PROPOSED PROFESSIONAL INFORMATION FOR

EPIKEPP 250 / 500 / 750 / 1 000

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

EPIKEPP 250 mg, film-coated tablets

EPIKEPP 500 mg, film-coated tablets

EPIKEPP 750 mg, film-coated tablets

EPIKEPP 1 000 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPIKEPP 250: Each film-coated tablet contains 250 mg levetiracetam.

Sugar free.

EPIKEPP 500: Each film-coated tablet contains 500 mg levetiracetam.

Sugar free.

EPIKEPP 750: Each film-coated tablet contains 750 mg levetiracetam.

Sugar free.

EPIKEPP 1 000: Each film-coated tablet contains 1 000 mg levetiracetam.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets

EPIKEPP 250: Light blue, capsule-shaped, biconvex, film-coated tablets plain on both sides.

EPIKEPP 500: Yellow, capsule-shaped, biconvex, film-coated tablets plain on both sides.

EPIKEPP 750: Pink, capsule-shaped, biconvex, film-coated tablets plain on both sides.

EPIKEPP 1 000: White, capsule-shaped, biconvex, film-coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

EPIKEPP 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.

The maximum daily dose is 3 000 mg.

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	150 mg twice daily	450 mg twice daily
20 kg	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg *	500 mg twice daily	1 500 mg twice daily

* 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 EPIKEPP in children under 12 years of age.

Special populations

Elderly (65 years and older)

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

Patients with renal impairment

The EPIKEPP 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:

~~eGFR (mℓ/min)~~ $CL_{cr} = \frac{[140 - \text{age (years)} \times \text{weight (kg)}]}{\text{Serum creatine } (\mu\text{mol/L})}$ (x 0,85 for women)

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 to 79	500 to 1 000 mg twice daily
Moderate	30 to 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 EPIKEPP.

(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

EPIKEPP 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

EPIKEPP is contraindicated in:

- patients with known hypersensitivity to levetiracetam or other pyrrolidone derivatives or to any of the excipients in EPIKEPP (see **section 6.1**).
- pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

Discontinuation

If EPIKEPP has to be discontinued, it is recommended to withdraw it gradually (e.g. 500 mg twice daily decrements every two to four weeks) in adults: 10 mg/kg twice daily decrements every two weeks in children). The administration of EPIKEPP to patients with renal impairment may require dose adaptation. Assessment of renal function is recommended before dose selection in patients with severely impaired hepatic function (see **section 4.2**). Plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg body weight due to its complete and linear absorption. Therefore, there is no need for plasma level monitoring of levetiracetam.

Behavioural Abnormalities and Psychotic Symptoms

EPIKEPP may cause behavioural abnormalities and psychotic symptoms. Patients treated with EPIKEPP should be monitored for psychiatric signs and symptoms.

Behavioural abnormalities

As reported in the studies carried out, in clinical studies, 13 % of adult medicine-treated patients and 38 % of paediatric medicine-treated patients (4 to 16 years of age) compared to 6 % and 19 % of adult and paediatric placebo-treated patients, experienced non-psychotic behavioural symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization,

depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder).

As reported in the studies carried out, a randomized double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioural effects of medicine as adjunctive therapy in paediatric patients (4 to 16 years of age). The results from an exploratory analysis indicated a worsening in medicine-treated patients on aggressive behaviour (one of eight behaviour dimensions) as measured in a standardized and systematic way using a validated instrument, the Achenbach Child Behaviour Checklist (CBCL/6-18).

As reported in the studies carried out, in clinical studies, 1,7 % of adult medicine-treated patients discontinued treatment due to behavioural adverse reactions, compared to 0,2 % of placebo-treated patients. The treatment dose was reduced in 0,8 % of adult medicine-treated patients and in 0,5 % of placebo-treated patients. Overall, 11 % of medicine-treated paediatric patients experienced behavioural symptoms associated with discontinuation or dose reduction, compared to 6 % of placebo-treated patients.

