

New Zealand Datasheet

Name of Medicine

Levetiracetam Tablets

Levetiracetam 250mg, 500mg and 750mg film coated tablets.

Presentation

Levetiracetam 250mg tablets are light blue, capsule shaped, biconvex film coated tablets, plain on both sides. Each tablet contains 250 mg levetiracetam.

Levetiracetam 500mg tablets are yellow, capsule shaped, biconvex film coated tablets, plain on both sides. Each tablet contains 500 mg levetiracetam.

Levetiracetam 750mg tablets are light orange, capsule shaped, biconvex film coated tablets, plain on both sides. Each tablet contains 750 mg levetiracetam.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

Uses

Actions

While the exact mechanism of action by which levetiracetam causes seizure protection still needs to be fully determined, this mechanism of action differs from the existing anti-epileptic drugs (AED's). Levetiracetam does not appear to alter basic cell characteristics and normal neurotransmission during *in vitro* and *in vivo* experiments. No interactions with traditional drug-targets involved in inhibitory and excitatory neuro-transmission have been observed. The mechanism of action may relate to an interaction with a specific and stereo-selective binding site that is only found within the central nervous system.

Levetiracetam *in vitro* studies, report the reduction in the release of Ca^{2+} from intraneuronal stores and the affect on intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents. Levetiracetam in addition reverses the reduction in: GABA-; and glycine gated currents induced by β -carbolines and zinc. *In vitro* studies for levetiracetam have shown binding to a specific site in the brain tissue of rodents. This specific site is believed to be involved in vesicle fusion and neurotransmitter exocytosis and is known as the synaptic vesicle protein 2A (SV2A). In audiogenic seizure-prone mice, a rank order of affinity was shown for SV2A by levetiracetam and related analogues, which correlated with the potency of their antiseizure activity. Levetiracetam's antiepileptic mechanism of action may be due to interaction with SV2A (synaptic vesicle protein 2A).

Pharmacodynamics

In animals

In the classical screening models of anticonvulsants, levetiracetam is not active, however levetiracetam in a broad range of animal models induces potent protection in both primary and partial generalised seizures.

By dose-dependently inhibiting the development of kindling, levetiracetam displays potential anti-epileptogenic properties. This occurs even after the discontinuation of levetiracetam.

Clinical studies in animals found that levetiracetam has an unusually high safety margin between therapeutic doses and doses inducing adverse effects. There was no decrease on the seizure threshold after withdrawal from chronic treatment. An absence of undesirable effects on cognitive function and anxiolytic action and have also been observed.

In seizure models, ucb L057, the major metabolite, is inactive.

In man

The broad spectrum preclinical pharmacological profile is confirmed in both generalised and partial human epilepsy models (photoparoxysmal response/epileptiform discharge).

Pharmacokinetics

Levetiracetam is a permeable and highly soluble compound with a linear pharmacokinetic profile and low inter-subject and intra-subject variability. After repeated administration there is no modification of clearance.

Levetiracetam 1500mg given twice daily by IV infusion for 4 days confirms this pharmacokinetic profile.

In both adults and children there is a significant correlation between saliva and plasma levetiracetam concentrations. The ratio of saliva to plasma concentrations is 1 to 1.6 for the oral tablets and an oral solution formulation, 4 hours post dose.

Race, gender or circadian differences do not affect pharmacokinetics. In adult patients, the pharmacokinetic profile is comparable between epileptic patients and healthy volunteers (without epilepsy).

Adults and Adolescents

Absorption

After oral administration, levetiracetam is rapidly and almost completely absorbed and has an oral absolute bioavailability close to 100%. At 1.3 hours after dosing, peak plasma concentrations (C_{max}) are reached. After a twice daily administration schedule for two days, steady state is achieved. (C_{max}) peak concentrations are typically 31 μ g/mL following a single 1000 mg dose and 43 μ g/mL following repeated 1000mg b.i.d. dosing. Absorption is dose-independent. Absorption is not altered by food, but food slightly reduces the rate of absorption.

