ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 250 mg film-coated tablets
Levetiracetam ratiopharm 500 mg film-coated tablets
Levetiracetam ratiopharm 750 mg film-coated tablets
Levetiracetam ratiopharm 1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levetiracetam ratiopharm 250 mg film-coated tablets
Each film-coated tablet contains 250 mg levetiracetam.

Levetiracetam ratiopharm 500 mg film-coated tablets
Each film-coated tablet contains 500 mg levetiracetam.

Levetiracetam ratiopharm 750 mg film-coated tablets
Each film-coated tablet contains 750 mg levetiracetam.

Levetiracetam ratiopharm 1000 mg film-coated tablets
Each film-coated tablet contains 1000 mg levetiracetam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Levetiracetam ratiopharm 250 mg film-coated tablets
The 250 mg film-coated tablets are blue, oblong and scored on one side.

Levetiracetam ratiopharm 500 mg film-coated tablets
The 500 mg film-coated tablets are yellow, oval and scored on one side.

Levetiracetam ratiopharm 750 mg film-coated tablets
The 750 mg film-coated tablets are light red, oblong and scored on both sides.

Levetiracetam ratiopharm 1000 mg film-coated tablets
The 1000 mg film-coated tablets are white, oblong and scored on both sides.

The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Levetiracetam ratiopharm is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Levetiracetam ratiopharm is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation 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 generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

4.2 Posology and method of administration

Posology

Partial onset seizures
The recommended dosing for monotherapy (from 16 years of age) and adjunctive therapy is the same; as outlined below.

All indications

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. However, a lower initial dose of 250 mg twice daily may be given based on physician assessment of seizure reduction versus potential side effects. This can be increased to 500 mg twice daily after two weeks.

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 250 mg or 500 mg twice daily increases or decreases every two to four weeks.

Adolescents (12 to 17 years) weighing below 50 kg and children from 1 month of age

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to weight, age and dose. Refer to *Paediatric population* section for dosing adjustments based on weight.

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 weighing 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 individualised according to renal function.

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 weighing 50 kg or more, 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 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose 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, for young adolescents, children and infants, using the following formula (Schwartz formula):

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

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescent patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose and frequency (1)	
		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 (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily

End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg)once daily [2] [4]	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily [3] [5]

[1] Levetiracetam ratiopharm 100 mg/ml 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 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
[3] A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
[4] Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.
[5] 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/1.73 m^2.

Paediatric population

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 infants and children under the age of 6 years. Levetiracetam ratiopharm 100 mg/ml 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 ratiopharm 100 mg/ml oral solution should be used.

Monotherapy

The safety and efficacy of Levetiracetam ratiopharm in children and adolescents below 16 years as monotherapy treatment have not been established.
No data are available.

Adolescents (16 and 17 years of age) weighing 50 kg or more with partial onset seizures with or without secondary generalisation with newly diagnosed epilepsy.
Please refer to the above section on *Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more*.

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 ratiopharm 100 mg/ml 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 ratiopharm 100 mg/ml 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 for all indications. The starting dose for a child or adolescent of 25 kg should be 250 mg twice daily with a maximum dose of 750 mg twice daily.

Dose in children 50 kg or greater is the same as in adults for all indications.
Please refer to the above section on *Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more* for all indications.

Add-on therapy for infants aged from 1 month to less than 6 months

The 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. After oral administration the bitter taste of levetiracetam may be experienced.
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 (see section 4.2).

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 (section 4.8).

Suicide

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 refer to section 4.2.

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 pre-existing cardiac disease or electrolyte disturbances.

Paediatric 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 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. Dose 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 and other pharmacokinetics interactions

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.

4.6 Fertility, pregnancy and lactation

Women of child bearing 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 1st 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.

Breast-feeding

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if levetiracetam treatment is needed during breast-feeding, the benefit/risk of the treatment should be weighed considering the importance of breast-feeding.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). 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

Summary of the safety profile

The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The adverse reaction profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3416 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 safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).

MedDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	Nasopharyngitis			Infection	
Blood and lymphatic system disorders			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis	
Immune system disorders				Drug reaction with eosinophilia and systemic symptoms (DRESS)[(1)], Hypersensitivity (including angioedema and anaphylaxis)	
Metabolism and nutrition disorders		Anorexia	Weight decreased, weight increase	Hyponatraemia	

MedDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Psychiatric disorders		Depression, hostility/ aggression, anxiety, insomnia, nervousness/ irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal, delirium	Obsessive compulsive disorder[(2)]
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia , paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated, Neuroleptic malignant syndrome[(3)]	
Eye disorders			Diplopia, vision blurred		
Ear and labyrinth disorders		Vertigo			
Cardiac disorders				Electrocardiogram QT prolonged	
Respiratory, thoracic and mediastinal disorders		Cough			
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis	
Hepatobiliary disorders			Liver function test abnormal	Hepatic failure, hepatitis	
Renal and Urinary Disorders				Acute Kidney injury	
Skin and subcutaneous tissue disorders		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme	

MedDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Musculoskeletal and connective tissue disorders			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased(3)	
General disorders and administration site conditions		Asthenia/ fatigue			
Injury, poisoning and procedural complications			Injury		

(1) See Description of selected adverse reactions.
(2) 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.
(3) Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Description of selected adverse reactions

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported rarely in patients treated with levetiracetam. Clinical manifestations may develop 2 to 8 weeks after starting treatment. These reactions are variable in expression, but typically present with fever, rash, facial oedema, lymphadenopathies, haematologic abnormalities and can be associated with involvement of different organ systems, mostly the liver. If multiorgan hypersensitivity reaction is suspected, levetiracetam should be discontinued.

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.

Cases 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.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Clinical efficacy and safety

Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy.

In adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50 % or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7 %, 31.6 % and 41.3 % for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6 % for patients on placebo.

Paediatric population

In paediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing).
44.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo had a 50 % or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4 % of the patients were seizure-free for at least 6 months and 7.2 % were seizure-free for at least 1 year.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was use in this study. The total daily dose was administered twice daily.
The primary measure of effectiveness was the responder rate (percent of patients with ≥ 50 % reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6 % of the patients were seizure-free for at least 6 months and 7.8 % were seizure-free for at least 1 year.
35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 - 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response.
Six-month seizure freedom was achieved in 73.0 % of levetiracetam-treated patients and 72.8 % of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2 % (95 % CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6 % and 58.5 % of subjects on levetiracetam and on carbamazepine CR respectively).

In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to levetiracetam adjunctive therapy (36 adult patients out of 69).

Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.
In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses.
58.3 % of the levetiracetam treated patients and 23.3 % of the patients on placebo had at least a 50 % reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6 % of the patients were free of myoclonic seizures for at least 6 months and 21.0 % were free of myoclonic seizures for at least 1 year.

Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses.
72.2 % of the levetiracetam treated patients and 45.2 % of the patients on placebo had a 50 % or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4 % of the patients were free of tonic-clonic seizures for at least 6 months and 31.5 % were free of tonic-clonic seizures for at least 1 year.

5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. 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).

Adults and adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %.
Peak plasma concentrations (Cmax) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.
Peak concentrations (Cmax) 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.

Biotransformation

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 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.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 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.

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 (see section 4.2).

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 (see section 4.2).

In anuric end-stage renal disease adult 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 (see section 4.2).

Paediatric population

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.

Infants and children (1 month to 4 years)

Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96 ml/min/kg).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.
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 reactions 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/m2 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/m2 basis) and 1200 mg/kg/day for fetuses.

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 fetuses (equal to the MRHD on a mg/m2 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/m2 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/m2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Macrogol 6000, Colloidal anhydrous silica, Crospovidone A, Cellulose powdered, Magnesium stearate.

Film-coating:

Levetiracetam ratiopharm 250 mg film-coated tablets
Poly(vinyl alcohol), Titanium dioxide (E171), Macrogol, Talc, Blue indigo carmine aluminium lake (E132)

Levetiracetam ratiopharm 500 mg film-coated tablets
Hypromellose (E464), Microcrystalline cellulose (E460), Macrogol 40 stearate type I, Anatase titanium dioxide (E171), Yellow Iron Oxide (E 172)

Levetiracetam ratiopharm 750 mg film-coated tablets

Hypromellose (E464), Microcrystalline cellulose (E460), Macrogol 40 stearate type I, Anatase titanium dioxide (E171), Yellow Iron Oxide (E172), Red Iron Oxide (E172)

Levetiracetam ratiopharm 1000 mg film-coated tablets
Hypromellose (E464), Microcrystalline cellulose (E460), Macrogol 40 stearate type I, Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blister packs.

Levetiracetam ratiopharm 250 mg film-coated tablets
Packs containing 20, 30, 50, 60 or 100 film-coated tablets or multipacks containing 200 (2 packs of 100) film-coated tablets.

Levetiracetam ratiopharm 500 mg film-coated tablets
Packs containing 10, 20, 30, 50, 60 or 100 film-coated tablets or multipacks containing 120 (2 packs of 60) or 200 (2 packs of 100) film-coated tablets.

Levetiracetam ratiopharm 750 mg film-coated tablets
Packs containing 20, 30, 50, 60, 80 or 100 film-coated tablets or multipacks containing 200 (2 packs of 100) film-coated tablets.

Levetiracetam ratiopharm 1000 mg film-coated tablets
Packs containing 10, 20, 30, 50, 60 or 100 film-coated tablets or multipacks containing 200 (2 packs of 100) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

8. MARKETING AUTHORISATION NUMBER(S)

Levetiracetam ratiopharm 250 mg film-coated tablets
EU/1/11/702/004
EU/1/11/702/005
EU/1/11/702/006
EU/1/11/702/007
EU/1/11/702/008
EU/1/11/702/009

Levetiracetam ratiopharm 500 mg film-coated tablets
EU/1/11/702/010
EU/1/11/702/011
EU/1/11/702/012
EU/1/11/702/013
EU/1/11/702/014
EU/1/11/702/015
EU/1/11/702/016
EU/1/11/702/017

Levetiracetam ratiopharm 750 mg film-coated tablets
EU/1/11/702/018
EU/1/11/702/019
EU/1/11/702/020
EU/1/11/702/021
EU/1/11/702/022
EU/1/11/702/023
EU/1/11/702/024

Levetiracetam ratiopharm 1000 mg film-coated tablets
EU/1/11/702/025
EU/1/11/702/026
EU/1/11/702/027
EU/1/11/702/028
EU/1/11/702/029
EU/1/11/702/030
EU/1/11/702/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2011
Date of latest renewal: 28. April 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml oral solution contains 100 mg levetiracetam.

Excipients with known effect:
Each ml contains 1.4 mg methyl parahydroxybenzoate (E 218), 0.27 mg propyl parahydroxybenzoate (E 216) and 3.1 mg potassium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Clear liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Levetiracetam ratiopharm is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Levetiracetam ratiopharm is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation 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 generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

4.2 Posology and method of administration

Posology

Partial onset seizures
The recommended dosing for monotherapy (from 16 years of age) and adjunctive therapy is the same; as outlined below.

All indications

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. However, a lower initial dose of 250 mg twice daily may be given based on physician assessment of seizure reduction versus potential side effects. This can be increased to 500 mg twice daily after two weeks.

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 250 mg or 500 mg twice daily increases or decreases every two to four weeks.

Adolescents (12 to 17 years) weighing below 50 kg and children from 1 month of age

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to weight, age and dose. Refer to *Paediatric population* section for dosing adjustments based on weight.

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 weighing 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 individualised according to renal function.

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 weighing 50 kg or more, the following formula:

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

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 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose and frequency
Normal	≥ 80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 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 1,000 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, for young adolescents, children and infants, using the following formula (Schwartz formula):

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

ks= 0.45 in Term infants to 1 year old; ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for infants, children and adolescent patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73 m^2)	Dose and frequency [1]	
		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 (0.07 to 0.21 ml/kg) twice daily	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	< 30	3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg (0.07 to 0.14 ml/kg)once daily [2] [4]	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily [3] [5]

[1] Levetiracetam ratiopharm 100 mg/ml 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 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
[3] A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
[4] Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.
[5] 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/1.73 m^2.

Paediatric population

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

Levetiracetam ratiopharm 100 mg/ml oral solution is the preferred formulation for use in infants and children under the age of 6 years. 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 ratiopharm 100 mg/ml oral solution should be used.

Monotherapy

The safety and efficacy of Levetiracetam ratiopharm in children and adolescents below 16 years as monotherapy treatment have not been established.
No data are available.

Adolescents (16 and 17 years of age) weighing 50 kg or more with partial onset seizures with or without secondary generalisation with newly diagnosed epilepsy
Please refer to the above section on *Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more*.

Add-on therapy for infants aged 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg

The initial therapeutic dose is 10 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased by 10 mg/kg twice daily every 2 weeks 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 for all indications.

Dose in children 50 kg or greater is the same as in adults for all indications.
Please refer to the above section on *Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more* for all indications.

Dose recommendations for infants from 6 months of age, children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
6 kg [(1)]	60 mg (0.6 ml) twice daily	180 mg (1.8 ml) 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 [(1)]	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 ratiopharm 100 mg/ml oral solution.
[(2)] Dose in children and adolescents 50 kg or more is the same as in adults.

Add-on therapy for infants aged from 1 month to less than 6 months

The initial therapeutic dose is 7 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased by 7 mg/kg twice daily every 2 weeks up to recommended dose of 21 mg/kg twice daily. Dose changes should not

exceed increases or decreases of 7 mg/kg twice daily every two weeks. The lowest effective dose should be used.
Infants should start the treatment with Levetiracetam ratiopharm 100 mg/ml oral solution.

