PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

LEVESEIZE XR 500 (extended-release tablets)

LEVESEIZE XR 750 (extended-release tablets)

LEVESEIZE XR 1 000 (extended-release tablets)

LEVESEIZE XR 1 500 (extended-release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEVESEIZE XR 500: Each extended-release tablet contains 500 mg levetiracetam.

LEVESEIZE XR 750: Each extended-release tablet contains 750 mg levetiracetam.

LEVESEIZE XR 1 000: Each extended-release tablet contains 1 000 mg levetiracetam.

LEVESEIZE XR 1 500: Each extended-release tablet contains 1 500 mg levetiracetam

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release tablets.

LEVESEIZE XR 500: Oval, biconvex, coated, bilayer tablet with blue layer having laser drill and a white to off-white layer, imprinted with “573” with black ink on one side and plain on the other side.

LEVESEIZE XR 750: Oval, biconvex, coated, bilayer tablet with blue layer having laser drill and white to off-white layer, imprinted with “576” with black ink on one side and plain on the other side.

LEVESEIZE XR 1 000 Oval, biconvex, coated, bilayer tablet with blue layer and white to off-white layer, having laser drill on blue layer and imprinted with "574" with black ink on one side and plain on the other side.

LEVESEIZE XR 1 500 Oval, biconvex, coated, bilayer tablet with blue layer and white to off-white layer, having laser drill on blue layer and imprinted with "575" with black ink on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

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

LEVESEIZE XR is indicated as adjunctive therapy:

In the treatment of partial onset seizures with or without secondary generalisation in adults and children over 16 years of age with epilepsy

In the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.

In the treatment of primary generalised tonic-clonic seizures in adults and children from 16 years of age with idiopathic generalised epilepsy

4.2 Posology and method of administration

LEVESEIZE XR tablets must be taken orally, swallowed with liquid and may be taken with or without food. LEVESEIZE XR is administered once daily.

Monotherapy

Adults and adolescents from 16 years of age:

The recommended starting dose of LEVESEIZE XR is 500 mg once a day, which should be increased to an initial therapeutic dose of 1 000 mg once a day, after two weeks. The dose can be further increased by 500 mg once a day every two weeks depending upon the clinical response.

The maximum daily dose of LEVESEIZE XR is 1 500 mg once a day.

Adjunctive (add-on therapy)

Adults (≥ 18 years) and adolescents (12 to 17 years) weighing 50 kg or more, when indicated (see section 4.1*):*

The initial therapeutic dose is 1 000 mg once a day. The 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 3 000 mg daily.

Dose changes can be made in 1 000 mg daily increases or decreases every two to four weeks.

The maximum daily dose is 3 000 mg.

Elderly (65 years and older):

Adjustment of the dose is recommended in elderly patients with compromised renal function (see 'Patients with renal impairment' below).

Adolescents (12 to 17 years) weighing less than 50 kg, when indicated (see section 4.1*):*

The initial therapeutic dose is 20 mg/kg once a day. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the dose can be increased up to 60 mg/kg daily. Dose changes should not exceed increases or decreases of 20 mg/kg daily every two weeks. The lowest effective dose should be used.

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

The medical practitioner should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

Recommended dosage for children and adolescents with normal renal function:

Weight	**Starting dose**	**Maximum dose**
	20 mg/kg once a day	60 mg/kg once a day
15 kg (1)	300 mg once a day	900 mg once a day
20 kg (1)	400 mg once a day	1 200 mg once a day
25 kg	500 mg once a day	1 500 mg once a day
From 50 kg (2)	1 000 mg once a day	3 000 mg once a day

(1) Children 20 kg or less should preferably start treatment with a levetiracetam containing oral solution (100 mg/mL; twice daily formulation).

(2) Dosage in children and adolescents 50 kg or more is the same as in adults.

Infants and children less than 12 years:

There are insufficient data to recommend the use of LEVESEIZE XR tablets in children under 12 years of age.