Distribution

Human tissue distribution data is not available. Neither the major metabolite ucb L057, or levetiracetam are significantly bound to plasma proteins (<10%). The volume of distribution of levetiracetam is close to the volume of distribution of intracellular and extracellular water which is approximately 0.5 to 0.7L/kg.

Metabolism

The major metabolite produced from levetiracetam is ucb L057 which results from an enzymatic hydrolysis of the acetamide group. This metabolic pathway for ucb L057 accounts for 24% of the dose. Acetamide group hydrolysis was measurable in a large number of tissues including whole blood, but not plasma. Production of ucb L057, the major metabolite is not supported by liver cytochrome P₄₅₀ isoforms.

Ucb L057, the major metabolite, is pharmacologically inactive.

Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (1.6% of dose), and opening of the 2-oxo-pyrrolidine ring in position 5 (0.9% of dose). There is no *in vivo* enantiomeric interconversion of levetiracetam or its major metabolite.

Only 0.6% of the dose accounted for other unidentified components.

Levetiracetam and its primary metabolite ucb L057, *in vitro*, do not inhibit the major human liver cytochrome P₄₅₀ isoforms (CYP3A4, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP1A2), epoxide hydrolysis and glucuronyl transferase (UGT1A1 and UGT1A6) activities. Valproic acid is not affected by *in vitro* glucuronidation by levetiracetam.

In a culture of human hepatocytes, levetiracetam had little effect on CYP1A1 and CYP1A2 or ethinylestradiol conjugation. There was mild induction of CYP3A4 and CYP2B6 by levetiracetam at high concentrations (680µg/mL), although at concentrations approximating C_{max} after repeated 1500mg twice daily dosage, the effects were not considered biologically relevant. Therefore the interaction of levetiracetam with other substances, or other substances interacting with levetiracetam, was considered unlikely.

Elimination

In adults, the plasma half-life was 7 ± 1 hours. The plasma half life did not vary with route of administration, repeated administration or dose. 0.96mL/min/kg was the mean total body clearance.

Excretion via urine, which was the major route of excretion, accounted for a mean of 95% of the dose. Approximately 93% of the dose was excreted within 48 hours. Faecal excretion accounted for only 0.3% of the dose. The cumulative urinary excretion of the major metabolite ucb L057 was 24%, while levetiracetam accounted for 66% during the first 48 hours.

The renal clearance is 0.6mL/min/kg, which indicates that levetiracetam excretion is via glomerular filtration, with subsequent tubular reabsorption.

The major metabolite ucb L057 is excreted by active tubular secretion, in addition to glomerular filtration, and the renal clearance is 4.2 mL/min/kg.

Elderly

The half-life is increased by 40% (10 to 11 hours) in elderly patients. This is attributed to the decrease in renal function in this patient population (refer Dosage and Administration).

Children (4 to 12 years of age)

In epileptic children (6 to 12 years of age) after a single dose of 20mg/kg, the half-life of levetiracetam was 6.0 ± 1.1 hours. In epileptic children (6 to 12 years of age) the apparent body clearance was approximately 30% higher than in epileptic adults.

In epileptic children (4 to 12 years of age), levetiracetam was rapidly absorbed following repeated administration of 20mg to 60mg/kg/day). Half an hour to one hour after dosing, peak plasma concentrations (C_{max}) were observed. Peak plasma concentrations and area under the curve were linear and dose proportional. The apparent body clearance was 1.1mL/min/kg and the elimination half-life was approximately 5 hours.

Infants and children (1 month to 4 years of age)

In epileptic children (1 month to 4 years of age) after a single dose of a 10% oral solution (20mg/kg) approx 1 hour after dosing, peak plasma concentrations were observed and levetiracetam was rapidly absorbed. The pharmacokinetic half life was shorter for children (5.3 hours) versus adults (7.2 hours) and the apparent clearance in children was faster (1.5mL/min/kg) versus adults (0.96mL/min/kg).

Renal impairment

Levetiracetam and its major metabolite ucb L057 apparent body clearances are correlated to the creatinine clearance. The levetiracetam daily maintenance dose should be adjusted based on creatinine clearance in patients with moderate and severe renal impairment (see Dosage and Administration).