Dose recommendations for infants aged from 1 month to less than 6 months:

Weight	Starting dose: 7 mg/kg twice daily	Maximum dose: 21 mg/kg twice daily
4 kg	28 mg (0.3 ml) twice daily	84 mg (0.85 ml) twice daily
5 kg	35 mg (0.35 ml) twice daily	105 mg (1.05 ml) twice daily
7 kg	49 mg (0.5 ml)twice daily	147 mg (1.5 ml) twice daily

Three presentations are available:

- A 300 ml bottle with a 10 ml oral syringe (delivering up to 1000 mg levetiracetam) graduated every 0.25 ml (corresponding to 25 mg).
  This presentation should be prescribed for children aged 4 years and older, adolescents and adults.
- A 150 ml bottle with a 3 ml oral syringe (delivering up to 300 mg levetiracetam) graduated every 0.1 ml (corresponding to 10 mg)
  In order to ensure the accuracy of the dosing this presentation should be prescribed for infants and young children aged from 6 months to less than 4 years.
- A 150 ml bottle with a 1 ml oral syringe (delivering up to 100 mg levetiracetam) graduated every 0.05 ml (corresponding to 5 mg)
  In order to ensure the accuracy of the dosing, this presentation should be prescribed for infants aged 1 month to less than 6 months.

Method of administration

The oral solution may be diluted in a glass of water or baby's bottle and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced.

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 (see section 4.2).

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 (section 4.8).

Suicide

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 refer to section 4.2.

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 pre-existing cardiac disease or electrolyte disturbances.

Paediatric population

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.

Excipients

Methyl parahydroxybenzoate (E 218) and propyl parahydroxybenzoate (E 216)
Levetiracetam ratiopharm 100 mg/ml oral solution contains methyl parahydroxybenzoate (E 218) and propyl parahydroxybenzoate (E 216) which may cause allergic reactions (possibly delayed).

Potassium
This medicinal product contains 1.2 mmol (or 46.65 mg) potassium per 15 ml. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 15 ml that is to say essentially ‘sodium-free’.

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 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. Dose 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 and other pharmacokinetics interactions

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.

4.6 Fertility, pregnancy and lactation

Women of child bearing 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 1st 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.

Breast-feeding

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if levetiracetam treatment is needed during breast-feeding, the benefit/risk of the treatment should be weighed considering the importance of breast-feeding.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). 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

Summary of the safety profile

The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The adverse reaction 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 safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).

MedDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	Nasopharyngitis			Infection	
Blood and lymphatic system disorders			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis	
Immune system disorders				Drug reaction with eosinophilia and systemic symptoms (DRESS)[(1)], Hypersensitivity (including angioedema and anaphylaxis)	
Metabolism and nutrition disorders		Anorexia	Weight decreased, weight increase	Hyponatraemia	
Psychiatric disorders		Depression, hostility/ aggression, anxiety, insomnia, nervousness/ irritability	Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	Completed suicide, personality disorder, thinking abnormal, delirium	Obsessive compulsive disorder[(2)]
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated, Neuroleptic malignant syndrome[(3)]	
Eye disorders			Diplopia, vision blurred		

MedDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Ear and labyrinth disorders		Vertigo			
Cardiac disorders				Electrocardiogram QT prolonged	
Respiratory, thoracic and mediastinal disorders		Cough			
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis	
Hepatobiliary disorders			Liver function test abnormal	Hepatic failure, hepatitis	
Renal and Urinary Disorders				Acute Kidney injury	
Skin and subcutaneous tissue disorders		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme	
Musculoskeletal and connective tissue disorders			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased[3]	
General disorders and administration site conditions		Asthenia/ fatigue			
Injury, poisoning and procedural complications			Injury		

[1] See Description of selected adverse reactions.
[2] 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.
[3] Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Description of selected adverse reactions

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported rarely in patients treated with levetiracetam. Clinical manifestations may develop 2 to 8 weeks after starting treatment. These reactions are variable in expression, but typically present with fever, rash, facial oedema, lymphadenopathies, haematologic

abnormalities and can be associated with involvement of different organ systems, mostly the liver. If multiorgan hypersensitivity reaction is suspected, levetiracetam should be discontinued.

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.

Cases 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.

In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

The adverse reaction 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Clinical efficacy and safety

Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy.

In adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50 % or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7 %, 31.6 % and 41.3 % for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6 % for patients on placebo.

Paediatric population

In paediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing).
44.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo had a 50 % or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4 % of the patients were seizure-free for at least 6 months and 7.2 % were seizure-free for at least 1 year.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six months and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 months to less than 4 years old, was use in this study. The total daily dose was administered twice daily.
The primary measure of effectiveness was the responder rate (percent of patients with ≥ 50 % reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6 % of the patients were seizure-free for at least 6 months and 7.8 % were seizure-free for at least 1 year.
35 infants aged less than 1 year with partial onset seizures have been exposed in placebo-control clinical studies of which only 13 were aged < 6 months.

Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 - 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response.
Six-month seizure freedom was achieved in 73.0 % of levetiracetam-treated patients and 72.8 % of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2 % (95 % CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6 % and 58.5 % of subjects on levetiracetam and on carbamazepine CR respectively).

In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to levetiracetam adjunctive therapy (36 adult patients out of 69).

Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.
In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses.
58.3 % of the levetiracetam treated patients and 23.3 % of the patients on placebo had at least a 50 % reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6 % of the

patients were free of myoclonic seizures for at least 6 months and 21.0 % were free of myoclonic seizures for at least 1 year.

Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses.
72.2 % of the levetiracetam treated patients and 45.2 % of the patients on placebo had a 50 % or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4 % of the patients were free of tonic-clonic seizures for at least 6 months and 31.5 % were free of tonic-clonic seizures for at least 1 year.

5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. 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).

Adults and adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %.
Peak plasma concentrations (Cmax) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule.
Peak concentrations (Cmax) 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.

Biotransformation

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 P450 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.

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 (see section 4.2).

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 (see section 4.2).

In anuric end-stage renal disease adult 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 (see section 4.2).

Paediatric population

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.

Infants and children (1 month to 4 years)

Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96 ml/min/kg).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing antiepileptic medicinal product.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.
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 reactions 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/m2 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/m2 basis) and 1200 mg/kg/day for fetuses.