Special populations

Patients with renal impairment:

LEVESEIZE XR 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_{cr} may be estimated from serum creatinine (mg/dL) determination using the following formula:

CL_{cr} (mL/min) = [140 - age (years)] x weight (kg)] (x 0,85 for women)

72 x serum creatinine (µmol/L)

Dosing adjustment for adult patients with impaired renal function:

Group	**Creatinine clearance (mL/min)**	**Dosage and frequency**
Normal	≥ 80	1 000 to 3 000 mg once a day
Mild	50 – 79	1 000 to 2 000 mg once a day
Moderate	30 – 49	500 to 1 500 mg once a day
Severe	< 30	500 to 1 000 mg once a day

Patients with hepatic impairment:

No dose adjustment is needed for 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 < 70 mL/min.

4.3 Contraindications

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or to any of the other ingredients of LEVESEIZE XR, listed in section 6.1.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Suicidal behaviour and ideation

Suicide, suicide attempt and suicidal ideation have been reported in patients treated with antiepileptic medicines, including LEVESEIZE XR. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

The increased risk of suicidal thoughts or behaviour with antiepileptic medicines has been observed as early as one week after starting treatment. Patients, their caregivers or families should be advised seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Behavioural abnormalities and psychotic symptoms

LEVESEIZE XR may cause behavioural abnormalities and psychotic symptoms including irritability and aggressiveness. Therefore, patients treated with LEVESEIZE XR should be monitored for psychiatric signs and symptoms.

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~~ medical practitioner 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.

Anaphylaxis and angioedema

LEVESEIZE XR can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms reported have included hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. In some reported cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, LEVESEIZE XR should be discontinued and appropriate therapy initiated. LEVESEIZE XR should be discontinued permanently if a clear alternative aetiology for the reaction cannot be established.

Serious dermatological reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), may occur with the treatment of LEVESEIZE XR. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with levetiracetam has also been reported. LEVESEIZE XR should be discontinued at the first sign of a rash, unless the rash is clearly not treatment related. If signs or symptoms suggest SJS/TEN, use of LEVESEIZE XR should not be resumed and alternative therapy should be considered.

Withdrawal of LEVESEIZE XR therapy

Withdrawal of LEVESEIZE XR or transition to another type of anti-epileptic therapy should be made gradually to minimise the potential of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Haematologic abnormalities

LEVESEIZE XR can cause haematologic abnormalities. Haematologic abnormalities may occur and include decreases in red blood cell (RBC) counts, haemoglobin, and haematocrit, and increases in eosinophil counts. Decreased white blood cell (WBC) and neutrophil counts may also occur. Cases of agranulocytosis, pancytopenia, and thrombocytopenia have been reported. A complete blood count is recommended in patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders.

Renal insufficiency

Clearance of levetiracetam is decreased in patients with renal impairment correlated with creatinine clearance. The administration of LEVESEIZE XR to patients with renal impairment may require dosage adjustment (see section 4.2).

Hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

Elderly patients

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see section 4.2).

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 remains unknown.

4.5 Interaction with other medicines and other forms of interaction

Anti-epileptic medicines

Levetiracetam, as in LEVESEIZE XR, did not influence the serum concentrations of existing anti-epileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these anti-epileptic medicines did not influence the pharmacokinetics of LEVESEIZE XR.

Probenecid

The administration of probenecid has been shown to inhibit the renal clearance of the primary metabolite (ucb L057), but not of the parent levetiracetem, as in LEVESEIZE XR. It is expected that other medicines excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of LEVESEIZE XR on probenecid was not studied. The effect of LEVESEIZE XR on other actively secreted medicines, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), sulphonamides is unknown.

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 medicines.

Oral contraceptives

Coadministration of oral contraceptives containing ethinylestradiol and levonorgestrel, did not influence the pharmacokinetics of levetiracetam, as in LEVESEIZE XR. The pharmacokinetics of the oral contraceptives were unaffected.

Digoxin

Coadministration of digoxin did not influence the pharmacokinetics of either digoxin or levetiracetam, as in LEVESEIZE XR.

Warfarin

Coadministration of warfarin did not affect the pharmacokinetics of either warfarin or levetiracetam, as in LEVESEIZE XR. Prothrombin times were not modified.

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 LEVESEIZE XR.

Food and alcohol

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

4.6 Fertility, pregnancy and lactation

Pregnancy

LEVESEIZE XR is contraindicated in pregnancy (see section 4.3).