In adult patients with anuric end stage renal disease, the half life was approx 25 hours during inter-dialytic periods and 3.1 hours during intra-dialytic periods respectively. During a typical 4 hour dialysis session the fractional removal of levetiracetam was 51%.

Hepatic impairment

In subjects with mild and moderate hepatic impairment, the clearance of levetiracetam was not changed. In most subjects with severe hepatic impairment, clearance was reduced by more than 50% compared to normal subjects, due to concomitant renal impairment (see Dosage and Administration).

Indications

Levetiracetam is indicated in epileptic patients aged 6 years and older, as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation.

Dosage and Administration

Levetiracetam film-coated tablets must be taken orally, with or without food, and swallowed with liquid. The daily dose is administered in two equal dose amounts ie 2 x 250mg or 2 x 500mg. Do not divide the tablet.

Adults (>18 years of age) and adolescents (aged 12-17 years of age) of 50kg or more

The therapeutic dose is 500mg twice daily as adjunctive therapy and this dose can be started on the first day of treatment.

The daily dose can be increased up to 1500mg twice daily depending upon the clinical response and tolerance. Every two to four weeks, dose changes can be made in 500mg

twice daily increments or decrements. The maximum recommended daily dose is 3000mg.

Elderly (65 years and older)

Adjustment of the dose is recommended in the elderly if they have compromised renal function (see Patients with renal impairment).

Children (aged 6 to 11 years of age) and adolescents (aged 12-17 years of age) of less than 50kg

The initial therapeutic dose is 10mg/kg twice a day (i.e. if 25kg then 250mg twice a day).

The daily dose can be increased up to 60mg/kg/daily (in two 30mg/kg/doses), dependent on clinical response and tolerance. 10mg/kg twice daily dose changes can be made in increments or decrements every two weeks. The lowest effective dosage should be used.

For children over 50kg the dosage is the same as in adults.

According to weight and dose, the physician should describe the most appropriate strength.

Recommended dosing in children aged 6 years and older.

Children 25kg

Starting dose: 250mg twice daily; Maximum dose: 750mg twice daily.

Children from 50kg*

Starting dose: 500mg twice daily. Maximum dose: 1500mg twice daily.

*The dosage in children and adolescents 50kg or greater is the same as adults.

Infants and children less than 6 years of age

Levetiracetam tablets are not recommended for use in children less than 6 years of age.

Patients with renal impairment

Dose adaptation may be required for the administration of levetiracetam in patients with renal impairment.

Table 1: Dosage schedule based on renal function (Adults)

Group	Creatinine clearance	Frequency	Dosage
	(mL/min)	(daily)	(mg)
End-stage renal disease patients undergoing dialysis (A 750mg loading dose is recommended on the first day of treatment with levetiracetam).	-	Once (following dialysis, a 250 to 500mg supplemental dose is recommended).	500 to 1,000
Severe	< 30	Twice	250 to 500
Moderate	30-49	Twice	250 to 750
Mild	50-79	Twice	500 to 1,000
Normal	> 80	Twice	500 to 1,500

In determining dosage, an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min is needed. The CL_{cr} in mL/min may be estimated from serum creatinine (mg/dL) using the following formula

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

Using (BSA) body surface area the CL_{cr} is adjusted using the following formulation:

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

For children with renal impairment, levetiracetam clearance is related to renal function, therefore dosage needs to be adjusted based on renal function. This advice is recommended based on an adult impaired renal function study.

Patients with impaired renal function

Monitoring of renal function in severe hepatic impaired patients is recommended before dose selection. The administration of levetiracetam to patients with renal impairment may require dose adaptation (see Dosage and Administration).

Patients with hepatic impairment

In patients with mild or moderate hepatic impairment no dose adjustment is needed. In patients with severe hepatic impairment when the creatinine clearance is < 70mL/min, a 50% reduction of the daily maintenance dose is recommended. This is because the creatinine clearance may underestimate the renal insufficiency.

Contraindications

This product should not be administered to patients who have known hypersensitivity to levetiracetam or any of the inactive ingredients in levetiracetam tablets (see Further Information).

Warnings and Precautions

Levetiracetam in accordance with current clinical practice should be withdrawn gradually if it has to be discontinued.

From placebo controlled clinical studies, an analysis of reports of suicidality (suicidal behaviour or ideation) on eleven medicines that were used to treat epilepsy, as well as psychiatric disorders and other conditions, revealed that compared to patients receiving placebo (0.22%), patients receiving antiepileptic drugs had approximately twice the risk of suicidal behaviour or suicidal ideation (0.43%).

After starting the anti-epileptic medicine, the increased risk of suicidal ideation and suicidal behaviour was observed as early as one week and continued through 24 weeks. Among the eleven medicines, the results were generally consistent. Patients who were treated for psychiatric disorders, epilepsy, and other conditions when compared to placebo were all at increased risk of suicidality. The increased risk could not be attributed to any specific demographic subgroup of patients. In the patients with epilepsy, the relative risk of suicidality was higher, compared to those patients who were given one of the medicines in the class for psychiatric or other conditions.

If starting any anti-epileptic drug, patients should be closely monitored for notable behaviour changes that could indicate the emergence or worsening of suicidal thoughts, suicidal behaviour or depression. Patients should also be closely monitored for the same notable behaviour changes (the emergence or worsening of suicidal thoughts, suicidal behaviour or depression) if they are also currently taking anti-epileptic drugs.

Patients, their families, and caregivers should be informed by Health Care Professionals of the potential for an increase in the risk of suicidality. If any symptoms suggestive of suicidality develop, prescribers should advise patients to immediately seek medical advice.

Plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight due to its complete and linear absorption. Levetiracetam should therefore not need any plasma level monitoring.

In patients less than 4 years of age, there is no data to date to support the use of levetiracetam.

There is no data available on the interaction of alcohol with levetiracetam.

Effects on fertility

Male and female fertility or reproductive performance was not observed to be adversely affected in rats administered at least two weeks prior to and throughout mating, at oral doses up to 1800mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m²). There is no human data on the effects of levetiracetam on male or female fertility.

Use in Pregnancy

In rabbits and rats, foetal levels of levetiracetam and/or its metabolites approximate maternal plasma levels as they cross the placenta. At doses similar to or greater than human therapeutic doses in rabbits and rats, there was evidence of developmental toxicity from levetiracetam.

At exposure levels similar, to or greater than, the human exposure in reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity (increased pup mortality, increase in skeletal variations/minor anomalies, retarded growth). In the rabbit, foetal effects were observed in the presence of maternal toxicity (increased malformations embryonic death, and increased skeletal anomalies). At the observed no effect level in the rabbit, the systemic exposure was about 4 to 5 times the human exposure.

In dogs and rats, in neonatal and juvenile studies, there were no adverse effects seen as demonstrated for any of the standard developmental or maturation endpoints at doses corresponding to 30 times the maximum recommended human dose i.e. up to 1800mg/kg/day.

As a result of antiepileptic medication, the risk of having an abnormal child is far outweighed by the dangers to the foetus and mother of uncontrolled epilepsy.

It is recommended that:

- Pre-pregnancy counselling is provided to women on (AEDs) antiepileptic drugs with regard to the risk of foetal abnormalities;
- During pregnancy AEDs should be continued and as the risk of abnormality is greater in women taking combined medication, monotherapy should be used if possible at the lowest effective dose;
- Four weeks prior to conception and for twelve weeks after conception, folic acid supplementation (5mg) should be taken;
- For the pregnant patient taking AED's, specialist prenatal diagnosis together with detailed mid-trimester ultrasound should be undertaken and offered.

Insufficient clinical data to date, on exposed pregnancies are available. Only if the potential benefit justifies the potential risk to the foetus should levetiracetam be used during pregnancy. Physiological changes during pregnancy may affect levetiracetam concentration, as with other antiepileptic drugs. Reports of decreased levetiracetam concentrations have been reported during pregnancy.

