Professional Information for LEVETIRACETAM BIOTECH

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LEVETIRACETAM 250 BIOTECH film-coated tablets

LEVETIRACETAM 750 BIOTECH film-coated tablets

LEVETIRACETAM 1000 BIOTECH film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg, 750 mg or 1 000 mg of levetiracetam respectively.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

LEVETIRACETAM 250 BIOTECH: Blue, oblong shaped scored film-coated tablet debossed with ‘H’ on one side and ‘87’ on other side.

LEVETIRACETAM 750 BIOTECH: Orange coloured, oblong shaped, scored, film coated tablets debossed with ‘H’ on one side and ‘90’ on other side.

LEVETIRACETAM 1000 BIOTECH: White, oblong shaped scored film-coated tablet debossed with ‘H’ on one side and ‘91’ on other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LEVETIRACETAM BIOTECH 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.

LEVETIRACETAM BIOTECH 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

Posology

Monotherapy

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 daily dose is 1 500 mg twice daily.

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 500 mg twice daily. 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 1 500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

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 10 mg/kg twice daily. 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 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

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

The physician 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 10 mg/kg twice daily**	**Maximum dose 30 mg/kg twice daily**
15 kg (1)	150 mg twice daily	450 mg twice daily
20 kg (1)	200 mg twice daily	600 mg twice daily

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25 kg	250 mg twice daily	750 mg twice daily
From 50 kg (2)	500 mg twice daily	1 500 mg twice daily

(1) Children 20 kg or less should preferably start treatment with an oral solution of levetiracetam.

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

Special populations

Infants and children less than 12 years:

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

Patients with renal impairment:

The LEVETIRACETAM BIOTECH 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, calculate creatinine clearance (eCl_{Cr}) according to the following formula:

For males:

$$eCl_{cr}\ (mL/minute) = \frac{[140 - age] \times Wt\ (kg)}{S_{cr}\ (\mu mol/L)}$$

For females:

The above formula x 0,85

Dosing adjustment for patients with impaired renal function:

Group	**Creatinine clearance (mL/min)**	**Dosage 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 BIOTECH.

(2) Following dialysis, a 250 mg to 500 mg supplemental dose is recommended.

Patients with 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 < 70 mL/min.

Method of administration

The film-coated tablets must be taken orally, swallowed with liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

4.3 Contraindications

Do not use LEVETIRACETAM BIOTECH if you are:

- Hypersensitive to levetiracetam or other pyrrolidone derivatives or any of the excipients of LEVETIRACETAM BIOTECH listed in section 6.1.
- Pregnant and lactating (see section 4.7).

4.4 Special warnings and precautions for use

Suicide:

Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines (including levetiracetam as in LEVETIRACETAM BIOTECH). 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 (see section 4.8).

Acute kidney injury:

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

Blood cell counts:

Infrequent cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

Abnormal and aggressive behaviours:

LEVETIRACETAM BIOTECH 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 "*Discontinuation*" below.

Worsening of seizures:

As with other types of antiepileptic medicines, LEVETIRACETAM BIOTECH may infrequently 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 discontinuation or dose decrease. Patients should be advised to consult their treating doctor immediately in case of aggravation of epilepsy.

Electrocardiogram QT interval prolongation

A few cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. LEVETIRACETAM BIOTECH
should be used with caution in patients with QTc-interval prolongation, in patients concomitantly treated with medicines affecting the QTc-interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Renal impairment:

Patients with renal impairment may require dose adaptation. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see sections 4.2 and 5.2).

Discontinuation:

If LEVETIRACETAM BIOTECH has to be discontinued, it is recommended to withdraw it gradually (e.g. 500 mg twice daily decrements every two to four weeks).

Monitoring:

There is no need for plasma level monitoring of levetiracetam. Due to the complete and linear absorption, plasma levels can be predicted from the oral dose of LEVETIRACETAM BIOTECH expressed as mg/kg bodyweight.

4.5 Interaction with other medicines and other forms of interaction

Anti-epileptic medicines:

Evidence indicates that LEVETIRACETAM BIOTECH does 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 do not influence the pharmacokinetics of LEVETIRACETAM BIOTECH.

Probenecid:

Probenecid (500 mg four times daily), a renal tubular secretion blocking medicine, has been shown to inhibit the renal clearance of the primary metabolite but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low. It is expected that other medicines excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicines, e.g. NSAIDs and 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 and other pharmacokinetic interactions:

Co-administration of LEVETIRACETAM BIOTECH 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 BIOTECH.

Antacids:

No data on the influence of antacids on the absorption of LEVETIRACETAM BIOTECH are available.

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 BIOTECH with alcohol are available.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Specialist advice should be given to women who are of childbearing potential. Treatment with LEVETIRACETAM BIOTECH 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 could be associated with a higher risk of congenital malformations than monotherapy, depending on the

associated antiepileptics.

Pregnancy

LEVETIRACETAM BIOTECH is contraindicated in pregnancy.

Breastfeeding

Levetiracetam is excreted in human breast milk. Patients using LEVETIRACETAM BIOTECH should not breastfeed their infants.

Fertility

No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

At the beginning of treatment or following a dosage increase patients might experience, somnolence or other CNS related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles, or operating machines.