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown (see section 4.3).

Physiological changes during pregnancy may affect LEVESEIZE XR concentration and there have been reports of decreased levetiracetam concentration during pregnancy.

This decrease is reported to be more pronounced during the third trimester.

Breastfeeding

Levetiracetam is excreted in breast milk. Patients using LEVESEIZE XR should not breastfeed (see section 4.3).

Safety in breastfeeding has not been established. There are no data on the effects of LEVESEIZE XR on the breastfed infant, or the effects on milk production.

Fertility

No data are available on the effect of LEVESEIZE XR on fertility.

4.7 Effects on ability to drive and use machines

LEVESEIZE XR may cause side effects, such as somnolence, fatigue or other central nervous system (CNS) related symptoms, especially at the beginning of treatment or following a dosage increase. Caution is advised before driving a vehicle or operating machinery until the effects of LEVESEIZE XR are known. 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 side effects are irritability, somnolence, asthenia, infection and dizziness.

Tabulated summary of adverse reactions:

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	infection, nasopharyngitis		
Blood and lymphatic system disorders	thrombocytopenia		
Metabolism and nutrition disorders	anorexia[1], weight increase	weight decrease	
Psychiatric disorders	agitation, emotional instability/mood swings, depression, insomnia, nervousness, irritability, anxiety, affect lability, hostility/aggression, personality disorders, thinking abnormal		
Nervous system disorders	somnolence; ataxia; dizziness, headache,		

	vertigo, amnesia, paraesthesia, convulsions, hyperkinesias, tremor, balance disorder, disturbance in attention, memory impairment		
Eye disorders	diplopia, blurred vision		
Ear and labyrinth disorders	vertigo		
Cardiac disorders		Electrocardiogram QT prolonged	
Respiratory, thoracic and mediastinal disorders	influenza, nasopharyngitis, pharyngitis, rhinitis, increased cough, sinusitis		respiratory failure, common cold, upper respiratory tract infection
Gastrointestinal disorders	nausea, diarrhoea, abdominal pain, dyspepsia, vomiting		mouth ulceration, pancreatitis
Skin and subcutaneous tissue disorders	rash, eczema, pruritis		alopecia
Musculoskeletal and connective tissue disorders	myalgia		
General disorders and administration site conditions	asthenia, pain, ataxia, fatigue		

Injury and poisoning	accidental injury		

[1] The risk of anorexia is higher when topiramate is co-administered with LEVESEIZE XR

Post-marketing experience

System organ class	**Frequent**	**Less Frequent**	**Frequency unknown**
Blood and lymphatic system disorders			agranulocytosis, leucopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases), thrombocytopenia
Immune system disorders			anaphylaxis, angioedema
Metabolism and nutrition disorders			weight loss, hyponatremia
Psychiatric disorders			abnormal behaviour, anger, anxiety, confusional state, hallucination, psychotic disorder, suicide, attempted suicide, suicidal ideation, panic attack

Nervous system disorders			choreoathetosis, paraesthesia, dyskinesia, muscular weakness
Gastrointestinal disorders			Pancreatitis
Hepatobiliary disorders			hepatic failure, hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders			toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, alopecia[2], drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders			acute kidney injury
Investigations			weight decreased

[2] Recovery was observed in majority of cases where treatment was discontinued.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LEVESEIZE XR is important. It allows continued monitoring of the benefit/risk balance of LEVESEIZE XR. Healthcare providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

There is no experience with doses greater than 5 000 mg/day orally. No serious adverse events were reported by healthy volunteers at single doses up to and including 5 000 mg orally. Symptoms of overdosage: somnolence, agitation, depressed level of consciousness, respiratory depression and coma.

Treatment

After an acute overdose, the stomach may be emptied by induction of emesis. There is no specific antidote for LEVESEIZE XR overdose. Treatment for an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the metabolite ucb L057.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including antiepileptics.

Pharmacotherapeutic group: Antiepileptics, other antiepileptics.

ATC code: N03AX14.

Mechanism of action

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

The precise mechanism of action by which levetiracetam induces seizure protection is unknown. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. The mechanism of action may relate to an interaction with a specific and stereoselective binding site that is only found within the central nervous system.

