[GSK Logo]

KEPPRA
Levetiracetam

NAME OF THE MEDICINAL PRODUCT

Levetiracetam, 250 mg, film-coated tablet
Levetiracetam, 500 mg, film-coated tablet
Levetiracetam, 1000 mg, film-coated tablet
Levetiracetam, 100 mg/ml, oral solution
Levetiracetam, 100 mg/ml, concentrate for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Levetiracetam, 250 mg, film-coated tablet
Each film-coated tablet contains 250 mg of levetiracetam.

Levetiracetam, 500 mg, film-coated tablet
Each film-coated tablet contains 500 mg of levetiracetam.

Levetiracetam, 1000 mg, film-coated tablet
Each film-coated tablet contains 1000 mg of levetiracetam.

Levetiracetam, 100 mg/ml, oral solution
Each ml contains 100 mg of levetiracetam.

Levetiracetam, 100 mg/ml, concentrate for solution for infusion
Each ml contains 100 mg of levetiracetam.

Excipients

Levetiracetam, 250 mg, film-coated tablet
Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate, Opadry 85F20694 Blue: Polyvinyl alcohol, Titanium dioxide (E171), Macrogol/PEG 3350, Talc, FD&C blue #2/Indigo carmine aluminium lake (E132)

Levetiracetam, 500 mg, film-coated tablet
Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate, Opadry 85F32004 Yellow: Polyvinyl alcohol, Titanium dioxide (E171), Macrogol/PEG 3350, Talc, Iron oxide yellow (E172)

Levetiracetam, 1000 mg, film-coated tablet
Sodium croscarmellose, Macrogol 6000, Colloidal anhydrous silica, Magnesium stearate, Opadry 85F18422 White: Polyvinyl alcohol, Titanium dioxide (E171), Macrogol/PEG 3350, Talc

Levetiracetam, 100 mg/ml, oral solution
Sodium citrate, Citric acid monohydrate, Methyl parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216), Ammonium glycyrrhizate, Glycerol 85 per cent (E422),

Maltitol liquid (E965), Acesulfame potassium (E950), Grape flavor Firmenich 501040A, Purified water.

Levetiracetam, 100 mg/ml, concentrate for solution for infusion
Sodium acetate trihydrate, Glacial acetic acid, Sodium chloride, Water for injection.

PHARMACEUTICAL FORM

Levetiracetam, 250 mg, film-coated tablets

Blue, oblong film-coated tablet scored and debossed with the code ucb and 250 on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Levetiracetam, 500 mg, film-coated tablets
Yellow, oblong film-coated tablet scored and debossed with the code ucb and 500 on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Levetiracetam, 1000 mg, film-coated tablets
White, oblong film-coated tablet scored and debossed with the code ucb and 1000 on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Levetiracetam, 100 mg/ml, oral solution
A clear liquid.

Levetiracetam, 100 mg/ml, concentrate for solution for infusion
Clear and colourless solution free from visible particulate matter.

CLINICAL INFORMATION

Indications

Keppra is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Keppra is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and children from 12 years of age with Idiopathic Generalised Epilepsy.

Keppra Concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

Dosage and Administration

Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

Film-coated tablets
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced. The daily dose is administered in two equally divided doses.

Oral solution
The oral solution may be diluted in a glass of water and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced. The daily dose is administered in two equally divided doses.

Concentrate for solution for infusion
Levetiracetam concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion (*see Section Incompatibilities and Use and Handling*)

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

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

Route of Administration

For oral use.

Levetiracetam, 250 mg, film-coated tablet
Levetiracetam, 500 mg, film-coated tablet
Levetiracetam, 1000 mg, film-coated tablet
Levetiracetam, 100 mg/ml, oral solution

For intravenous use.
Levetiracetam, 100 mg/ml, concentrate for solution for infusion

Adults

Monotherapy

Adults and adolescents from 16 years of age

The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.

Add-on therapy

Adults (≥ 18 years) and adolescents (12 to 17 years) weighing 50 kg or more

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerability, the daily dose can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Children

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

The tablet formulation is not adapted for use in children under the age of 6 years. Levetiracetam oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases levetiracetam oral solution should be used.

The safety and efficacy of levetiracetam concentrate for solution for infusion in infants and children less than 4 years have not been established.