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 fetuses with cardiovascular/skeletal anomalies. The NOAEL was < 200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m2 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/m2 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/m2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Acesulfame potassium (E950)
Grape flavour
Citric acid monohydrate
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Finished product: 36 months
After first opening: 4 months

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

300 ml brown glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 10 ml graduated oral syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

150 ml brown glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 3 ml graduated oral syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

150 ml brown glass bottle (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a 1 ml graduated oral syringe (polypropylene, polyethylene) and an adaptor for the syringe (polyethylene).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/001
EU/1/11/702/002
EU/1/11/702/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2011
Date of latest renewal: 28 April 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Merckle GmbH
Ludwig-Merckle-Strasse 3
89143 Blaubeuren
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for blister packs

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 250 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 250 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/004
EU/1/11/702/005
EU/1/11/702/006
EU/1/11/702/007
EU/1/11/702/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer wrapper label on multipacks wrapped in transparent foil - including the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 250 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 250 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 200 (2 packs of 100) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
See outer carton

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/009

13. BATCH NUMBER

Lot
See outer carton

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Multipack Carton for blister packs- without the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 250 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 250 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 250 mg film-coated tablets
levetiracetam

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for blister packs

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 500 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/010
EU/1/11/702/011
EU/1/11/702/012
EU/1/11/702/013
EU/1/11/702/014
EU/1/11/702/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer wrapper label on multipacks wrapped in transparent foil - including the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 500 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 200 (2 packs of 100) film-coated tablets

Multipack: 120 (2 packs of 60) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
See outer carton

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/016
EU/1/11/702/017

13. BATCH NUMBER

Lot
See outer carton

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Multipack Carton for blister packs- without the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 500 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets
Component of a multipack, can't be sold separately

60 film-coated tablets
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/016
EU/1/11/702/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 500 mg film-coated tablets
levetiracetam

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for blister packs

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 750 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 750 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
80 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/018
EU/1/11/702/019
EU/1/11/702/020
EU/1/11/702/021
EU/1/11/702/022
EU/1/11/702/023

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 750 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer wrapper label on multipacks wrapped in transparent foil - including the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 750 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 750 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 200 (2 packs of 100) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
See outer carton

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/024

13. BATCH NUMBER

Lot
See outer carton

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Multipack Carton for blister packs- without the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 750 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 750 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/024

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 750 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 750 mg film-coated tablets
levetiracetam

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for blister packs

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 1000 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1000 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/025
EU/1/11/702/026
EU/1/11/702/027
EU/1/11/702/028
EU/1/11/702/029
EU/1/11/702/030

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer wrapper label on multipacks wrapped in transparent foil - including the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 1000 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1000 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 200 (2 packs of 100) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
See outer carton

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/031

13. BATCH NUMBER

Lot
See outer carton

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Multipack Carton for blister packs- without the Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 1000 mg film-coated tablets
levetiracetam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1000 mg levetiracetam.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
info@ratiopharm.de

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/031

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 1000 mg film-coated tablets
levetiracetam

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for bottles - 300 ml (10 ml syringe)

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 100 mg/ml oral solution
levetiracetam

For adults and children aged 4 years and older.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml oral solution contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains methyl and propyl parahydroxybenzoate and potassium.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

300 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Use the 10 ml syringe included in the package.

[Text for pictogram]
300 ml 10 ml 4+ years

To take as follows:
[Box for the prescription dose]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Do not use after 4 months of first opening the bottle.
First Opening:

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 100 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label - 300 ml (10 ml syringe)

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 100 mg/ml oral solution
levetiracetam

For adults and children aged 4 years and older.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml oral solution contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains methyl and propyl parahydroxybenzoate and potassium.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

300 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Use the 10 ml syringe included in the package.

[Text for pictogram]
300 ml 10 ml 4+ years

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Do not use after 4 months of first opening the bottle.

First Opening:

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

In case no outer packaging is used
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

In case no outer packaging is used
PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for bottles - 150 ml (3 ml syringe)

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 100 mg/ml oral solution
levetiracetam

For children aged 6 months to less than 4 years.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml oral solution contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains methyl and propyl parahydroxybenzoate and potassium.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

150 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Use the 3 ml syringe included in the package.

[Text for pictogram]
150 ml 3 ml 6-48 months

To take as follows:
[Box for the prescription dose]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Do not use after 4 months of first opening the bottle.
First Opening:

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 100 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label - 150 ml (3 ml syringe)

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 100 mg/ml oral solution
levetiracetam

For children aged 6 months to less than 4 years.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml oral solution contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains methyl and propyl parahydroxybenzoate and potassium.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

150 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Use the 3 ml syringe included in the package.

[Text for pictogram]
150 ml 3 ml 6-48 months

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Do not use after 4 months of first opening the bottle.

First Opening:

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

In case no outer packaging is used
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

In case no outer packaging is used
PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for bottles - 150 ml (1 ml syringe)

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 100 mg/ml oral solution
levetiracetam

For children aged 1 month to less than 6 months.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml oral solution contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains methyl and propyl parahydroxybenzoate and potassium.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

150 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use
Use the 1 ml syringe included in the package.

[Text for pictogram]
150 ml 1 ml 1-6 months

To take as follows:
[Box for the prescription dose]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Do not use after 4 months of first opening the bottle.
First Opening:

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levetiracetam ratiopharm 100 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label - 150 ml (1 ml syringe)

1. NAME OF THE MEDICINAL PRODUCT

Levetiracetam ratiopharm 100 mg/ml oral solution
levetiracetam

For children aged 1 month to less than 6 months.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml oral solution contains 100 mg levetiracetam.

3. LIST OF EXCIPIENTS

Contains methyl and propyl parahydroxybenzoate and potassium.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

150 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Use the 1 ml syringe included in the package.

[Text for pictogram]
150 ml 1 ml 1-6 months

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Do not use after 4 months of first opening the bottle.

First Opening:

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/702/003

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14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

In case no outer packaging is used
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

In case no outer packaging is used
PC:
SN:
NN:

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Levetiracetam ratiopharm 250 mg film-coated tablets
Levetiracetam ratiopharm 500 mg film-coated tablets
Levetiracetam ratiopharm 750 mg film-coated tablets
Levetiracetam ratiopharm 1000 mg film-coated tablets

levetiracetam

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Levetiracetam ratiopharm is and what it is used for
2. What you need to know before you take Levetiracetam ratiopharm
3. How to take Levetiracetam ratiopharm
4. Possible side effects
5. How to store Levetiracetam ratiopharm
6. Contents of the pack and other information

1. What Levetiracetam ratiopharm is and what it is used for

Levetiracetam is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Levetiracetam ratiopharm is used:
- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat a certain form of epilepsy. Epilepsy is a condition where the patients have repeated fits (seizures). Levetiracetam is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation). Levetiracetam has been given to you by your doctor to reduce the number of fits.
- as an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age
  - myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy
  - primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in adults and adolescents from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

2. What you need to know before you take Levetiracetam ratiopharm

Do not take Levetiracetam ratiopharm
- If you are allergic to levetiracetam, pyrrolidone derivatives or any of the other ingredients of this medicine (listed in Section 6).