4.8 Undesirable effects

The most frequently reported side effects are somnolence, headache, asthenia, dizziness and nasopharyngitis.

Undesirable effects are listed in the table below.

Tabulated list of adverse reactions

System organ class	***Frequency:* Side effect**
Infections and infestations	*Frequent:* Nasopharyngitis *Less frequent:* Infection

Blood and lymphatic system disorders	*Less frequent:* Thrombocytopenia, leukopenia, pancytopenia, neutropenia, agranulocytosis
Immune system disorders	*Less frequent:* Drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)
Metabolism and nutrition disorders	*Frequent:* Anorexia *Less frequent:* Weight decreased, weight increase, hyponatraemia
Psychiatric disorders	*Frequent:* Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability *Less frequent:* 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	*Frequent:* Somnolence, headache, convulsion, balance disorder, dizziness, lethargy, tremor *Less frequent:* Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention, choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated
Eye disorders	*Less frequent:* Diplopia, vision blurred
Ear and labyrinth disorders	*Frequent:* Vertigo
Cardiac disorders	*Less frequent:* Electrocardiogram QT prolonged

Respiratory, thoracic and mediastinal disorders	*Frequent:* Cough
Gastrointestinal disorders	*Frequent:* Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea *Less frequent:* Pancreatitis
Hepatobiliary disorders	*Less frequent:* Liver function test abnormal, hepatic failure, hepatitis
Renal and urinary disorders	*Less frequent:* Acute kidney injury
Skin and subcutaneous tissue disorders	*Frequent:* Rash *Less frequent:* Alopecia, eczema, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	*Less frequent:* Muscular weakness, myalgia, rhabdomyolysis, blood creatine phosphokinase increased
General disorders and administration site conditions	*Frequent:* Asthenia, fatigue
Injury, poisoning and procedural complications	*Less frequent:* Injury

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 suspected adverse reactions

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

4.9 Overdose

Symptoms of overdosage could include: somnolence, agitation, depressed level of consciousness, respiratory depression and coma.

In acute, significant overdosage, the stomach may be emptied by induction of emesis. There is no specific antidote for levetiracetam. Treatment for an overdose will be symptomatic and may include haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including anti-epileptics.

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). LEVETIRACETAM BIOTECH is an anti-epileptic product.

The precise mechanism of action is unknown, but may be related to an interaction with a specific and stereoselective binding site that is only found within the central nervous system. The mechanism of action appears unrelated to the mechanisms of current medicines and does not alter

basic cell characteristics and normal neurotransmission. No interactions with traditional medicine targets involved in inhibitory and excitatory neurotransmission have been observed.

5.2 Pharmacokinetic properties

Absorption:

Levetiracetam is rapidly absorbed from the gastrointestinal tract after oral administration. Oral absolute bioavailability is close to 100 %. Peak plasma concentrations are usually achieved within 1,3 hours after dosing and steady-state is achieved after two days of a twice daily administration schedule. The extent of absorption is dose-independent and is not altered by food, but the rate of absorption was slightly reduced by food.

Distribution:

Plasma protein binding is less than 10 %. 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.

Metabolism:

The major metabolic pathway (24 % of the dose) is enzymatic hydrolysis of the acetamide group. Production of this metabolite, ucb L057, is not supported by the liver cytochrome P450 isoforms. Two minor metabolites, one obtained by hydroxylation of the pyrrolidone ring and the other one by opening of the pyrrolidone ring, were also identified.

Elimination:

Around 95 % of a dose is excreted in the urine, 65 % of which is unchanged levetiracetam. The plasma elimination half-life has been reported to be about 7 hours in adults and children aged 12 years and over; the half-life may be shorter in younger children.

Special populations

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 metabolite ucb L057 is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2).

In anuric end-stage renal disease 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 four-hour dialysis session.

Hepatic impairment:

In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50 % due to a concomitant renal impairment (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Croscarmellose sodium

Magnesium stearate

Maize starch

Povidone

Talc.

LEVETIRACETAM 250 BIOTECH contains Opadry II blue (consisting of FD&C blue, indigo carmine aluminium lake, polyvinyl alcohol, macrogol, talc and titanium dioxide).

LEVETIRACETAM 750 BIOTECH contains Opadry II orange (consisting of FD&C yellow and sunset yellow, iron oxide red, polyvinyl alcohol, macrogol, talc and titanium dioxide).

LEVETIRACETAM 1000 BIOTECH Opadry II white (consisting of polyvinyl alcohol, macrogol, talc and titanium dioxide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

The blister strips must be kept in the outer carton until required for use.

6.5 Nature and contents of container

LEVETIRACETAM BIOTECH tablets are packed in plain aluminium foil, clear PVC or clear PVC/PVdC blister strips. Each blister strip contains 10 tablets each. Three, five, six or ten blisters are packed in an outer carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground floor, Block K West, Central Park,

400 16th Road, Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBERS

LEVETIRACETAM 250 BIOTECH: 45/2.5/0711

LEVETIRACETAM 750 BIOTECH: 45/2.5/0712

LEVETIRACETAM 1000 BIOTECH: 45/2.5/0713

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2013

10. DATE OF REVISION OF THE TEXT

29 July 2022

Signed: