of coordination), depression, ecchymosis (bruising), emotional lability (mood swings), hostility, nervousness, personality disorder, pharyngitis (sore throat), rhinitis (runny nose), sinusitis (stuffed head), tooth disorders (toothache), vertigo (sensation of rotation).

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

- Mood and behavior changes such as anxiety, irritability or anger, and depression can also happen to some people.

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

What To Do In Case Of Overdose

Contact your doctor or nearest hospital emergency department or your regional Poison Control Centre, even though you may not feel sick.

How To Store Novo-Levetiracetam

Store tablets between 15-30°C (59-86°F).

Keep out of reach of children.

What Does Novo-Levetiracetam Contain?

The active medicinal ingredient is Levetiracetam. Novo-Levetiracetam is available as tablets containing 750 mg levetiracetam. Nonmedicinal ingredients in the tablets include croscarmellose sodium, magnesium stearate, povidone, purified water, starch and coloring agents.

The individual tablets contain the following coloring agents:
750 mg: Iron Oxide Yellow, FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake and Iron Oxide Red.

Who Manufactures Levetiracetam ?

Novo-Levetiracetam tablets are manufactured by Novopharm Ltd.

Reminder: 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.

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 10μM 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 displayed 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 to1800 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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