

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TORLEVA SYRUP

1. Generic Name

Levetiracetam Oral Solution I.P.

2. Qualitative and quantitative composition

Each ml contains:

Levetiracetam I.P.100mg

Flavored syrupy base..... q.s.

Other Inactive Ingredient Are Sucralose, Propylene Glycol Glycerin, Sorbitol Soln., Citric acid Monohydrate, Sodium Citrate, Methyl Paraben, Propyl Paraben, Selecta Banana Flavour.

3. Dosage form and strength

Dosage form: Syrup

Strength: 100 mg/ml Oral Solution

4. Clinical particulars

4.1 Therapeutic indication

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

4.2 Posology and method of administration

Posology

Monotherapy for adults and adolescents from 16 years of age

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

Add-on therapy for adults (≥ 18 years) and adolescents (12 to 17 years) weighing 50 kg or more

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Discontinuation

If levetiracetam has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents 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:

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

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

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

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	Creatinine clearance (ml/min/1.73m 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.

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 $< 60 \text{ ml/min/1.73 m}^2$.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or other pyrrolidone derivatives.

4.4 Special warnings and precautions for use

Renal Impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

Acute Kidney injury

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

Blood cell counts

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

Suicide

Suicide, suicide attempt, suicidal ideation and 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 sign 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.

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.

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.

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.

4.5 Drugs interactions

Antiepileptic medicinal products

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

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

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. 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 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

Laxatives

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

Food and alcohol

The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced. No data on the interaction of levetiracetam with alcohol are available.

4.6 Use in Special Populations

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 post marketing 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.

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

4.8 Undesirable effects

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 reported 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$).

MedDRA SOC	Frequency category			
	Very common	Common	Uncommon	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), 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
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
Eye disorders			Diplopia, vision blurred	

Ear and labyrinth disorders		Vertigo		
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*
General disorders and administration site conditions		Asthenia/fatigue		

Injury, poisoning and procedural complications			Injury	
--	--	--	--------	--

* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is co-administered with topiramate. In several cases of alopecia, recovery was observed when levetiracetam was discontinued. Bone marrow suppression was identified in some of the cases of pancytopenia. 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 reported 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 reported 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 reported 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 reported, 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 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 any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

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 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 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.

5.2 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 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 reported 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 reported 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 used in this study. The total daily dose was administered twice daily.

The primary measure of effectiveness was the responder rate (percent of patients with $\geq 50\%$ 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 reported 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 reported 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 reported 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 reported 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 reported 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.

5.3 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 (C_{max}) are achieved at 1.3 hours after dosing. Steady-state is achieved after two days of a twice daily administration schedule. Peak concentrations (C_{max}) are typically 31 and 43 $\mu\text{g/ml}$ following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively. The extent of absorption is dose-independent and is not altered by food.

Distribution

No tissue distribution data are available in humans.

Neither levetiracetam nor its primary metabolite 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 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 TORLEVA 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.

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 TORLEVA, based on creatinine clearance in patients with moderate and severe renal impairment.

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.

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

6. Nonclinical properties

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.

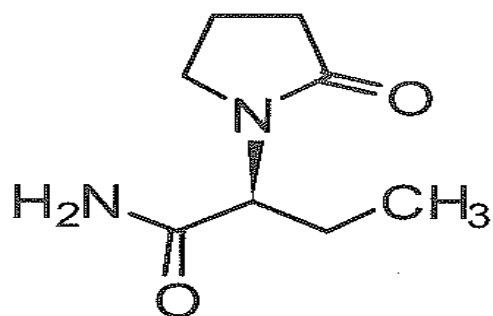
Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. 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 reported; was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was \geq 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)

7. Description

Levetiracetam is (2S)-2-(2-oxopyrrolidin-1-yl)butanamide. Having molecular weight 170.2 and molecular formula is C₈H₁₄N₂O₂. The chemical structure is:



Levetiracetam is a white or almost white powder. Very soluble in water; soluble in acetonitrile; Practically insoluble in hexane.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Amber colored pet bottle filled with clear colorless solution with characteristic banana flavor.

8.4 Storage and handing instructions

Store in a well-closed container at a temperature not exceeding 30°C. Keep out of reach of children.

9. Patient counselling information

TORLEVA SYRUP

(Levetiracetam) Oral Solution I.P.

Read all of this leaflet carefully before you 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.

What is in this leaflet?

9.1. What TORLEVA is and what it is used for

9.2. What you need to know before you take TORLEVA

9.3. How to take TORLEVA

9.4.Possible side effects

9.5.How to store TORLEVA

9.6.Contents of the pack and other information

9.1 What TORLEVA is and what it is used for

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

TORLEVA 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).

9.2 What you need to know before you take TORLEVA

Do not take TORLEVA

- If you are allergic to levetiracetam, pyrrolidone derivatives or any of the other ingredients of this medicine

Warnings and precautions

- Talk to your doctor before taking TORLEVA.
- 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 slowdown 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 TORLEVA have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.
- Worsening of seizures: Patients should be advised to consult their physician immediately in case of aggravation of epilepsy.
- Electrocardiogram QT interval prolongation: 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.

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.

Children and adolescents

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

Other medicines and TORLEVA

- Tell your doctor or pharmacist if you are taking or 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 result in a reduction of its effect.

Pregnancy and breast-feeding

- If you are pregnant or breastfeeding, 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

- TORLEVA 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.

9.3 How to take TORLEVA

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

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

Monotherapy

- **Dose in adults and adolescents (from 16 years of age):**

General dose: TORLEVA is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500mg) and 15 ml (1500mg).

When you will first start taking TORLEVA your doctor will prescribe you a lower dose during 2 weeks before giving you the lowest general dose.

Add-on therapy

- **Dose in adults and adolescents (12 to 17 years) weighing 50 kg or more:**

General dose: TORLEVA is taken twice daily, in two equally divided doses, each individual dose being measured between 5 ml (500mg) and 15 ml (1500mg).

When you will first start taking TORLEVA your doctor will prescribe you a lower dose during 2 weeks before giving you the lowest general dose.

- **Dose in infants (1 month to 23 months), children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg:**

Your doctor will prescribe the most appropriate pharmaceutical form of TORLEVA according to the age, weight and dose.

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

Duration of treatment

- TORLEVA is used as a chronic treatment. You should continue TORLEVA 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 TORLEVA than you should

The possible side effects of an overdose of TORLEVA are sleepiness, agitation, aggression, decrease of alertness, inhibition of breathing and coma.

Contact your doctor if you took more TORLEVA than you should. Your doctor will establish the best possible treatment of overdose.

If you forget to take TORLEVA:

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 TORLEVA

If stopping treatment, TORLEVA should be discontinued gradually to avoid an increase of seizures.

Should your doctor decide to stop your TORLEVA treatment, he/she will instruct you about the gradual withdrawal of TORLEVA.

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

9.4 Possible side effects

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

Tell your doctor immediately or contact the casualty department at your nearest hospital, if you get any of the following serious side effects:

- 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) and enlarged lymph nodes (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 1,000 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);
- uncontrollable muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperkinesia (hyperactivity);
- 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 multiform), 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.

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 any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store TORLEVA SYRUP

Store in a well-closed container at a temperature not exceeding 30°C.

9.6 Contents of the pack and other information

Each ml contains:

Levetiracetam I.P.100mg

Flavored syrupy base..... q.s.

Other Inactive Ingredient Are Sucralose, Propylene Glycol Glycerin, Sorbitol Soln., Citric acid Monohydrate, Sodium Citrate, Methyl Paraben, Propyl Paraben, Selecta Banana Flavour.

Amber colored pet bottle filled with clear colorless solution with characteristic banana flavor. Available in 100 ml pack.

10. Details of manufacturer

TORRENT PHARMACEUTICALS LTD.

Indrad-382 721, Dist. Mehsana, INDIA.

At: Plot No. 1175, Post: Dabhsa, Tal: Padra,

Dist: Vadodara, Gujrat 391 440.

11. Details of permission or licence number with date

Mfg Lic No.: G/1994-A issued on 14.02.2013

12. Date of revision

April/2021

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/TORLEVA SYRUP 100 mg/APR-21/08/PI