Monotherapy

The safety and efficacy of levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established.

There are no data available.

Add-on therapy

Add-on therapy for children (4 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg

Levetiracetam oral solution is the preferred formulation for use in children under the age of 6 years.

For children 6 years and above, levetiracetam oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

The initial therapeutic dose is 10 mg/kg twice daily.

Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks.

The lowest effective dose should be used.

Dose in children 50 kg or greater is the same as in adults.

Dose recommendations for children and adolescents:

Weight	**Starting dose** **10 mg/kg twice daily**	**Maximum dose** **30 mg/kg twice daily**
10 kg [(1)]	100 mg (1 ml) twice daily	300 mg (3 ml) twice daily
15 kg [(1)]	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg [(1)]	200 mg (2 ml) twice daily	600 mg (6 ml) twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg [(2)]	500 mg twice daily	1500 mg twice daily

[(1)] Children 25 kg or less should preferably start the treatment with levetiracetam 100 mg/ml oral solution
[(2)] Dose in children and adolescents 50 kg or more is the same as in adults

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal impairment

The daily dose must be individualised according to renal function *(see Section Warnings and Precautions).*

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighting 50 kg or more, using the following formula:

$$\text{CLcr (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ for women})$$

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

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

Dosing adjustment for adult and adolescent patients weighing more than 50kg 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 [(2)]

[(1)] A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.
[(2)] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function.
This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m^2 may be estimated from serum creatinine (mg/dl) determination using, for young adolescents and children using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{Height (cm) x ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks = 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for children and adolescents patients weighing less than 50 kg with impaired renal function

Group	**Creatinine clearance (ml/min/1.73m^2)**	**Children and adolescents weighing less than 50 kg**
Normal	≥80	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg (0.10 to 0.20 ml/kg)once daily [(2)] [(3)]

(1) Levetiracetam oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.
(2) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(3) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

Hepatic impairment

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.

Contraindications

Levetiracetam is contraindicated in:

- Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.

Warnings and Precautions

Discontinuation
If levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks).

Renal or hepatic impairment
The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (*see Section Dosage and Administration*).

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

Blood cell counts
Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders *(see Section Adverse Reactions)*.

Depression and/or suicidal ideation
Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products has shown a

small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.

Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Abnormal and aggressive behaviours
Levetiracetam may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness. Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood and/or personality changes. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered. If discontinuation is considered, please see Section *Discontinuation* in *Warnings and Precautions*.

Worsening of seizures
As with other types of antiepileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after levetiracetam initiation or increase of the dose, and was reversible upon drug discontinuation or dose decrease. Patients should be advised to consult their physician immediately in case of aggravation of epilepsy. Lack of efficacy or seizure worsening has for example been reported in patients with epilepsy associated with sodium voltage-gated channel alpha subunit 8 (SCN8A) mutations.

Electrocardiogram QT interval prolongation
Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant preexisting cardiac disease or electrolyte disturbances.

Paediatric population
The tablet formulation is not adapted for use in children under the age of 6 years.

Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

*Excipient*s

<u>Oral solution</u>
Levetiracetam 100 mg/ml oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

It also includes maltitol liquid; patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

It contains glycerol which may cause headache, stomach upset and diarrhoea.

<u>Solution for infusion</u>

This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.83 mmol (or 19 mg) per vial). It should be taken into consideration by patients on a controlled sodium diet.

Interactions

Antiepileptic medicinal products

Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of levetiracetam.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20% higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dosage adjustment is not required.

Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low.

Methotrexate
Concomitant administration of levetiracetam and methotrexate has been 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, digoxin and warfarin
Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

Laxatives
There have been isolated reports of decreased levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.

Food and alcohol

The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced.

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

Pregnancy and Lactation

Fertility

No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

Women of childbearing potential

Specialist advice should be given to women who are of childbearing potential. Treatment with levetiracetam should be reviewed when a woman is planning to become pregnant. As with all antiepileptic medicines, sudden discontinuation of levetiracetam should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple antiepileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Pregnancy

A large amount of postmarketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the first trimester) do not suggest an increase in the risk for major congenital malformations. Only limited evidence is available on the neurodevelopment of children exposed to levetiracetam monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays.

Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended.

Physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured.

Lactation

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.

Ability to perform tasks that require judgement, motor or cognitive skills

Levetiracetam has minor or moderate influence on the ability to drive and use machines.

Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially 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. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

Adverse Reactions

Clinical Trial Data and Post Marketing Data

Summary of the safety profile

The adverse event profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3,416 patients treated with levetiracetam. These data are supplemented with the use of levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data)

Infections and infestations
Very common: nasopharyngitis
Rare: infection

Blood and lymphatic system disorders
Uncommon: thrombocytopenia, leukopenia
Rare: neutropenia, pancytopenia, agranulocytosis

Immune system disorders
Rare: drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)

Metabolism and nutrition disorders
Common: anorexia
Uncommon: weight decreased, weight increase
Rare: hyponatraemia

Psychiatric disorders
Common: depression, hostility/aggression, anxiety, insomnia, nervousness/irritability
Uncommon: suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation
Rare: completed suicide, personality disorder, thinking abnormal, delirium
Very rare: Obsessive compulsive disorder**

Nervous system disorders
Very common: somnolence, headache
Common: convulsion, balance disorder, dizziness, lethargy, tremor
Uncommon: amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention
Rare: choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated, Neuroleptic malignant syndrome*

Eye disorders
Uncommon: diplopia, vision blurred

Ear and labyrinth disorders
Common: vertigo

Cardiac disorders
Rare: electrocardiogram QT prolonged

Respiratory, thoracic and mediastinal disorders
Common: cough

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
Rare: pancreatitis

Hepatobiliary disorders
Uncommon: liver function test abnormal
Rare: hepatic failure, hepatitis

Renal and urinary disorders
Rare: acute kidney injury

Skin and subcutaneous tissue disorders
Common: rash
Uncommon: alopecia, eczema, pruritus
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Musculoskeletal and connective tissue disorders
Uncommon: muscular weakness, myalgia
Rare: rhabdomyolysis and blood creatine phosphokinase increased*

General disorders and administration site conditions
Common: asthenia/fatigue

Injury, poisoning and procedural complications
Uncommon: injury

* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.
**Very rare cases of development of obsessive-compulsive disorders (OCD) in patients with underlying history of OCD or psychiatric disorders have been observed in post-marketing surveillance.

Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is co-administered with topiramate.

In several cases of alopecia, recovery was observed when levetiracetam was discontinued.

Bone marrow suppression was identified in some of the cases of pancytopenia.

Case of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Paediatric population

In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

The adverse event profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that levetiracetam was not

different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

Overdosage

Symptoms and signs

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses.

Treatment

There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Clinical Pharmacology

Pharmacodynamics

Pharmacotherapeutic group

Antiepileptics; Other Antiepileptics

ATC Code

N03AX14

Mechanism of Action

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

The mechanism of action of levetiracetam still remains to be fully elucidated. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

In vitro studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in

in vitro studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.

In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

Pharmacokinetics

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and intersubject variability. There is no modification of the clearance after repeated administration. The time independent pharmacokinetic profile of levetiracetam was also confirmed following 1500 mg intravenous infusion for 4 days with twice daily dosing.

There is no evidence for any relevant gender, race or circadian variability. 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 bodyweight. Therefore there is no need for plasma level monitoring of levetiracetam.

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

The pharmacokinetic profile has been characterized following oral administration. A single dose of 1500 mg levetiracetam diluted in 100 ml of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1500 mg levetiracetam oral intake, given as three 500 mg tablets.

The intravenous administration of doses up to 4000 mg diluted in 100 ml of 0.9% sodium chloride infused over 15 minutes and doses up to 2500 mg diluted in 100 ml of 0.9% sodium chloride infused over 5 minutes was evaluated. The pharmacokinetic and safety profiles did not identify any safety concerns.

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %.

Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.

Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1000 mg dose and repeated 1000 mg twice daily dose, respectively.
The extent of absorption is dose-independent and is not altered by food.

Distribution
No tissue distribution data are available in humans.

Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (<10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

Peak plasma concentration (C_{max}) observed in 17 subjects following a single intravenous dose of 1500 mg infused over 15 minutes was 51 ± 19 µg/mL (arithmetic average ± standard deviation).