Warnings and precautions
Talk to your doctor before taking Levetiracetam ratiopharm

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- A small number of people being treated with anti-epileptics such as Levetiracetam ratiopharm have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.
- If you have a family or medical history of irregular heart rhythm (visible on an electrocardiogram), or if you have a disease and/or take a treatment that make(s) you prone to heartbeat irregularities or salt imbalances.

Tell your doctor or pharmacist if any of the following side effects gets serious or last longer than a few days:
- Abnormal thoughts, feeling irritable or reacting more aggressively than usually, or if you or your family and friends notice important changes in mood or behaviour.
- Aggravation of epilepsy:
  Your seizures may rarely become worse or happen more often, mainly during the first month after the start of the treatment or increase of the dose.
  In a very rare form of early-onset epilepsy (epilepsy associated with SCN8A mutations) that causes multiple types of seizures and loss of skills you may notice that the seizures remain present or are becoming worse during your treatment.

If you experience any of these new symptoms while taking Levetiracetam ratiopharm, see a doctor as soon as possible.

Children and adolescents

- Levetiracetam ratiopharm is not indicated in children and adolescents below 16 years on its own (monotherapy).

Other medicines and Levetiracetam ratiopharm
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take macrogol (a drug used as laxative) for one hour before and one hour after taking levetiracetam as this may results in a loss of its effect**.**

Pregnancy and breast-feeding
If you are pregnant or breast-feeding think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Levetiracetam can be used during pregnancy, only if after careful assessment it is considered necessary by your doctor.
You should not stop your treatment without discussing this with your doctor.
A risk of birth defects for your unborn child cannot be completely excluded. Breast-feeding is not recommended during treatment.

Driving and using machines
Levetiracetam ratiopharm may impair your ability to drive or operate any tools or machinery, as it may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

3. How to take Levetiracetam ratiopharm

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Take the number of tablets following your doctor's instructions.

Levetiracetam ratiopharm must be taken twice a day, once in the morning and once in the evening, at about the same time each day.

Adjunctive Therapy and monotherapy (from 16 years of age)

- **Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more:**
  Recommended dose: between 1000 mg and 3000 mg each day.
  When you will first start taking Levetiracetam ratiopharm, your doctor will prescribe you a **lower dose** during 2 weeks before giving you the lowest daily dose.
  Example: if your daily dose is intended to be 1000 mg, your reduced starting dose is 1 tablet of 250 mg in the morning and 1 tablet of 250 mg in the evening, and the dose will be gradually incremented to reach 1000 mg daily after 2 weeks.

- **Adolescents (12 to 17 years) weighing 50 kg or less:**
  Your doctor will prescribe the most appropriate pharmaceutical form of Levetiracetam ratiopharm according to weight and dose.

Dose in infants (1 month to 23 months) and children (2 to 11 years) weighing less than 50 kg:
Your doctor will prescribe the most appropriate pharmaceutical form of Levetiracetam ratiopharm according to the age, weight and dose.

Levetiracetam ratiopharm 100 mg/ml oral solution is a formulation more appropriate to infants and children under the age of 6 years and to children and adolescent (from 6 to 17 years) weighing less than 50 kg and when tablets don't allow accurate dosage.

Method of administration
Swallow Levetiracetam ratiopharm film-coated tablets with a sufficient quantity of liquid (*e.g*. a glass of water). You may take Levetiracetam ratiopharm with or without food. After oral administration the bitter taste of levetiracetam may be experienced.

Duration of treatment
- Levetiracetam ratiopharm is used as a chronic treatment. You should continue Levetiracetam ratiopharm treatment for as long as your doctor has told you.
- Do not stop your treatment without your doctor's advice as this could increase your seizures.

If you take more Levetiracetam ratiopharm than you should
The possible side effects of an overdose of Levetiracetam ratiopharm are sleepiness, agitation, aggression, decrease of alertness, inhibition of breathing and coma.
Contact your doctor if you took more tablets than you should. Your doctor will establish the best possible treatment of overdose.

If you forget to take Levetiracetam ratiopharm
Contact your doctor if you have missed one or more doses.
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Levetiracetam ratiopharm
If stopping treatment, Levetiracetam ratiopharm should be discontinued gradually to avoid an increase of seizures. Should your doctor decide to stop your Levetiracetam ratiopharm treatment, he/she will instruct you about the gradual withdrawal of Levetiracetam ratiopharm.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately, or go to your nearest emergency department, if you experience:

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- swelling of the face, lips, tongue and throat (Quincke's oedema)
- flu-like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia), enlarged lymph nodes and the involvement of other body organs (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS])
- symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, as this may be a sign of sudden decrease of kidney function
- a skin rash which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*)
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*)
- a more severe form of rash causing skin peeling in more than 30 % of the body surface (*toxic epidermal necrolysis*)
- signs of serious mental changes or if someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements. These could be symptoms of an encephalopathy.

The most frequently reported side effects are nasopharyngitis, somnolence (sleepiness), headache, fatigue and dizziness. At the beginning of the treatment or at dose increase side effects like sleepiness, tiredness and dizziness may be more common. These effects should however decrease over time.

Very common: may affect more than 1 in 10 people
- nasopharyngitis;
- somnolence (sleepiness), headache.

Common: may affect up to 1 in 10 people
- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety, insomnia, nervousness or irritability;
- convulsion, balance disorder (equilibrium disorder), dizziness (sensation of unsteadiness), lethargy (lack of energy and enthusiasm), tremor (involuntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia/fatigue (tiredness).

Uncommon: may affect up to 1 in 100 people
- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional instability/mood swings, agitation;
- amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination/ataxia (impaired coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- elevated/abnormal values in a liver function test;
- hair loss, eczema, pruritus;

- muscle weakness, myalgia (muscle pain);
- injury.

Rare: may affect up to 1 in 1000 people
- infection;
- decreased number of all blood cell types;
- severe allergic reactions (DRESS, anaphylactic reaction [severe and important allergic reaction], Quincke's oedema [swelling of the face, lips, tongue and throat]);
- decreased blood sodium concentration;
- suicide, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- delirium;
- encephalopathy (see sub-section "Tell your doctor immediately" for a detailed description of symptoms);
- seizures may become worse or happen more often;
- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- change of the heart rhythm (Electrocardiogram);
- pancreatitis;
- liver failure, hepatitis;
- sudden decrease in kidney function;
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*), a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens–Johnson syndrome*), and a more severe form causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*);
- rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients;
- limp or difficulty walking;
- combination of fever, muscle stiffness, unstable blood pressure and heart rate, confusion, low level of consciousness (may be signs of a disorder called *neuroleptic malignant syndrome*). Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Very rare: may affect up to 1 in 10000 people
- repeated unwanted thoughts or sensations or the urge to do something over and over again (Obsessive Compulsive Disorder).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Levetiracetam ratiopharm

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the carton box and blister after EXP.
The expiry date refers to the last day of the month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Levetiracetam ratiopharm contains
The active substance is called levetiracetam.

