KEPPRA Tablets

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

KEPPRA® 250 mg film-coated tablets

KEPPRA® 500 mg film-coated tablets

KEPPRA® 750 mg film-coated tablets

KEPPRA® 1 000 mg film-coated tablets

COMPOSITION:

Each film-coated tablet contains 250 mg, 500 mg, 750 mg, or 1 000 mg of levetiracetam.

Excipients:

Tablet core: sodium croscarmellose, macrogol 6 000, colloidal anhydrous silica, magnesium stearate.

Tablet coating: polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol 3350, talc and the additional agents as listed below:

250 mg film-coated tablets: indigo carmine aluminium lake (E132)

500 mg film-coated tablets: iron oxide yellow (E172)

750 mg film-coated tablets: sunset yellow FCF aluminium lake (E110), iron oxide red (E172).

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Levetiracetam has anticonvulsive properties. 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 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.

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 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 μg/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 major metabolite ucb L057 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 volume of distribution of intracellular and extracellular water.

Metabolism: The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. 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 enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its major metabolite ucb L057.

Elimination: The plasma half-life in adults was 7±1 hours and did not vary with dose, route of administration or repeated administration. The total body clearance was a mean of 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 major 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 re-absorption and that 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.

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 KEPPRA, based on creatinine clearance in patients with moderate and severe renal impairment (see DOSAGE AND DIRECTIONS FOR USE).

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 DOSAGE AND DIRECTIONS FOR USE).

INDICATIONS:

KEPPRA 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.

KEPPRA 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.

CONTRA-INDICATIONS:

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients.

The use of KEPPRA is contra-indicated in pregnancy and lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS:

Discontinuation: If KEPPRA 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).

Seizure frequency:

An increase in seizure frequency of more than 25 % was reported in 14 % of KEPPRA 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 KEPPRA 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 DOSAGE AND DIRECTIONS FOR USE).

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

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.

Effects on ability to drive and use machines: No studies on the effect on the ability to drive and use machines have been performed.
Patients might 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.

INTERACTIONS:

Anti-epileptic medicines:

Data indicate that KEPPRA did not influence the serum concentrations of existing antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these anti-epileptic medicines did not influence the pharmacokinetics of KEPPRA.

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. 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 drugs, e.g. NSAIDs, sulphonamides and methotrexate is unknown.

Oral contraceptives and other pharmacokinetic interactions: KEPPRA 1 000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl oestradiol and levonorgestrel); endocrine parameters (luteinising hormone (LH) and progesterone) were not modified. KEPPRA 2 000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

Antacids: No data on the influence of antacids on the absorption of levetiracetam 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 with alcohol are available.

PREGNANCY AND LACTATION:

There is no adequate information on the use of KEPPRA during pregnancy. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown (see CONTRA-INDICATIONS).

Physiological changes during pregnancy may affect KEPPRA levetiracetam concentration. There have been reports of decreased levetiracetam concentration during pregnancy.

KEPPRA is contra-indicated in pregnancy.

Levetiracetam is excreted in human breast milk. Patients using KEPPRA should not breast-feed. Safety in breast-feeding has not been established (see CONTRA-INDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

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.

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 INDICATIONS):

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.

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 INDICATIONS):

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	Maximum dose

	10 mg/kg twice daily	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
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg (2)	500 mg twice daily	1500 mg twice daily

(1) Children 20 kg or less should preferably start treatment with KEPPRA 100 mg/ml oral solution.
(2) Dosage in children and adolescents 50 kg or more is the same as in adults.
The graduated syringe contains up to 1000 mg levetiracetam (corresponding to 10 ml) with a graduation every 25 mg (corresponding to 0,25 ml).

Infants and children less than 12 years:

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

Patients with renal impairment:

The KEPPRA daily dose must be individualised according to renal function. For adult patients refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CLcr = \frac{[140 - \text{age (years)} \times \text{weight (kg)}]}{\text{serum creatinine (µmol/l)}} \quad (\times 0{,}85 \text{ for women})$$

Dosing adjustment for adult patients with impaired renal function.

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	> 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 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 1000 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 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.

SIDE EFFECTS:

The most commonly reported side effects are somnolence, asthenia and dizziness.

The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of KEPPRA in adults.

Clinical trial data:

Undesirable effects reported in clinical studies (adults and children), the frequency is defined as follows:

Very common (≥ /10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1 000 to < 1/100)

Rare (≥ 1/10 000 to < 1/1 000)

Very rare (< 1/ 10 000), including isolated reports, not known (cannot be estimated on available data).

System Organ Class	Frequency: Side effect
Infections and infestations	Common: infection, nasopharyngitis.
Blood and lymphatic system disorders	Common: thrombocytopenia
Metabolism and nutrition disorders	Common: anorexia, weight increase. The risk of anorexia is higher when topiramate is co-administered with KEPPRA.

Psychiatric disorders	Common: agitation, depression, emotional instability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal.
Nervous system disorders	Very common: somnolence Common: Amnesia, ataxia, convulsions, dizziness, headache, hyperkinesias, tremor, balance disorder, disturbance in attention, memory impairment.
Eye disorders	Common: diplopia, blurred vision.
Ear and labyrinth disorders	Common: vertigo.
Respiratory, thoracic and mediastinal disorders	Common: increased cough.
Gastrointestinal disorders	Common: diarrhoea, abdominal pain, dyspepsia, nausea, vomiting.
Skin and subcutaneous tissue disorders	Common: rash, eczema, pruritus.
Musculoskeletal, connective tissue and bone disorders	Common: myalgia.
General disorders and administrative site conditions	Very common: asthenia/fatigue
Injury and poisoning	Common: accidental injury.

Post marketing data:

In addition to adverse events reported during clinical studies, and listed above, the following adverse events have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

Nervous system disorders: paraesthesia

Psychiatric disorders: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicide ideation

Gastrointestinal disorders: pancreatitis

Hepatobiliary disorders: hepatic failure, hepatitis, liver function test abnormal

Metabolism and nutritional disorders: weight loss

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia

Blood and lymphatic system disorders: leucopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases), thrombocytopenia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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. In acute, significant overdosage, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. 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.

IDENTIFICATION:

KEPPRA 250 mg: Blue, oblong film-coated tablet scored and debossed with the code ucb-250 on one side.

KEPPRA 500 mg film-coated tablets: Yellow, oblong film-coated tablet debossed with the code ucb-500 on one side.

KEPPRA 750 mg: Orange, oblong film-coated tablet scored and debossed with the code ucb-750 on one side.

KEPPRA 1000 mg film-coated tablets: White, oblong film-coated tablet debossed with the code ucb-1000 on one side.

PRESENTATION:

KEPPRA 250 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 20, 30, 50, 60 & 100 tablets.

1.3 South African labelling and packaging
1.3.1 South African Package Insert
1.3.1.1 Package insert

KEPPRA 500 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 10, 20, 30, 50, 60, 100, 120 & 200 tablets.

KEPPRA 750 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 20, 30, 50, 60, 80 & 100 tablets.

KEPPRA 1000 mg film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing 20, 30, 50, 60, 100, 120 & 200 tablets.

STORAGE INSTRUCTIONS:

Store below 25 °C.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

KEPPRA 250 mg: 36/2.5/0088

KEPPRA 500 mg: 36/2.5/0089

KEPPRA 750 mg: 36/2.5/0090

KEPPRA 1 000 mg: 36/2.5/0091

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

11 October 2013

1.3 South African labelling and packaging
1.3.1 South African Package Insert
1.3.1.1 Package insert

PDS-04

Namibia:

Keppra 250 mg Tablet - Reg No 04/2.5/1712 NS2

Keppra 500 mg Tablet - Reg No 04/2.5/1713 NS2

Keppra 750 mg Tablet - Reg No 07/2.5/0013 NS2

HISTORY:

Clinical Recommendation: 11 April 2008; Final PI Submitted: 16 September 2008 Approved July 2009
Amended: 21 January 2010 in-line with approved PI for oral solution. MCC approval pending
Amended: 19 April 2010 (Transfer of applicant to GSK) – 250 mg/750 mg approved 23/02/2011
Amended: 12 April 2011: in-line with PDS04
Amended: 16 January 2013 (in line with CCC recommendations dated 17/08/201). **Approved: 11 October 2013**

Amended: 30 January 2014 (safety update NCDSv1-5) – safety update in process with MCC
Amended: 27 January 2015 (to bring in line with PI guideline v5) - notification