5.2 Pharmacokinetic properties

Bioavailability of LEVESEIZE XR tablets is similar to that of the immediate-release levetiracetam tablets. The pharmacokinetics (AUC and C_{max}) were shown to be dose proportional after single dose administration of 1 000 mg, 2 000 mg, and 3 000 mg extended-release levetiracetam. Plasma half-life of extended-release levetiracetam is approximately 7 hours.

Absorption

Levetiracetam is almost completely absorbed after oral administration. The pharmacokinetics of levetiracetam are linear and time-invariant, with low intra- and inter-subject variability. Extended-release levetiracetam peak plasma concentrations occur in about 4 hours. Intake of a high fat, high calorie breakfast before the administration of extended-release levetiracetam tablets resulted in a higher peak concentration, and longer median time to peak. The median time to peak (T_{max}) was 2 hours longer in the fed state.

Distribution

No tissue distribution data are available in humans. Levetiracetam and its major metabolite are not significantly protein bound (< 10 % bound). The volume of distribution of levetiracetam is close to the volume of intracellular and extracellular water. The volume of distribution of levetiracetam is approximately 0,5 to 0,7 L/kg, a value close to the volume of distribution of intracellular and extracellular water.

Biotransformation

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24 % of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (1,6 % of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (0,9 % of dose). Other unidentified components accounted only for 0,6 % of the dose. There is no enantiomeric interconversion of levetiracetam or its major metabolite ucb L057.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged medicine which represents 95 % of administered dose. Excretion via faeces accounted for only 0,3 % of the dose. The total body clearance is 0,96 mL/min/kg and the renal clearance is 0,6 mL/min/kg. The renal

clearance of ucb L057 is 4,2 mL/min/kg.

The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg.

Special populations

Elderly:

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

Gender:

Extended-release levetiracetam C_{max} was 21 – 30 % higher and AUC was 8 – 18 % higher in women compared to men. However, clearances adjusted for body weight were comparable.

Renal impairment:

The apparent body clearance of both levetiracetam and of its metabolite ucb L057 is correlated to the creatinine clearance.

Levetiracetam clearance is reduced in patients with impaired renal function. It is therefore recommended to adjust the daily dose of levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2).

Hepatic impairment:

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50 % that of normal subjects, but decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Amino methacrylate copolymer

Colloidal silicon dioxide

Crospovidone (E1202)

FD&C aluminium lake blue No. 1 (colourant)

Hypromellose (E464)

Magnesium stearate (E572)

Microcrystalline cellulose, silicified

Povidone (E1201)

Sodium laurilsulfate (E487)

Talc (E553b)

Film-coating:

Dibutyl sebacate

Ethyl cellulose aqueous dispersion

Opadry II Clear (containing macrogol (E1521), polysorbate 80 (E433) and talc (E553b)).

Polysorbate 20 (E432)

Triethyl citrate (E1505)

Talc (E553b)

Printing ink:

Opacode Black (containing ammonium hydroxide (E527), iron oxide black (E172) and propylene glycol (E1520).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the tablets in the original container until required for use.

6.5 Nature and contents of container

Leveseize XR 500 and Leveseize XR 750:

White, HDPE screw neck bottle with a white polypropylene child-resistant cap, a silica gel desiccant and a white to off-white low moister polyester coil.

Pack size: 60 tablets.

The container is packed in an outer carton.

Not all pack sizes may be marketed.

LEVESEIZE XR 1 000 and LEVESEIZE XR 1 500:

White, HDPE screw neck bottle with a white polypropylene child-resistant cap, a silica gel desiccant and a white to off-white low moister polyester coil.

Pack size: 30 tablets.

OR

White opaque PVC and aluminium foil blister strips, placed in an outer carton.

Pack size: 28 tablets.

The container is packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext.1, Roodepoort

Johannesburg

1724

8. REGISTRATION NUMBERS

LEVESEIZE XR 500: 52/2.5/0256

LEVESEIZE XR 750: 52/2.5/0257

LEVESEIZE XR 1 000 : 52/2.5/0258

LEVESEIZE XR 1 500 : 52/2.5/0259

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10. DATE OF REVISION OF THE TEXT:

13 October 2023