KEPPRA Oral Solution

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

KEPPRA® 100 mg oral solution

COMPOSITION:

KEPPRA 100 mg oral solution contains 100 mg levetiracetam per milliliter.

Preservatives: methylparahydroxybenzoate 0,027 % *m/v* and propylparahydroxybenzoate 0,003 % *m/v.*

Contains sugar (as maltitol 300 mg/ml).

Contains sweetener (as acesulfame potassium 4,50 mg/ml)

Excipients: The oral solution also contains sodium citrate, citric acid monohydrate, ammonium glycyrrhizate, glycerol, grape flavour and purified water.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Levetiracetam has anticonvulsant 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 hour 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.

Children (4 to 12 years): Following single dose administration (20 mg/kg) to epileptic children, the half-life of levetiracetam was 6,0 hours. The apparent clearance was 1,43 ml/min/kg.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0,5 to 1,0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1,1 ml/min/kg.

Infants and children (1 month to 4 years): Following single dose administration (20 mg/kg) of a 10 % oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5,3 hours) than for adults (7,2 hours) and apparent clearance was faster (1,5 ml/min/kg) than for adults (0,96 ml/min/kg). Based on this study, elimination in infants less than 6 months may be reduced by 30 %.

The exposure to the major metabolite, was lower in children than in adults.

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 DOSAGE AND DIRECTIONS FOR USE).
In anuric end-stage renal disease adult subjects, the half-life was approximately 25 and 3,1 hours during interdialytic and intradialytic periods respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

Hepatic Impairment: In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50 % due to a concomitant renal impairment (see DOSAGE AND DIRECTIONS FOR USE).

INDICATIONS:

KEPPRA is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adults and children from 4 years of age with epilepsy.

CONTRA-INDICATIONS:

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients. Patients with rare hereditary problems of fructose intolerance should not take KEPPRA oral solution.
The use of KEPPRA is contra-indicated in pregnancy and lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS:

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.

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.

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 somnolence or other CNS related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

Excipients: Among its excipients, KEPPRA oral solution includes glycerol which can cause headache, stomach upset and diarrhoea and maltitol which has a mild laxative effect.

Patients with rare hereditary condition of sorbitol/maltitol/lactitol intolerance should not take KEPPRA oral solution.

INTERACTIONS:

Antiepileptic medicines:

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

As in adults, there is no clear evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day KEPPRA.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) showed that adjunctive therapy with KEPPRA did not significantly influence the steady state serum concentrations of concomitantly administered carbamazepine and valproate. A similar finding was observed for topiramate and lamotrigine. However, data suggested a 22 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dosage adjustment is not required.

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 medicines excreted by active tubular secretion could reduce the renal clearance of the metabolite. The effect of KEPPRA on probenecid and other actively secreted medicine like 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 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 KEPPRA are available.

Food and alcohol:

The extent of absorption of KEPPRA was not altered by food, but the rate of absorption was slightly reduced. No data on the interaction of KEPPRA 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 levetiracetam concentration. There have been reports of decreased levetiracetam concentration during pregnancy.

Safety in breastfeeding has not been established. Levetiracetam is excreted in human breast milk. Patients using KEPPRA should not breastfeed their babies (see CONTRA-INDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

The oral solution may be diluted in a glass of water and may be taken with or without food. A graduated oral syringe and instructions for use in the patient information leaflet are provided with the oral solution. The daily dose is administered in two equal divided doses.

Adults (> 18 years) and adolescents (12 to 17 years):

As adjunctive therapy, the initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerance, the daily dose can be increased up to 1 500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements 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).

Children aged 4 to 11 years:

The initial dose is 10 mg/kg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerance, the daily dose can be increased up to 30 mg/kg twice daily. Dose changes can be made in 10 mg/kg twice daily increments or decrements every two weeks. Dosage in children 50 kg or greater is the same as in adults.

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
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 a levetiracetam 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 1 000 mg levetiracetam (corresponding to 10 ml) with a graduation every 25 mg (corresponding to 0,25 ml).

Infants and children less than 4 years:

There is insufficient data to recommend the use of KEPPRA in children under 4 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:

Then Clcr for children is adjusted for body surface area (BSA) as follows:

$$\text{Clcr} = \frac{[140 - \text{age (years)} \times \text{weight (kg)}]}{\text{serum creatinine } (\mu\text{mol}/\ell)} \quad (\times 0{,}85 \text{ for women})$$

$$\text{Clcr (ml/min/1,73m}^2) = \frac{\text{Clcr (ml/min)}}{\text{BSA subject (m}^2)} \times 1{,}73$$

Dosing adjustment for adult 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.
(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 (≥ 1/10)
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	aggression, agitation, depression, emotional lability/mood swings, hostility, insomnia, irritability, nervousness, personality disorders, abnormal thinking
Nervous system disorders	Very common Common	somnolence/fatigue amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremour, 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	cough increased
Gastrointestinal disorders	Common	abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
Skin and subcutaneous tissue disorders	Common	eczema, pruritus, rash
Musculoskeletal, connective tissue and bone disorders	Common	myalgia
General disorders and administrative site conditions	Very common	asthenia
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).

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:

Clear, colourless solution with grape flavour.

PRESENTATION:

KEPPRA 100 mg oral solution is supplied in a 300 ml amber glass bottle with a white polypropylene, child-resistant closure. It is packed in a cardboard box and may or may not

contain a 10 ml graduated syringe made of polyethylene with a polystyrene piston and an adaptor for the syringe.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Due to sensitivity to light, store in the original container.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/2.5/0587

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

GlaxoSmithKline South Africa (Pty) Ltd

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Namibia Reg No. 07/2.5/0086 NS2

Botswana Reg No. BOT1402618 S2

328 **Manufacturer:**

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333 **HISTORY:**

334 Approved October 2009
335 Amended: 19/04/2010 (Transfer of applicancy to GSK). Approved 11 November 2010
336 Amended: 12 April 2011: in-line with PDS04
337 Amended: 16 January 2013 (in line with CCC recommendations dated 17/08/2012) – annotated
338 Amended: 06 June 2013 (in line with CCC recommendations dated 08/04/2013) – clean
339 Amended: 06 August 2013 (in response to CCC recommendations dated 30/07/2013). **Approved 11 October 2013**
340 Amended: 19 January 2012 (CMC - D2011-3869 – inclusion of adaptor). **Approved 10 Jun 2014**
341 Amended: 18 July 2016 (CMC – Type: B4a; D2014-8015.v0002 – CTD rebaseline dossier). Implemented 16-08-2016
342
343 **Amended: 20 Feb 2018 (to bring in line with Regulation 11 and 12 of Act 101/1965 as amended). Implemented 21-**
344 **Feb-2018**
345