One film-coated tablet of Levetiracetam ratiopharm 250 mg contains 250 mg levetiracetam.
One film-coated tablet of Levetiracetam ratiopharm 500 mg contains 500 mg levetiracetam.
One film-coated tablet of Levetiracetam ratiopharm 750 mg contains 750 mg levetiracetam.
One film-coated tablet of Levetiracetam ratiopharm 1000 mg contains 1000 mg levetiracetam.

The other ingredients are:

Tablet core:
Macrogol 6000, Colloidal anhydrous silica, Crospovidone, Cellulose powdered, Magnesium stearate.

Film-coating:
Levetiracetam ratiopharm 250 mg
Poly(vinyl alcohol), Titanium dioxide (E171), Macrogol, Talc, Blue indigo carmine aluminium lake (E132)

Levetiracetam ratiopharm 500 mg
Hypromellose (E464), Microcrystalline cellulose (E460), Macrogol 40 stearate type I, Anatase titanium dioxide (E171), Yellow Iron Oxide (E 172)

Levetiracetam ratiopharm 750 mg
Hypromellose (E464), Microcrystalline cellulose (E460), Macrogol 40 stearate type I, Anatase titanium dioxide (E171), Yellow Iron Oxide (E172), Red Iron Oxide (E172)

Levetiracetam ratiopharm 1000 mg
Hypromellose (E464), Microcrystalline cellulose (E460), Macrogol 40 stearate type I, Titanium dioxide (E171)

What Levetiracetam ratiopharm looks like and contents of the pack

Levetiracetam ratiopharm 250 mg
Film-coated tablets are blue, oblong and scored on one side and are supplied in packs of 20, 30, 50, 60 or 100 film-coated tablets or multipacks of 200 (2 packs of 100) film-coated tablets.

Levetiracetam ratiopharm 500 mg
Film-coated tablets are yellow, oval and scored on one side and are supplied in packs of 10, 20, 30, 50, 60 or 100 film-coated tablets or multipacks of 120 (2 packs of 60) or 200 (2 packs of 100) film-coated tablets.

Levetiracetam ratiopharm 750 mg
Film-coated tablets are light red coloured, oblong and scored on both sides and are supplied in packs of 20, 30, 50, 60, 80 or 100 film-coated tablets or multipacks of 200 (2 packs of 100) film-coated tablets.

Levetiracetam ratiopharm 1000 mg
Film-coated tablets are white, oblong and scored on both sides and are supplied in packs of 10, 20, 30, 50, 60 or 100 film-coated tablets or multipacks of 200 (2 packs of 100) film-coated tablets.

The tablets can be divided into equal halves.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
ratiopharm GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany
Email: info@ratiopharm.de

Manufacturer
Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tél/Tel: +32 38207373

България
Тева Фарма ЕАД
Тел.: +359 24899585

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251007111

Danmark
Teva Denmark A/S
Tlf.: +45 44985511

Deutschland
ratiopharm GmbH
Tel: +49 73140202

Eesti
UAB Teva Baltics Eesti filiaal
Tel: +372 6610801

Ελλάδα
TEVA HELLAS A.E.
Τηλ: +30 2118805000

España
Teva Pharma, S.L.U.
Tel: +34 913873280

France
Teva Santé
Tél: +33 155917800

Lietuva
UAB Teva Baltics
Tel: +370 52660203

Luxembourg/Luxemburg
ratiopharm GmbH
Allemagne/Deutschland
Tél/Tel: +49 73140202

Magyarország
Teva Gyógyszergyár Zrt.
Tel.: +36 12886400

Malta
Teva Pharmaceuticals Ireland
L-Irlanda
Tel: +44 2075407117

Nederland
Teva Nederland B.V.
Tel: +31 8000228400

Norge
Teva Norway AS
Tlf: +47 66775590

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 1970070

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 223459300

Portugal
ratiopharm - Comércio e Indústria de Produtos Farmacêuticos, Lda.
Tel: +351 214767550

Hrvatska
Pliva Hrvatska d.o.o.
Tel: +385 13720000

Ireland
Teva Pharmaceuticals Ireland
Tel: +44 2075407117

Ísland
Teva Pharma Iceland ehf.
Sími: +354 5503300

Italia
Teva Italia S.r.l.
Tel: +39 028917981

Κύπρος
TEVA HELLAS A.E.
Ελλάδα
Τηλ: +30 2118805000

Latvija
UAB Teva Baltics filiāle Latvijā
Tel: +371 67323666

România
Teva Pharmaceuticals S.R.L.
Tel: +40 212306524

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 15890390

Slovenská republika
TEVA Pharmaceuticals Slovakia s.r.o.
Tel: +421 257267911

Suomi/Finland
Teva Finland Oy
Puh/Tel: +358 201805900

Sverige
Teva Sweden AB
Tel: +46 42121100

This leaflet was last revised in {month/YYYY}.
Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu

Package Leaflet: Information for the patient

Levetiracetam ratiopharm 100 mg/ml oral solution.
levetiracetam

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Levetiracetam ratiopharm is and what it is used for
2. What you need to know before you take Levetiracetam ratiopharm
3. How to take Levetiracetam ratiopharm
4. Possible side effects
5. How to store Levetiracetam ratiopharm
6. Contents of the pack and other information

1. What Levetiracetam ratiopharm is and what it is used for

Levetiracetam is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Levetiracetam ratiopharm is used:
- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat a certain form of epilepsy. Epilepsy is a condition where the patients have repeated fits (seizures). Levetiracetam is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation). Levetiracetam has been given to you by your doctor to reduce the number of fits.
- as an add-on to other antiepileptic medicines to treat:
  - partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age
  - myoclonic seizures (short, shock-like jerks of a muscle or group of muscles) in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy,
  - primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in adults and adolescents from 12 years of age with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

2. What you need to know before you take Levetiracetam ratiopharm

Do not take Levetiracetam ratiopharm
- If you are allergic to levetiracetam, pyrrolidone derivatives or any of the other ingredients of this medicine (listed in Section 6).

Warnings and precautions
Talk to your doctor before taking Levetiracetam ratiopharm
- If you suffer from kidney problems, follow your doctor’s instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.

- A small number of people being treated with anti-epileptics such as Levetiracetam ratiopharm have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.
- If you have a family or medical history of irregular heart rhythm (visible on an electrocardiogram), or if you have a disease and/or take a treatment that make(s) you prone to heartbeat irregularities or salt imbalances.