Metabolism
Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6% of the dose) and the other one by opening of the pyrrolidone ring (0.9% of the dose).

Other unidentified components accounted only for 0.6% of the dose.

No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P_{450} isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

In human hepatocytes in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4. The in vitro data and in vivo interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, the interaction of levetiracetam with other substances, or vice versa, is unlikely.

Elimination
The plasma half-life in adults was 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg.

The major route of excretion was via urine, accounting for a mean 95% of the dose (approximately 93% of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3% of the dose.

The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66% and 24% of the dose, respectively during the first 48 hours.

The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Levetiracetam elimination is correlated to creatinine clearance.

Special patient populations

Children

Children (4 to 12 years)
Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half-life of levetiracetam was 6.0 hours. The apparent body weight adjusted clearance was approximately 30% higher than in epileptic adults.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 ml/min/kg.

Elderly

In the elderly, the half-life is increased by about 40 % (10 to 11 hours). This is related to the decrease in renal function in this population.

Renal impairment

The apparent body clearance of both levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment.

In anuric end-stage renal disease subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively.
The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

Hepatic impairment

In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam.
In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50% due to a concomitant renal impairment.

Clinical Studies

Not relevant for this product.

NON-CLINICAL INFORMATION

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity.

Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.

No adverse effects on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m^2 or exposure basis) in parents and F1 generation.

Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m^2 basis) and 1200 mg/kg/day for foetuses.

Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of foetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the foetuses (equal to the MRHD on a mg/m^2 basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m^2 basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6–17 the MRHD on a mg/m^2 basis).

Environmental Risk Assessment (ERA)

The use of levetiracetam in accordance with the product information is not likely to result in an unacceptable environmental impact *(see Section Incompatibilities and Use and Handling).*

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date is indicated on the packaging.

Storage

Keppra 250 mg Film Coated Tablet: Store below 30°C.
Keppra 500 mg Film Coated Tablet: Store below 30°C.
Keppra 1000 mg Film Coated Tablet: Store below 30°C.
Keppra Concentrate for Solution for Infusion 500 mg/5 ml: Store below 30°C.
Keppra Oral Solution 100 mg/ml: Store below 30°C.

Nature and Contents of Container

Keppra 250 mg, 500 mg and 1000 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 60 or 100 film-coated tablets.

Keppra Oral Solution is packaged in a 300 ml amber glass bottle with a white child-proof resistant closure in a cardboard box containing a graduated oral syringe.

Keppra Concentrate is packed in glass vials with Teflon faced stoppers or rubber stoppers and sealed with an aluminium/polypropylene flip off cap. The vials are placed into cartons of 10 vials. Each single use vial contains 5 ml of concentrate.

Incompatibilities and Use and Handling

Levetiracetam, 100 mg/ml concentrate for solution for infusion

Table presents the recommended preparation and administration of levetiracetam concentrate to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg, or 3000 mg in two divided doses.

Dose	**Withdrawal Volume**	**Volume of Diluent**	**Infusion time**	**Frequency of administration**	**Total Daily Dose**
250 mg	2.5 ml (half 5 ml vial)	100 ml	15 minutes	Twice daily	500 mg/day
500 mg	5 ml (one 5 ml vial)	100 ml	15 minutes	Twice daily	1000 mg/day
1000 mg	10 ml (two 5 ml vials)	100 ml	15 minutes	Twice daily	2000 mg/day

1500 mg	15 ml (three 5 ml vials)	100 ml	15 minutes	Twice daily	3000 mg/day

This medicinal product is for single use only, any unused solution should be discarded. This medicinal product must not be mixed with other medicinal products except those mentioned below. Levetiracetam concentrate was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15- 25°C.

Diluents:
• Sodium chloride (0.9%) injection
• Lactated Ringer's injection
• Dextrose 5% injection

Medicinal product with particulate matter or discolouration should not be used.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MANUFACTURER

Film coated tablets
UCB Pharma SA
Braine-I'Alleud, Belgium

Oral solution
NextPharma SAS
Limay, France

Concentrate for solution for infusion
Patheon Italia S.p.A.
Monza, Italy

Version Number: 09
Reference: NCDS12
Date of local revision: 26 July 2023