Levipram®

Levetiracetam

1. Name of the medicinal product

Levipram® 250: Film coated tablets; Box of 100.
Levipram® 500: Film coated tablets; Box of 100.
Levipram® 750: Film coated tablets; Box of 100.
Levipram® 1000: Film coated tablets; Box of 100.

2. Qualitative and quantitative composition

Levipram® 250: Each film-coated tablet contains 250 mg levetiracetam.
Levipram® 500: Each film-coated tablet contains 500 mg levetiracetam.
Levipram® 750: Each film-coated tablet contains 750 mg levetiracetam.
Levipram® 1000: Each film-coated tablet contains 1000 mg levetiracetam.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Levipram® is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy.
Levipram® is indicated as adjunctive therapy:
• in the treatment of partial onset seizures with or without secondary generalization in adults, adolescents, children and infants from 1 month 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 generalized tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalized Epilepsy.

4.2 Posology and method of administration

Posology

Monotherapy for 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 for 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 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.
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 infants older than 6 months, children and adolescents weighting less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).
Special populations
- *Elderly (65 years and older)*
Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Renal impairment" below).
- *Renal impairment*
The daily dose must be individualized according to renal function.
Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:
•Creatinine clearance > 80 ml/min/1.73m^2 (Normal): 500 to 1,500 mg twice daily;
•Creatinine clearance 50-79 ml/min/1.73m^2 (Mild): 500 to 1,000 mg twice daily;
•Creatinine clearance 30-49 ml/min/1.73m^2 (Moderate): 250 to 750 mg twice daily;
•Creatinine clearance < 30 ml/min/1.73m^2 (Severe): 250 to 500 mg twice daily;
•End-stage renal disease patients undergoing dialysis (A 750 mg loading dose is recommended on the first day of treatment with levetiracetam): 500 to 1,000 mg once daily (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.
Dosing adjustment for infants, children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m^2)	Dose and frequency	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg twice daily	10 to 30 mg/kg twice daily
Mild	50-79	7 to 14 mg/kg twice daily	10 to 20 mg/kg twice daily
Moderate	30-49	3.5 to 10.5 mg/kg twice daily	5 to 15 mg/kg twice daily
Severe	< 30	3.5 to 7 mg/kg twice daily	5 to 10 mg/kg twice daily
End-stage renal disease patients undergoing dialysis	- -	7 to 14 mg/kg once daily (1) (3)	10 to 20 mg/kg once daily (2) (4)

(1) A 10.5 mg/kg loading dose is recommended on the first day of treatment with levetiracetam.
(2) A 15 mg/kg loading dose is recommended on the first day of treatment with levetiracetam.
(3) Following dialysis, a 3.5 to 7 mg/kg supplemental dose is recommended.
(4) Following dialysis, a 5 to 10 mg/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/1.73 m^2.
- Pediatric population
Monotherapy:
The safety and efficacy of Levetiracetam tablets in children and adolescents below 16 years as monotherapy treatment have not been established. There are no data available.
Add-on therapy for infants aged from 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:
Levetiracetam oral solution is the preferred formulation for use in infants and children under the age of 6 years.
For children 6 years and above, Levetiracetam oral solution 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 lowest effective dose should be used. The starting dose for a child or adolescent of 25kg should be 250mg twice daily with a maximum dose of 750mg twice daily.
Dose in children 50 kg or greater is the same as in adults.
Add-on therapy for infants aged from 1 month to less than 6 months:
Levetiracetam oral solution is the formulation to use in infants.
Method of administration
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

4.3 Contraindications

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Renal 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.
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.
Suicide
Suicide, suicide attempt, suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents (including levetiracetam).
Therefore, patients should be monitored for signs of depression and/or suicidal ideation and behaviors and appropriate treatment should be considered.
Pediatric population
The tablet formulation is not adapted for use in infants and 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 pediatric patients receiving up to 60 mg/kg/day levetiracetam.
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 and other pharmacokinetics interactions
Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 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.

4.6 Fertility, pregnancy and lactation

Pregnancy: Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity.
Levipram® is not recommended during pregnancy and in women of childbearing potential not using contraception unless clinically necessary.
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. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.
Breastfeeding: Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

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However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.
Fertility: No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness.
Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed below as per System Organ Class and per frequency. Adverse reactions are presented in the order of decreasing seriousness and their frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).
Infections and infestations: nasopharyngitis (very common); infection (rare).
Blood and lymphatic system disorders: thrombocytopenia, leucopenia (uncommon); neutropenia, pancytopenia, agranulocytosis (rare).
Immune system disorders: drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis) (rare).
Metabolism and nutrition disorders: anorexia (common); weight increase, weight decrease (uncommon); hyponatraemia (rare).
Psychiatric disorders: depression, hostility/ aggression, anxiety, insomnia, nervousness/irritability (common); suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state , panic attack, affect lability/mood swings, agitation (uncommon); completed suicide, personality disorder, thinking abnormal (rare).
Nervous system disorders: somnolence, headache (very common); convulsion, balance disorder, dizziness, lethargy, tremor (common); Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention (uncommon); choreoathetosis, dyskinesia, hyperkinesia (rare).
Eye disorders: diplopia, vision blurred (uncommon).
Ear and labyrinth disorders: vertigo (common).
Respiratory, thoracic and mediastinal disorders: cough (common).
Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, vomiting, nausea (common); pancreatitis (rare).
Hepatobiliary disorders: liver function test abnormal (uncommon); hepatic failure, hepatitis (rare).
Renal and Urinary Disorders: acute kidney injury (rare).
Skin and subcutaneous tissue disorders: rash (common); alopecia, eczema, pruritus, (uncommon); toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme (rare).
Musculoskeletal and connective tissue disorders: muscular weakness, myalgia (uncommon); rhabdomyolysis and blood creatine phosphokinase increased (rare).
General disorders and administration site conditions: asthenia/fatigue (common).
Injury, poisoning and procedural complications: injury (uncommon).
The risk of anorexia is higher when levetiracetam is coadministered 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.

4.9 Overdose

Symptoms
Somnolence, agitation, aggression, depressed level of consciousness; respiratory depression and coma were observed with Levipram® overdoses.
Management of overdose
After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyzer extraction efficiency is 60 % for levetiracetam and 74 % for the primary metabolite.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX14.
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.
Mechanism of action
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.

5.2 Pharmacokinetic properties

Adults and adolescents
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 1,000 mg dose and repeated 1,000 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 is 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.
Biotransformation: Levetiracetam is not extensively metabolized 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 P_{450} 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.
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.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet Core:
- Starch, croscarmellose sodium, povidone, colloidal silicon dioxide, magnesium stearate, talc (Levipram® 750) and Crospovidone (Levipram® 250, Levipram® 500 & Levipram® 1000).

Film-coating:
- Polyvinyl alcohol, titanium dioxide, polyethylene gylcol, talc, indigo carmine (Levipram® 250 & Levipram® 750), yellow iron oxide (Levipram® 500), red iron oxide (Levipram® 750).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
Keep in original pack in intact conditions.

Date of Revision:

July 2017

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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