Psychotic symptoms

As reported in the studies carried out, in clinical studies, 1 % of medicine-treated adult patients, 2 % of medicine-treated paediatric patients 4 to 16 years of age, and 17 % of medicine-treated paediatric patients 1 month to <4 years of age experienced psychotic symptoms, compared to 0,2 %, 2 %, and 5 % in the corresponding age groups treated with placebo. In a controlled study that assessed the neurocognitive and behavioural effects of medicine in paediatric patients 4 to 16 years of age, 1,6 % of medicine-treated patients experienced paranoia, compared to 0 % of

placebo-treated patients. In the same study, 3,1 % of medicine-treated patients experienced confusional state, compared to 0 % of placebo-treated patients.

As reported in the studies carried out, in clinical studies, two (0,3 %) medicine-treated adult patients were hospitalized and their treatment was discontinued due to psychosis. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. There was no difference between drug and placebo-treated patients in the incidence of the paediatric patients who discontinued treatment due to psychotic and non-psychotic adverse reactions.

Seizure frequency

As reported in the studies carried out, an increase in seizure frequency of more than 25 % was reported in 14 % of EPIKEPP treated adult and paediatric patients, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.

Renal insufficiency

The administration of EPIKEPP to 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 **section 4.2**).

Suicide

Suicide, suicide attempt and suicidal ideation have been reported in patients treated with EPIKEPP. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Antiepileptic drugs (medicines) (AEDs), including EPIKEPP, increase the risk of suicidal thoughts or behaviour in patients taking these medicines for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

As reported in the studies carried out, on pooled analyses of 199 placebo-controlled clinical trials (mono-and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1,8, 95 % CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27 863 AED-treated patients was 0,43 %, compared to 0,24 % among 16 029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among medicines in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did

not vary substantially by age (5 to 100 years) in the clinical trials analysed. Table shows absolute and relative risk by indication for all evaluated AEDs.

Table: Risk by Indication for Antiepileptic medicines in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1 000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1 000 Patients
Epilepsy	1,0	3,4	3,5	2,4
Psychiatric	5,7	8,5	1,5	2,8
Other	1,0	1,8	1,9	0,9
Total	2,4	4,3	1,8	1,9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing EPIKEPP or any other AED must balance the risk of suicidal thoughts or behaviours with the risk of untreated illness. Epilepsy and many other illnesses for

which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Monitoring

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.

Somnolence and Fatigue

EPIKEPP may cause somnolence and fatigue. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on EPIKEPP to gauge whether it adversely affects their ability to drive or operate machinery.

Somnolence

As reported in the studies carried out, in controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 15 % of medicine-treated patients reported somnolence, compared to 8 % of placebo-treated patients. There was no clear dose response up to 3 000 mg/day. In a study where there was no titration, about 45 % of patients receiving 4 000 mg/day reported somnolence. The somnolence was considered serious in 0,3 % of medicine-treated patients, compared to 0 % in the placebo group. About 3 % of medicine-treated patients discontinued treatment due to somnolence, compared to 0,7 % of placebo-treated patients. In

1,4 % of medicine-treated patients and 0,9 % of placebo-treated patients, the dose was reduced, while 0,3 % of the medicine-treated patients were hospitalized due to somnolence.

Asthenia

As reported in the studies carried out, in controlled clinical studies of adult patients with epilepsy experiencing partial-onset seizures, 15 % of medicine-treated patients reported asthenia, compared to 9 % of placebo-treated patients. Treatment was discontinued due to asthenia in 0,8 % of medicine-treated patients as compared to 0,5 % of placebo-treated patients. In 0,5 % of medicine-treated patients and in 0,2 % of placebo-treated patients, the dose was reduced due to asthenia.

As reported in the studies carried out on, somnolence and asthenia occurred most frequently within the first 4 weeks of treatment. In general, the incidences of somnolence and fatigue in the paediatric partial-onset seizure studies, and in paediatric and adult myoclonic and primary generalized tonic-clonic seizure studies were comparable to those of the adult partial-onset seizure studies.

Anaphylaxis and Angioedema

EPIKEPP can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms in cases reported in the post marketing setting 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, EPIKEPP should be discontinued and the patient should seek immediate medical attention. EPIKEPP

should be discontinued permanently if a clear alternative etiology for the reaction cannot be established.

Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both paediatric and adult patients treated with medicine. 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 medicine has also been reported. EPIKEPP should be discontinued at the first sign of a rash, unless the rash is clearly not drug related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic medicines, including EPIKEPP. These events can be fatal or life-threatening, particularly if diagnosis and treatment do not occur as early as possible. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated

immediately. EPIKEPP should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Coordination Difficulties

EPIKEPP may cause coordination difficulties.

As reported in the studies carried out, in controlled clinical studies in adult patients with partial-onset seizure studies, 3,4 % of adult medicine-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1,6 % of placebo-treated patients. A total of 0,4 % of patients in controlled clinical studies discontinued medicine treatment due to ataxia, compared to 0% of placebo-treated patients. In 0,7 % of medicine-treated patients and in 0,2 % of placebo-treated patients, the dose was reduced due to coordination difficulties, while one of the medicine-treated patients was hospitalized due to worsening of pre-existing ataxia. These events occurred most frequently within the first 4 weeks of treatment.

Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on EPIKEPP to gauge whether it could adversely affect their ability to drive or operate machinery.

Hematologic Abnormalities

EPIKEPP can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in white blood cell (WBC), neutrophil, and red blood cell (RBC) counts; decreases in haemoglobin and haematocrit; and increases in eosinophil counts. Cases of agranulocytosis, pancytopenia, and thrombocytopenia have been reported in the postmarketing setting. A complete blood count is recommended in patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders.

Partial-Onset Seizures

Adults

As reported in the studies carried out on, minor, but statistically significant, decreases compared to placebo in total mean RBC count (0,03 × 106/mm^3), mean haemoglobin (0,09 g/dL), and mean haematocrit (0,38 %), were seen in medicine-treated patients in controlled trials.

As reported in the studies carried out, a total of 3,2 % of medicine-treated and 1,8 % of placebo-treated patients had at least one possibly significant (≤2,8 × 10^9/L) decreased WBC, and 2,4 % of medicine-treated and 1,4 % of placebo-treated patients had at least one possibly significant (≤1,0 × 10^9/L) decreased neutrophil count. Of the medicine-treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Paediatric Patients 4 Years to < 16 Years

As reported in the studies carried out, statistically significant decreases in WBC and neutrophil counts were seen in medicine-treated patients as compared to placebo. The mean decreases from baseline in the medicine-treated group were -0,4 × 10^9/L and -0,3 × 10^9/L, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1,7 % in medicine-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

As reported in the studies carried out, in the controlled trial, more medicine-treated patients had a possibly clinically significant abnormally low WBC value (3 % of medicine-treated patients

versus 0 % of placebo-treated patients), however, there was no apparent difference between treatment groups with respect to neutrophil count (5 % of medicine-treated patients versus 4,2 % of placebo-treated patients). No patient was discontinued secondary to low WBC or neutrophil counts.

As reported in the studies carried out, in the controlled cognitive and neuropsychological safety study, 5 patients (8,6 %) in the medicine-treated group and two patients (6,1 %) in the placebo-treated group had high eosinophil count values that were possibly clinically significant (≥ 10 % or ≥ 0,7 × 10^9/L).

4.5 Interaction with other medicines and other forms of interaction

Anti-epileptic medicines

Data indicate that EPIKEPP 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 affect the pharmacokinetics of EPIKEPP.

Medicines excreted by active tubular secretion

A renal tubular secretion blocking medicine, probenecid (500 mg four times daily) inhibits the renal clearance of the primary metabolite but not of EPIKEPP. However, 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 EPIKEPP on probenecid was not studied and the effect of levetiracetam on other actively secreted medicines, e.g. NSAIDs, sulphonamides and methotrexate is unknown.

Oral contraceptives (ethinyl oestradiol and levonorgestrel)

EPIKEPP 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl oestradiol and levonorgestrel); endocrine parameters (luteinising hormone (LH) and progesterone) were not modified.

Digoxin and warfarin

EPIKEPP 2 000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with warfarin, and digoxin did not influence the pharmacokinetics of levetiracetam.

Antacids

No data on the influence of antacids on the absorption of levetiracetam are available.

Effect of food on EPIKEPP

Food did not alter the extent of absorption of levetiracetam, but the rate of absorption was slightly reduced.

Interaction with alcohol

No data on the interaction of levetiracetam with alcohol are available.

4.6 Fertility, pregnancy and lactation

The use of EPIKEPP during pregnancy and lactation is not recommended as safety and efficacy have not been established.

Pregnancy

There is no adequate information on the use of EPIKEPP during pregnancy. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown (see **section 4.3**).

Physiological changes during pregnancy may affect EPIKEPP levetiracetam concentration.

There have been reports of decreased levetiracetam concentration during pregnancy.

EPIKEPP is contraindicated in pregnancy.

Breastfeeding

Levetiracetam is excreted in human breast milk. Patients using EPIKEPP should not breastfeed.

Safety in breastfeeding has not been established (see **section 4.3**).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients may experience, at the beginning of treatment or following a dosage increase, somnolence or other CNS-related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles, or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Infection, nasopharyngitis.
Blood and lymphatic system disorders	Frequent	Thrombocytopenia.
	Frequency unknown	Pancytopenia, Leucopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases), thrombocytopenia.
Psychiatric disorders	Frequent	Agitation, depression, emotional instability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal.
	Less frequent	Anxiety, apathy
	Frequency unknown	Abnormal behaviour, anger, confusion, hallucinations, psychotic disorders. Suicide, suicide attempt and suicide ideation

Nervous system disorders	Frequent	Somnolence (sleepiness or unusual drowsiness) predominantly occurs during the first four weeks of treatment. Amnesia, ataxia (clumsiness or unsteadiness, problems with muscle control or co-ordination), convulsions, dizziness, headache, hyperkinesias, tremor, balance disorder, disturbance in attention, memory impairment, vertigo (dizziness or light-headedness, feeling of constant movement of surroundings, sensation of spinning),
	Less frequent	Emotional lability, hostility, nervousness, paraesthesia (burning, crawling, itching, numbness, prickling, pins and needles or tingling feelings).
	Frequency unknown	Insomnia, tremor.
Eye disorders	Frequent	Diplopia (double vision), blurred vision.
Ear and labyrinth disorders	Frequent	Vertigo.

Respiratory, thoracic and mediastinal disorders	Frequent	Pharyngitis (increased cough, dryness or soreness of throat, fever, hoarseness, runny nose, tender, swollen glands in the neck, trouble in swallowing, voice changes).
	Less frequent	Sinusitis (pain or tenderness around eyes and cheekbones, fever, stuffy or runny nose, headache, cough, shortness of breath or troubled breathing, tightness of chest or wheezing), rhinitis (sneezing, stuffy nose and runny nose).
Gastrointestinal disorders	Frequent	Anorexia (loss of appetite and weight loss), diarrhoea, abdominal pain, dyspepsia and nausea.
	Frequency unknown	Pancreatitis
Metabolism and nutrition disorders	Frequent	Anorexia, weight increase The risk of anorexia is higher when topiramate is co-administered with EPIKEPP.
	Frequency unknown	Weight loss
	Frequent	Rash, eczema, pruritus.

Skin and subcutaneous tissue disorders	Frequency unknown	Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), erythema multiforme and alopecia.
Musculoskeletal, connective tissue and bone disorders	Frequent	Myalgia.
General disorders and administrative site conditions	Frequent	Headache, asthenia (loss of strength or energy, muscle pain or weakness, unusual weak feeling), infection (fever or chills, cough or hoarseness, lower back or side pain, painful or difficult urination), and fatigue.
Injury and poisoning	Frequent	Accidental injury.
Hepatobiliary disorders	Frequency unknown	Hepatic failure, hepatitis, liver function test abnormal

Immune system disorder	Frequency unknown	Anaphylaxis and Angioedema: Hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity: Fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection.

Reporting of suspected adverse reactions Updated in-line with current SAHPRA PI guideline.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse drug reaction and quality problem reporting form**" found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

There is no experience with doses greater than 5 000 mg/day orally. No serious adverse events were reported from studies done in healthy volunteers at single doses up to and including 5000 mg orally.

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

In acute, significant overdosage, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Symptomatic treatment is recommended for an overdosage and may include haemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the metabolite ucb L057. Approximately 50 % is removed in 4 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: Antiepileptics, other antiepileptics.

ATC code: N03AX14

Mechanism of action

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.

Pharmacodynamic effects

Levetiracetam has anticonvulsive properties. Levetiracetam is an anti-epileptic substance. Levetiracetam is a pyrrolidine derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), which is chemically unrelated to existing anti-epileptic active substances.

5.2 Pharmacokinetic properties

The pharmacokinetic profile is dose linear with low intra- and inter-subject variability. 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.

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 and after 4 hours post-dose for oral solution formulation).

Absorption

Levetiracetam is rapidly, almost completely absorbed after oral administration.

It is not bound to plasma proteins. Oral absolute bioavailability is close to 100 % with peak plasma concentrations (Cmax) being reached at 1,3 hours after dosing. After two days of a twice daily administration schedule steady-state is reached. Peak concentrations (Cmax) are typically 31 and 43 µg/mL following a single 1 000 mg dose and repeated 1 000 mg twice daily dose, respectively. The extent of absorption is not altered by food and is dose-independent.

Distribution

No tissue distribution data are available in humans. Neither levetiracetam nor its major metabolite ucb L057 is 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 volume of distribution of intracellular and extracellular water.

Biotransformation

Enzymatic hydrolysis of the acetamide group is the major metabolic pathway (24 % of the dose). Production of this metabolite, ucb L057, is not supported by the liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including whole blood but not plasma. 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 evidence of any enantiometric interconversions *in vivo* for either levetiracetam or its major metabolite ucb L057 was detected.

Elimination

The plasma half-life has been reported to be 7 ± 1 hours in adults and does not vary with dose, route of administration or repeated administration. The total body clearance has been reported as a mean of 0,96 mL/min/kg. The major route of excretion is 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 major metabolite accounted for 66 % and 24 % of the dose, respectively, during the first 48 hours. The renal clearance of levetiracetam and its major metabolite ucb L057 is 0,6 and 4,2 mL/min/kg, respectively. This indicates that levetiracetam is excreted by glomerular filtration with subsequent tubular re-absorption and that its major metabolite ucb L057 is also excreted by active tubular secretion in addition to glomerular filtration.

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.

Paediatric population

Following single dose administration (20 mg/kg) to epileptic children 6 to 12 years, the half-life of levetiracetam was reported to be 6,0 hours. The apparent clearance was approximately 30 % higher than in epileptic adults.

Renal impairment

The apparent body clearance of both levetiracetam and of its metabolite ucb L057 is correlated to the creatinine clearance. Based on creatinine clearance in patients with moderate and severe renal impairment, it is therefore recommended to adjust the maintenance daily dose of levetiracetam. (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**).

Linearity/non-linearity

The pharmacokinetic profile is dose linear with low intra- and inter-subject variability.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica (Aerosil 200)

Croscarmellose sodium (Ac-di-sol)

Magnesium stearate

Povidone PVPK – 30

Starch (Corn starch 400 L)

Coating Material

EPIKEPP 250: Opadry Blue 03B50643

EPIKEPP 500: Opadry Yellow 03B52573

EPIKEPP 750: Opadry Pink 03B54276

EPIKEPP 1000: Opadry White 04F58804

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

EPIKEPP 250: packed in plain aluminium blister foil strip with non-toxic, clear transparent, well thermoformable PVC/PE/PVDC film of 10 tablets packed in 60s per carton.

EPIKEPP 500: packed in plain aluminium blister foil strip with non-toxic, clear transparent, well thermoformable PVC/PE/PVDC film of 10 tablets packed in 60s per carton.

EPIKEPP 750: packed in plain aluminium blister foil strip with non-toxic, clear transparent, well thermoformable PVC/PE/PVDC film of 10 tablets packed in 60s per carton.

EPIKEPP 1 000: packed in plain aluminium blister foil strip with non-toxic, clear transparent, well thermoformable PVC/PE/PVDC film of 10 tablets packed in 30s per carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

EPIKEPP 250: 43/2.5/1164

EPIKEPP 500: 43/2.5/1165

EPIKEPP 750: 43/2.5/1166

EPIKEPP 1 000: 43/2.5/1167

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 01 October 2015

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

To be allocated.