Use in Lactation

In lactating rats, levetiracetam and/or its metabolites are excreted in milk. Three hours after oral administration, peak milk concentrations occur (milk/plasma ratio of 0.9).

In human breast milk, levetiracetam is excreted. A decision should be made whether to discontinue breastfeeding or discontinue levetiracetam because of the potential for serious adverse reactions in breastfeeding infants. Such a decision should take into account the importance of levetiracetam to the mother.

Effects on Ability to Drive or Use Machines

No studies have been completed to evaluate the effects of levetiracetam on the ability of levetiracetam patients to drive and use machines. Some patients, due to different patient sensitivity, might experience somnolence or other CNS related symptoms at the beginning of treatment or following a dosage increase. In those patients, caution is recommended when performing skilled tasks e.g. driving vehicles, or operating machinery.

Adverse Effects

The prescriber should be aware that the adverse event incidence figures in the following tables were obtained when levetiracetam was added to concurrent antiepileptic therapy. It is not possible in all cases to determine which agent/s, if any, were responsible for the adverse effects.

The following tables identify adverse experiences during clinical studies. Patient characteristics and other factors may differ in the course of usual medical practice and therefore the following studies make it difficult to predict the frequency of adverse experiences.

Adult patients

Levetiracetam has been administered to more than 3000 subjects and patients. 185 for > 3 years, 366 for > 2 years, 592 for > 1 year and 780 patients were treated for > 6 months.

In controlled clinical trials in a total of 1023 adult patients with epilepsy, levetiracetam was used to treat 672 patients and 351 were given placebo.

Serious drug-related treatment-emergent adverse events were experienced by patients in placebo controlled trials. Patients in the levetiracetam group that experienced serious drug-related treatment-emergent adverse events accounted for 2.4% and in the placebo group this was 2.0%. In placebo controlled studies, 46.4% of levetiracetam patients experienced drug-related treatment-emergent adverse events and 42.2% of placebo patients.

Very common adverse events ($\geq 10\%$)

The very common adverse events (>10%) were accidental injury, asthenia, infection, headache and somnolence. Accidental injury was more common in the placebo group while asthenia, infection and somnolence appeared to occur more frequently in levetiracetam treated patients, and headache was similarly reported in the two groups.

Table 2: Incidence percentages of very common treatment-emergent adverse events in placebo-controlled studies in adults – as defined by body system:

Body System / Adverse Event	Number of placebo patients = 351	Number of patients treated with Levetiracetam = 672
	Percentage (%)	Percentage (%)
Nervous System Somnolence	9.7	14.9
Whole Body Accidental Injury	16.5	10.3
Headache	13.7	13.1
Asthenia	9.7	14.1
Infection	7.4	13.2

Incidence and severity of CNS related adverse effects in the pooled safety analysis decrease over time, although there was no clear dose-response relationship.

The term “infection” includes symptoms of community acquired infections (common cold and upper respiratory tract infections), more than 93% of the events are categorised under the COSTART preferred term “infection”. The other infections (urinary tract infections, lower respiratory tract infections etc) had no increase in incidence.

Although small, statistically significant decreases were seen in mean hemoglobin (0.9g/L), mean hematocrit (0.38%) and in total mean RBC count ($0.03 \times 10^6/\text{mm}^2$) in levetiracetam treated patients compared to those given the placebo.

A total of 2.4% of treated and 1.4% of placebo patients had at least one possibly significant ($\leq 1.0 \times 10^9/\text{L}$) decreased neutrophil count and 3.2% of treated and 1.8% of placebo patients had at least one possibly significant ($\leq 2.8 \times 10^9/\text{L}$) decreased WBC count. With the continuation of treatment, all but one of the treated patients with a low neutrophil count rose towards or to baseline treatment. The low neutrophil counts were not a cause for discontinuation of treatment for any patients.

Common adverse events ($\geq 1\%$, $< 10\%$):

Table 3: Common treatment-emergent adverse events percentage incidence in placebo-controlled studies:

Body System / Adverse Event	Number of placebo patients	Number of patients treated with Levetiracetam
	= 351	= 672
	Percentage (%)	Percentage (%)
Nervous system		
Amnesia	0.3	1.6
Anxiety	1.1	1.6
Ataxia	1.4	2.5
Convulsion	6.8	6.0
Depression	2.3	4.0
Dizziness	4.3	9.2
Emotional Lability	0.3	1.6
Insomnia	2.8	3.0
Nervousness	1.7	3.9
Paraesthesia	1.7	1.9
Thinking abnormal	1.4	1.5
Tremor	1.7	1.5
Vertigo	1.4	2.5
Digestive System		
Anorexia	2.0	2.4
Diarrhoea	5.1	4.2
Dyspepsia	3.4	2.8
Gastroenteritis	0.9	1.2
Gingivitis	0.6	1.2
Nausea	4.6	4.2
Tooth Disorder	0.6	1.5
Vomiting	2.0	2.2
Whole Body		
Abdominal Pain	5.1	3.7
Back Pain	4.6	4.0
Chest Pain	1.1	1.3
Drug Level Increased	0.9	1.3
Fever	1.7	1.3
Flu Syndrome	6.0	4.2

Hostility	0.6	2.1
Pain	6.6	6.5
Nutritional/Metabolic Disorders		
Weight gain	1.1	1.2
Lymph and Haemic System		
Ecchymosis	1.1	1.5
Skin and Appendages		
Rash	4.0	2.8
Urogenital System		
Urinary Tract Infection	3.4	1.9
Special Senses		
Amblyopia	1.4	1.2
Diplopia	1.7	2.4
Otitis media	0.9	1.2
Respiratory System		
Bronchitis	1.4	1.3
Cough Increased	1.7	2.1
Pharyngitis	3.7	5.7
Rhinitis	2.6	4.3
Sinusitis	0.9	2.1

The incidence of serious adverse events in placebo controlled studies was 8.9% in the placebo group compared to 9.9% in the levetiracetam group. For a population of patients with epilepsy many of these adverse events are typical. The serious adverse events which occurred in more than 1% of patients were accidental injury (1.6% in both levetiracetam and placebo group) and convulsion (1.8% in levetiracetam group compared to 1.4% in placebo group).

Paediatric patients

A paediatric patient study (4 to 16 years of age) showed that 40.2% in the placebo group and 55.4% of the levetiracetam paediatric patients experienced undesirable effects. With paediatric patients that experienced serious undesirable effects, 1.0% were taking placebo and 0.0% were taking levetiracetam. 20.6% of patients receiving placebo and 16.8% receiving levetiracetam, in the paediatric clinical study, either discontinued or had a dose reduction as a result of an adverse event. In the paediatric population the most commonly reported undesirable effects were hostility, somnolence, emotional lability, nervousness, anorexia, agitation, headache and asthenia. In paediatric patients, safety results were consistent with the safety profile of levetiracetam in adults, except for psychiatric and behavioural undesirable effects which were less common in adults than in children (18.6% in adults compared to 38.6% in children). There was also a lower incidence of behavioural psychiatric adverse events in the adult placebo group (10.5%)

compared to the children placebo group (27.8%) which confirmed that the relative risk was similar in children to adults.

Table 4: Treatment-emergent adverse events percentage incidence (adverse events that occurred in at least 2% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients) in a placebo-controlled, add-on study in paediatric patients aged 4-16 years, by body system.

Body System / Adverse Event	Number of placebo patients = 97 Percentage (%)	Number of patients treated with Levetiracetam = 101 Percentage (%)
Nervous System		
Somnolence	11	23
Hostility	6	12
Nervousness	2	10
Personality Disorder	7	8
Dizziness	2	7
Emotional Lability	4	6
Agitation	1	6
Depression	1	3
Vertigo	1	3
Reflexes Increased	1	2
Confusion	0	2
Lymph and Haemic System		
Ecchymosis	1	4
Whole Body		
Accidental Injury	10	17
Asthenia	3	9
Pain	3	6
Flu Syndrome	2	3
Face Oedema	1	2
Neck Pain	1	2
Viral Infection	1	2
Digestive System		
Vomiting	13	15
Anorexia	8	13
Diarrhoea	7	8
Gastroenteritis	2	4
Constipation	1	3
Urogenital System		

Albuminuria	0	4
Urine Abnormality	1	2
Special Senses		
Conjunctivitis	2	3
Amblyopia	0	2
Ear Pain	0	2
Appendages and Skin		
Pruritis	0	2
Skin Discolouration	0	2
Vesiculobullous Rash	0	2
Respiratory System		
Rhinitis	8	13
Cough Increased	7	11
Pharyngitis	8	10
Asthma	1	2

In paediatric patients on placebo versus levetiracetam, the following adverse effects occurred in 2% or more of paediatric patients and were more frequent in placebo patients: sinusitis, abdominal pain, status epilepticus (not otherwise specified), allergic reaction, convulsion, ataxia, epistaxis, fever, headache, hyperkinesia, infection, insomnia, nausea, otitis media, tremor, rash, thinking abnormal, and urinary incontinence.

Other Controlled Clinical Trials

In additional controlled clinical trials, the following adverse effects, listed by body system, have been observed:

General disorders: Very common: fatigue.

Lymphatic and Blood system disorders: Common: thrombocytopenia.

Eye disorders: Common: vision blurred.

Respiratory system: Common: nasopharyngitis.

Nervous system: Common: memory impairment, disturbance in attention balance disorder.

Connective tissue and Musculoskeletal disorders: Common: myalgia.

Psychiatric disorders: Common: personality disorder, irritability, mood swings.

Skin and subcutaneous tissue disorders: Common: pruritis, eczema.

Post-marketing Experience

Psychiatric and nervous system disorders have been most frequently reported in post-marketing experience. Additional to the adverse effects mentioned and listed above, the following have been reported during clinical studies post-marketing. There is insufficient data to determine an incidence estimate in the population to be treated.

Psychiatric disorders: Aggression, abnormal behaviour, confusion, anger, hallucination, suicide, psychotic disorder, suicidal ideation and attempted suicide.

Blood and lymphatic system disorders: Neutropenia, pancytopenia with bone marrow suppression identified in some cases, and leucopenia.

Biliary and Liver disorders: Abnormal liver function test, hepatitis, and hepatic failure.

Nutritional and Metabolic disorders: Pancreatitis, weight loss.

Subcutaneous and Skin disorders: Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, alopecia (in several alopecia cases upon levetiracetam being discontinued, recovery was observed).

Interactions

Levetiracetam did not cause enzyme induction in human culture hepatocytes. Levetiracetam and its major metabolite (ucb L057) *in vitro*, do not inhibit the major human liver cytochrome P₄₅₀ isoforms, epoxide hydroxylase and glucuronyl transferase, activities.

The renal clearance of the major metabolite (ucb L057), has been shown to be inhibited by Probenecid (500 mg four times daily) although levetiracetam is not inhibited by Probenecid. The concentration of ucb L057 remains low nevertheless. It is expected the renal clearance of the metabolite ucb L057 could also be reduced by other drugs that are excreted by active tubular secretion. The effect of probenecid interacting with levetiracetam was not studied and the effect of levetiracetam on other actively secreted drugs e.g. methotrexate, NSAIDs, and sulphonamides, is not known.

In adults, pre-marketing data from clinical studies conducted indicate that levetiracetam did not influence the following existing antiepileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) serum concentrations. Levetiracetam pharmacokinetics was not influenced by these antiepileptic medicinal products.

In paediatric patients receiving up to 60mg/kg/day, there has been no clear evidence of clinically significant drug interactions, which is consistent with formal pharmacokinetic studies in adults.

In children to adolescents with epilepsy (4 to 17 years) a retrospective assessment of pharmacokinetic interactions confirmed that adjunctive therapy with levetiracetam did not influence the steady-state serum concentrations of concomitantly administered valproate, carbamazepine, topiramate and lamotrigine. Data suggests that levetiracetam clearance increased by 22% as a result of enzyme-inducing antiepileptic medicinal products. Dosage adjustment is not required.

Levetiracetam pharmacokinetic studies demonstrated a lack of interaction with warfarin, oral contraceptives (levonorgestrel and ethinylestradiol) and digoxin. Prothrombin times and endocrine parameters (progesterone and LH) were not modified.

No data on the absorption of levetiracetam through the influence of antacids are available.

Overdosage

In the clinical development program, the highest known dose of levetiracetam received was 6000mg/day. There were no adverse events in the few known cases of overdose in clinical trials except for drowsiness.

In post-marketing cases of levetiracetam overdose cases the following adverse events were observed: agitation, aggression, coma, depressed level of consciousness, somnolence and respiratory depression.

Levetiracetam has no specific antidote for overdose. The stomach may be emptied by gastric lavage or by induction of emesis after an acute overdose. Symptomatic treatment will be required for an overdose and may include haemodialysis.

The levetiracetam dialyser extraction efficiency is 60% and for the major metabolite (ucb L057) dialyser extraction efficiency is 74%.

Pharmaceutical Precautions

Levetiracetam film-coated tablets should be stored at or below 25°C.

Medicine Classification

Prescription Only Medicine.

Package quantities

Levetiracetam 250mg film coated tablets are available in blisters of 60 tablets.

Levetiracetam 500mg film coated tablets are available in blisters of 60 tablets.

Levetiracetam 750mg film coated tablets are available in blisters of 60 tablets.

Further information

Excipients

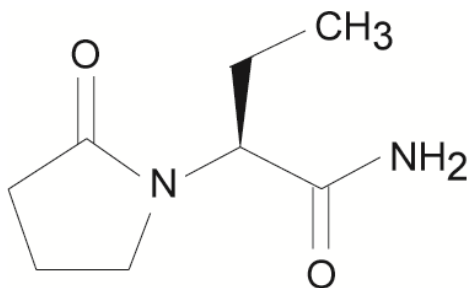
Levetiracetam 250mg film coated tablets contain corn starch, povidone, purified water, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, opadry 03B50643 blue coloured coating.

Levetiracetam 500mg film coated tablets contain corn starch, povidone, purified water, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, opadry 03B52573 yellow coloured coating.

Levetiracetam 750mg film coated tablets contain corn starch, povidone, purified water, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, opadry 03B54276 pink coloured coating.

Levetiracetam tablets do NOT contain gluten or lactose.

Structural formula



Empirical formula: C₈H₁₄N₂O₂

Molecular weight: 170.21

Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs).

Levetiracetam is a white to off-white powder with a bitter taste and a faint odour.

Levetiracetam is practically insoluble in n-hexane, sparingly soluble in acetonitrile (5.7g/100mL), soluble in ethanol (16.5g/100mL) and in methanol (53.6g/100mL), and freely soluble in chloroform (65.3g/100mL) and in water (104g/100mL).

CAS-102767-28-2 and structure indicated above:

Carcinogenesis

There was no evidence of carcinogenicity in rats that were given levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800mg/kg/day. The highest dose corresponds to 3000mg on a mg/m² basis, which is approximately 6 times the maximum recommended daily human dose (MRHD) of 3000mg and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD.

A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960mg/kg/day where the high dose is equivalent to 2 times the MRHD on a mg/m² or exposure basis. No evidence for carcinogenicity was seen in this study.

A further study was completed at the higher dose rates in mice using oral gavage for 2 years at 1000, 2000 and 4000mg/kg/day. This high dose of 4000mg/kg/day was reduced to 3000mg/kg/day due to poor survival. 3000mg/kg/day is equivalent to 12 times the MHRD. No evidence of carcinogenicity was seen in this study.

Genotoxicity

In gene mutation studies, levetiracetam was negative in the bacterial Chinese hamster ovary/HGPRT locus assay. Levetiracetam was also negative in chromosomal damage *in vitro* and *in vivo* (using Chinese hamster ovary cells, mouse nucleus test). The major metabolite of levetiracetam, (ucb L057 and the hydrolysis product), was not mutagenic in the *in vitro* mouse lymphoma study or mutagenic in the bacterial reverse mutation assays.

Name and Address

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Date of Preparation

9 September 2010