Tell your doctor or pharmacist if any of the following side effects gets serious or last longer than a few days:
- Abnormal thoughts, feeling irritable or reacting more aggressively than usually, or if you or your family and friends notice important changes in mood or behaviour.
- Aggravation of epilepsy:
  Your seizures may rarely become worse or happen more often, mainly during the first month after the start of the treatment or increase of the dose.
  In a very rare form of early-onset epilepsy (epilepsy associated with SCN8A mutations) that causes multiple types of seizures and loss of skills you may notice that the seizures remain present or are becoming worse during your treatment.

If you experience any of these new symptoms while taking Levetiracetam ratiopharm, see a doctor as soon as possible.

Children and adolescents
- Levetiracetam ratiopharm is not indicated in children and adolescents below 16 years on its own (monotherapy)

Other medicines and Levetiracetam ratiopharm
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take macrogol (a drug used as laxative) for one hour before and one hour after taking levetiracetam as this may results in a reduction of its effect.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. Levetiracetam can be used during pregnancy, only if after careful assessment it is considered necessary by your doctor.
You should not stop your treatment without discussing this with your doctor.
A risk of birth defects for your unborn child cannot be completely excluded.
Breast-feeding is not recommended during treatment.

Driving and using machines
Levetiracetam ratiopharm may impair your ability to drive or operate any tools or machinery, as it may make you feel sleepy. This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

Levetiracetam ratiopharm contains methyl parahydroxybenzoate, propyl parahydroxybenzoate, potassium and sodium.
Levetiracetam ratiopharm oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).
This medicine contains 1.2 mmol (or 46.65 mg) potassium per 15 ml. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.
This medicine contains less than 1 mmol sodium (23 mg) per 15 ml that is to say essentially ‘sodium-free’.

3. How to take Levetiracetam ratiopharm

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
Levetiracetam ratiopharm must be taken twice a day, once in the morning and once in the evening, at about the same time each day.
Take the oral solution following your doctor's instructions.

Monotherapy (from 16 years of age)

Adults (≥18 years) and adolescents (from 16 years of age):
Measure the appropriate dosage using the 10 ml syringe included in the package for patients 4 years and above.
Recommended dose: Levetiracetam ratiopharm is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500 mg) and 15 ml (1500 mg).
When you will first start taking Levetiracetam ratiopharm, your doctor will prescribe you a **lower dose** during 2 weeks before giving you the lowest daily dose.

Add-on therapy

Dose in adults and adolescents (12 to 17 years):
Measure the appropriate dosage using the 10 ml syringe included in the package for patients of 4 years and above.
Recommended dose: Levetiracetam ratiopharm is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500mg) and 15 ml (1500mg).

Dose in children 6 months and older:
Your doctor will prescribe the most appropriate pharmaceutical form of Levetiracetam ratiopharm according to the age, weight and dose.
For children 6 months to 4 years, measure the appropriate dosage using the 3 ml syringe included in the package.
For children above 4 years, measure the appropriate dosage using the 10 ml syringe included in the package.
Recommended: Levetiracetam ratiopharm is taken twice daily, in two equally divided doses, each individual dose being measured between 0.1 ml (10 mg) and 0.3 ml (30 mg), per kg bodyweight of the child. (see table below for dose examples).

Dose in children 6 months and older

Weight	Starting dose: 0.1 ml/kg twice daily	Maximum dose: 0.3 ml/kg twice daily
6 kg	0.6 ml twice daily	1.8 ml twice daily
8 kg	0.8 ml twice daily	2.4 ml twice daily
10 kg	1 ml twice daily	3 ml twice daily
15 kg	1.5 ml twice daily	4.5 ml twice daily
20 kg	2 ml twice daily	6 ml twice daily
25 kg	2.5 ml twice daily	7.5 ml twice daily
From 50 kg	5 ml twice daily	15 ml twice daily

Dose in infants (1 month to less than 6 months):
For infants 1 month to less than 6 months, measure the appropriate dosage using the **1 ml** syringe included in the package.
Recommended dose: Levetiracetam ratiopharm is taken twice daily, in two equally divided doses, each individual dose being measured between 0.07 ml (7 mg) and 0.21 ml (21 mg), per kg bodyweight of the infant. (see table below for dose examples).

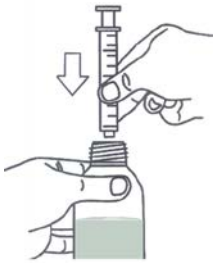
Dose in infants (1 month to less than 6 months):

Weight	Starting dose: 0.07 ml/kg twice daily	Maximum dose: 0.21 ml/kg twice daily
4 kg	0.3 ml twice daily	0.85 ml twice daily
5 kg	0.35 ml twice daily	1.05 ml twice daily
6 kg	0.45 ml twice daily	1.25 ml twice daily
7 kg	0.5 ml twice daily	1.5 ml twice daily

Method of administration
After measuring the correct dose with an appropriate syringe, Levetiracetam ratiopharm oral solution may be diluted in a glass of water or baby's bottle. You may take Levetiracetam ratiopharm with or without food. After oral administration the bitter taste of levetiracetam may be experienced.

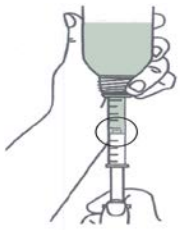
Instructions for use:

- Open the bottle: press the cap and turn it anticlockwise.
- Take the syringe and put it in the opening of the bottle.
  For this the piston must be completely pushed into the syringe
  (figure ①)



①

- Hold bottle and syringe securely tight. Then turn bottle and syringe upside down (figure ②).



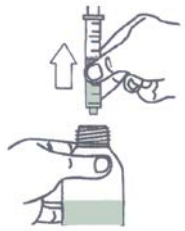
②

- Fill the syringe with the liquid by pulling the piston to the graduation mark corresponding to the quantity in millilitre (ml) prescribed by your doctor.

- You can read the corresponding millilitre at the beginning of the thicker part of the piston figure ③).

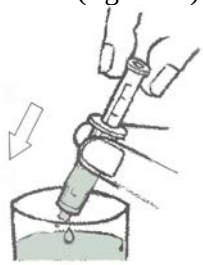
③

- If bubbles occur push the piston into the syringe again and fill the syringe once more slowly.
- Move bottle and the filled syringe back in starting position.
- Remove the filled syringe from the bottle (figure ④).



④

- Empty the contents of the syringe in a glass of water by pushing the piston into the syringe (figure ⑤).



⑤

- Close the bottle with the plastic screw cap after every usage.
- Drink the whole contents of the glass.
- Wash the syringe afterwards with clear water by filling and emptying the syringe repeatedly.

Duration of treatment
- Levetiracetam ratiopharm is used as a chronic treatment. You should continue Levetiracetam ratiopharm treatment for as long as your doctor has told you.
- Do not stop your treatment without your doctor's advice as this could increase your seizures.

If you take more Levetiracetam ratiopharm than you should
The possible side effects of an overdose of Levetiracetam ratiopharm are sleepiness, agitation, aggression, decrease of alertness, inhibition of breathing and coma.
Contact your doctor if you took more Levetiracetam ratiopharm than you should. Your doctor will establish the best possible treatment of overdose.

If you forget to take Levetiracetam ratiopharm
Contact your doctor if you have missed one or more doses.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Levetiracetam ratiopharm
If stopping treatment, Levetiracetam ratiopharm should be discontinued gradually to avoid an increase of seizures. Should your doctor decide to stop your Levetiracetam ratiopharm treatment, he/she will instruct you about the gradual withdrawal of Levetiracetam ratiopharm.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately, or go to your nearest emergency department, if you experience:

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- swelling of the face, lips, tongue and throat (Quincke's oedema)
- flu-like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia), enlarged lymph nodes and the involvement of other body organs (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]).
- symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, as this may be a sign of sudden decrease of kidney function
- a skin rash which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*)
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*)
- a more severe form of rash causing skin peeling in more than 30 % of the body surface (*toxic epidermal necrolysis*)
- signs of serious mental changes or if someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements. These could be symptoms of an encephalopathy.

The most frequently reported adverse reactions were nasopharyngitis, somnolence (sleepiness), headache, fatigue and dizziness. At the beginning of the treatment or at dose increase side effects like sleepiness, tiredness and dizziness may be more common. These effects should however decrease over time.

Very common: may affect more than 1 in 10 people
- nasopharyngitis;
- somnolence (sleepiness), headache.

Common: may affect up to 1 in 10 people
- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety, insomnia, nervousness or irritability;
- convulsion, balance disorder (equilibrium disorder), dizziness (sensation of unsteadiness), lethargy (lack of energy and enthusiasm), tremor (involuntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia/fatigue (tiredness).

Uncommon: may affect up to 1 in 100 people
- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional instability/mood swings, agitation;
- amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination/ataxia (impaired coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- elevated/abnormal values in a liver function test;
- hair loss, eczema, pruritus;
- muscle weakness, myalgia (muscle pain);
- injury.

Rare: may affect up to 1 in 1000 people
- infection;

- decreased number of all blood cell types;
- severe allergic reactions (DRESS, anaphylactic reaction [severe and important allergic reaction], Quincke's oedema [swelling of the face, lips, tongue and throat]);
- decreased blood sodium concentration;
- suicide, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- delirium;
- encephalopathy (see sub-section "Tell your doctor immediately" for a detailed description of symptoms);
- seizures may become worse or happen more often;
- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- change of the heart rhythm (Electrocardiogram);
- pancreatitis;
- liver failure, hepatitis;
- sudden decrease in kidney function;
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*), a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens–Johnson syndrome*), and a more severe form causing skin peeling in more than 30% of the body surface (*toxic epidermal necrolysis*);
- rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients;
- limp or difficulty walking;
- combination of fever, muscle stiffness, unstable blood pressure and heart rate, confusion, low level of consciousness (may be signs of a disorder called *neuroleptic malignant syndrome*). Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Very rare: may affect up to 1 in 10000 people
- repeated unwanted thoughts or sensations or the urge to do something over and over again (Obsessive Compulsive Disorder).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Levetiracetam ratiopharm

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the cardboard box and bottle after EXP.
The expiry date refers to the last day of the month.

Keep the bottle in the outer carton in order to protect from light.

Do not use after 4 months of first opening the bottle.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Levetiracetam ratiopharm contains
The active substance is called levetiracetam. Each ml contains 100 mg of levetiracetam.

The other ingredients are: methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), citric acid monohydrate, sodium hydroxide, purified water, acesulfame potassium (E 950), grape flavour.

What Levetiracetam ratiopharm looks like and contents of the pack
Levetiracetam ratiopharm oral solution is a clear liquid.

The 300 ml glass bottle of Levetiracetam ratiopharm oral solution (for children aged 4 years and above, adolescents and adults) is packed in a cardboard box containing a 10 ml oral syringe (graduated every 0.25 ml) and an adaptor for the syringe.
The 150 ml glass bottle of Levetiracetam ratiopharm oral solution (for infants aged 6 months and above and children aged 2 to 4 years) is packed in a cardboard box containing a 3 ml oral syringe (graduated every 0.1 ml) and an adaptor for the syringe.
The 150 ml glass bottle of Levetiracetam ratiopharm oral solution (for infants aged 1 month to less than 6 months) is packed in a cardboard box containing a 1 ml oral syringe (graduated every 0.05 ml) and an adaptor for the syringe.

Marketing Authorisation Holder
ratiopharm GmbH
Graf-Arco-Str. 3
89079 Ulm
Germany
e-mail: info@ratiopharm.de

Manufacturer
Merckle GmbH
Ludwig-Merckle-Str. 3
89143 Blaubeuren
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tél/Tel: +32 38207373

България
Тева Фарма ЕАД
Тел.: +359 24899585

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251007111

Danmark
Teva Denmark A/S
Tlf.: +45 44985511

Deutschland
ratiopharm GmbH

Lietuva
UAB Teva Baltics
Tel: +370 52660203

Luxembourg/Luxemburg
ratiopharm GmbH
Allemagne/Deutschland
Tél/Tel: +49 73140202

Magyarország
Teva Gyógyszergyár Zrt.
Tel.: +36 12886400

Malta
Teva Pharmaceuticals Ireland
L-Irlanda
Tel: +44 2075407117

Nederland
Teva Nederland B.V.

Tel: +49 73140202

Eesti
UAB Teva Baltics Eesti filiaal
Tel: +372 6610801

Ελλάδα
TEVA HELLAS A.E.
Τηλ: +30 2118805000

España
Teva Pharma, S.L.U.
Tel: +34 913873280

France
Teva Santé
Tél: +33 155917800

Hrvatska
Pliva Hrvatska d.o.o.
Tel: +385 13720000

Ireland
Teva Pharmaceuticals Ireland
Tel: +44 2075407117

Ísland
Teva Pharma Iceland ehf.
Sími: +354 5503300

Italia
Teva Italia S.r.l.
Tel: +39 028917981

Κύπρος
TEVA HELLAS A.E.
Ελλάδα
Τηλ: +30 2118805000

Latvija
UAB Teva Baltics filiāle Latvijā
Tel: +371 67323666

Tel: +31 8000228400

Norge
Teva Norway AS
Tlf: +47 66775590

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 1970070

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 223459300

Portugal
ratiopharm - Comércio e Indústria de Produtos Farmacêuticos, Lda.
Tel: +351 214767550

România
Teva Pharmaceuticals S.R.L.
Tel: +40 212306524

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 15890390

Slovenská republika
TEVA Pharmaceuticals Slovakia s.r.o.
Tel: +421 257267911

Suomi/Finland
Teva Finland Oy
Puh/Tel: +358 201805900

Sverige
Teva Sweden AB
Tel: +46 42121100

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu