

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

TORLEVA XR

1. Generic Name

Levetiracetam Prolonged-Release Tablets I.P

2. Qualitative and quantitative composition

Torleva XR 500

Each film coated prolonged-release tablet contains:

Levetiracetam I.P.500mg

Color: Titanium Dioxide I.P.

Torleva XR 750

Each film coated prolonged-release tablet contains:

Levetiracetam I.P.750mg

Color: Titanium Dioxide I.P.

Torleva XR 1000

Each film coated prolonged-release tablet contains:

Levetiracetam I.P.1000mg

Color: Titanium Dioxide I.P.

The other excipients are Microcrystalline Cellulose, Hypromellose, Copovidone, Iso Propyl Alcohol, Colloidal Silicon Dioxide, Hypromellose, Magnesium Stearate, Hydroxy Propyl Methyl Celu, Polyethylene Glycol 400, Titanium Dioxide.

3. Dosage form and strength

Dosage Form: Prolonged-Release Tablets

Strength: 500, 750, 1000

4. Clinical particulars

4.1 Therapeutic indication

Torleva XR is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

4.2 Posology and method of administration

Posology

Add-on therapy for adults (≥ 18 years)

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, 500 mg decreases twice daily every two to four 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 (CL_{cr}) in ml/min is needed. The CL in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults weighting 50 kg or more, the following formula:

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

Then CL_{cr} is adjusted for body surface area (BSA) as follows:

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

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

Group	Creatinine clearance (ml/min/1.73m²)	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 ml/min/1.73 m.

Paediatric population

Not recommended to be used in patients below 18 years of age.

Method of administration

The 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.

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 placebocontrolled 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.

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 children under the age of 18 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.

Patients should not be concerned if they occasionally notice something that looks like swollen pieces of the original tablet in their stool.

4.5 Drugs interactions

Antiepileptic medicinal products

Pre-marketing data from reported 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.

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. Coadministration 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

Reportedly, 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 ($< 1/10,000$).

<u>MedDRA SOC</u>	<u>Frequency category</u>			
	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
<u>Infections and infestations</u>	Nasopharyngitis			Infection
<u>Blood and lymphatic system disorders</u>			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis
<u>Immune system disorders</u>				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)

<u>Metabolism and nutrition disorders</u>		Anorexia	Weight decreased, weight increase	Hyponatraemia
<u>Psychiatric disorders</u>		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
<u>Nervous system disorders</u>	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
<u>Eye disorders</u>			Diplopia, vision blurred	
<u>Ear and labyrinth disorders</u>		Vertigo		
<u>Cardiac disorders</u>				Electrocardiogram QT prolonged
<u>Respiratory, thoracic and mediastinal disorders</u>		Cough		

<u>Gastrointestinal disorders</u>		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis
<u>Hepatobiliary disorders</u>			Liver function test abnormal	Hepatic failure, hepatitis
<u>Renal and Urinary Disorders</u>				Acute Kidney injury
<u>Skin and subcutaneous tissue disorders</u>		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
<u>Musculoskeletal and connective tissue disorders</u>			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*
<u>General disorders and administration site conditions</u>		Asthenia/ fatigue		
<u>Injury, poisoning and procedural complications</u>			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.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. 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:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting

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

Mechanism of action

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

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

Reported *in vitro* studies show that levetiracetam affects intraneuronal Ca levels by partial inhibition of N-type Ca currents and by reducing the release of Ca 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

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

In adults, levetiracetam efficacy has been demonstrated in 3 reported double-blind, placebocontrolled 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.

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.

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.

Reportedly, *in vitro*, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P 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 XR 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 XR, 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Reported 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.

Reportedly 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.

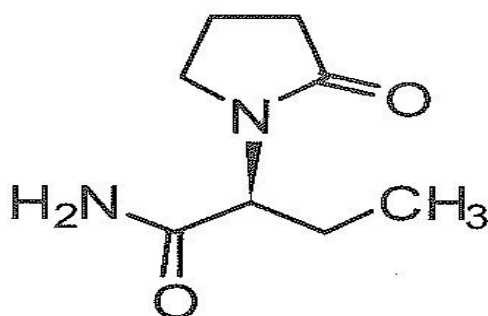
As per reported data, four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of fetuses with cardiovascular/skeletal 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)

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.

Product description:

TORLEVA XR 500 and 1000

White to off white, capsule shaped, biconvex, film coated tablets, plain on both sides.

TORLEVA XR 750

White to off white, oval shaped, biconvex, film coated tablets, plain on both sides.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

Available in blister of 10 tablets

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, protected from moisture.

Keep out of reach of children.

9. Patient counselling information

TORLEVA XR

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 XR is and what it is used for

9.2. What you need to know before you take TORLEVA XR

9.3. How to take TORLEVA XR

9.4. Possible side effects

9.5. How to store TORLEVA XR

9.6. Contents of the pack and other information

9.1 What TORLEVA XR is and what it is used for

TORLEVA XR contains Levetiracetam, an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

TORLEVA XR is used as an add-on to other antiepileptic medicines to treat partial onset seizures in adults

9.2 What you need to know before you take TORLEVA XR

Do not take TORLEVA XR:

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

You should not be concerned if you occasionally notice something that looks like swollen pieces of the original tablet in your stool.

Warnings and precautions

Talk to your doctor before taking TORLEVA XR

- 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 XR have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

Tell your doctor 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 XR is not indicated in children and adolescents below 18 years.

Other medicines and TORLEVA XR

Tell your doctor 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 result in a loss 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 XR 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 XR

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.

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

Method of administration

Swallow TORLEVA XR tablets with a sufficient quantity of liquid (e.g. a glass of water). You may take TORLEVA XR with or without food. After oral administration the bitter taste of levetiracetam may be experienced.

Duration of treatment

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

The possible side effects of an overdose of TORLEVA XR 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 TORLEVA XR:

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 TORLEVA XR:

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

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

9.4 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) 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 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 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 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.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. 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:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting

9.5 How to store TORLEVA XR

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.

Store at a temperature not exceeding 30°C, protected from moisture.

9.6 Contents of the pack and other information

TORLEVA XR is available in blister pack of 10 Tablets.

10. Details of Manufacturer

Torrent Pharmaceutical Ltd,
 32 No. Middle camp, NH-10.

East District, Gangtok, Sikkim-737 135.

11. Details of permission or licence number with date

M/563/2010 issued on 12.06.2018

12. Date of revision

APR-2021

MARKETED BY



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IN/TORLEVA XR 500, 750, 1000mg/APR-21/05/PI