SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

KEPPRA 100 mg oral solution

Levetiracetam 100 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

Preservatives: methyl parahydroxybenzoate 0,27 % *m/v* and propyl parahydroxybenzoate 0,03 % *m/v.*

Contains sugar (as maltitol liquid 300 mg/mL).

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

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Oral solution

A clear liquid.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

4.2 Posology and method of administration:

Posology:

The daily dose is administered in two equal divided doses.

Adjunctive therapy in adults (> 18 years) and adolescents (12 to 17 years):

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).

Adjunctive therapy in 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 (1,5 mL) twice daily	450 mg (4,5 mL) twice daily
20 kg (1)	200 mg (2 mL) twice daily	600 mg (6 mL) 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).

Paediatric population:

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:

$$\text{Clcr (mL/min)} = \frac{[140\text{-age (years)} \times \text{weight (kg)}]}{72 \times \text{serum creatinine mg/dL}} \text{ (x 0,85 for women)}$$

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

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

The Clcr in mL/min/1,73 m^2 may be estimated from serum creatinine (mg/dL) determination using, for young adolescents and children using the following formula (Schwartz formula):

$$\text{Clcr (mL/min/1,73 m}^2\text{)} = \frac{\text{Height (cm) x ks}}{\text{Serum Creatinine (mg/dL)}}$$

Where

ks= 0,55 in children to less than 13 years and in adolescent female;

ks= 0,7 in adolescent male

Dosing adjustment for and adolescent adult patients weighing more than 50 kg 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.

Dosing adjustment for children and adolescent patients weighing less than 50 kg with impaired renal function:

Group	Creatinine clearance (mL/min/1,73m^2)	Dosage and frequency
Normal	≥ 80	10 to 30 mg/kg (0,10 to 0,30 mL/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0,10 to 0,20 mL/kg) twice daily
Moderate	30-49	5 to 15 mg/kg (0,05 to 0,15 mL/kg) twice daily
Severe	< 30	5 to 10 mg/kg (0,05 to 0,10 mL/kg) twice daily
End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg (0,10 to 0,20 mL/kg) once daily (2) (3)

(1) KEPPRA oral solution should be used for doses under 250 mg and for patients unable to swallow tablets.

(2) A 15 mg/kg (0,15 mL/kg) loading dose is recommended on the first day of treatment with levetiracetam.

(3) Following dialysis, a 5 to 10 mg/kg (0,05 to 0,10 mL/kg) 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.

Paediatric population:

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

KEPPRA oral solution is the preferred formulation for use in children under the age of 6 years. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all the above cases, KEPPRA oral solution should be used.

Monotherapy:

The safety and efficacy of KEPPRA in children and adolescents below 16 years as monotherapy treatment has not been established.

Method of administration:

The oral solution may be diluted in a glass of water and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced.
A graduated oral syringe and instructions for use in the patient information leaflet are provided with the oral solution.

4.3 Contraindications:

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.

4.4 Special warnings and precautions for use:

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 and adolescents weighing more than 50 kg: 10 mg/kg twice daily decrements every two weeks in children and adolescents weighing less than 50 kg.

Renal and hepatic insufficiency: The administration of KEPPRA to patients with renal impairment may require dose adjustment. 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 KEPPRA. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Worsening of seizures: As with other types of anti-epileptic drugs, levetiracetam may rarely exacerbate seizure frequency or severity. This paradoxical effect was mostly reported within the first month after levetiracetam initiation or increase of the dose and was reversible upon drug discontinuation or dose decrease. Patients should be advised to consult their physician immediately in case of aggravation of epilepsy. Lack of efficacy or seizure worsening has for example, been reported in patients with epilepsy associated with sodium voltage-gated channel alpha subunit 8 (SCN8A) mutations.

Electrocardiogram QT interval prolongation: Rare cases of ECG QT interval prolongation have been observed during the post-marketing surveillance. Levetiracetam should be used with caution in patients with QTc-interval

prolongation, in patients concomitantly treated with drugs affecting the QTc-interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Paediatric population:

Available data in children did not suggest impact on growth and puberty. However long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remains unknown.

Acute kidney injury:

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

Blood cell counts:

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leukopenia, 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 (see Section 4.8).

Abnormal and aggressive behaviours:

Levetiracetam 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 see subheading ‘Discontinuation’ above.

Excipients:

KEPPRA oral solution contains:

Glycerol which can cause headache, stomach upset and diarrhoea.

It also contains maltitol liquid which has a mild laxative effect. Patients with rare hereditary problems of fructose intolerance should not take this KEPPRA oral solution.

It also contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

4.5 Interactions with other medicines and other forms of interaction:

Anti-epileptic medicines:

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

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:

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.

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 KEPPRA.

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.

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 should be reviewed when a woman is planning to become pregnant. As with all anti-epileptic 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 anti-epileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated anti-epileptics.

Pregnancy:

A large amount of post-marketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the first trimester) do not suggest an increase in the risk for major congenital malformations. Only limited evidence is available on the neurodevelopment of children exposed to levetiracetam monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays.

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

Breastfeeding:

Safety in breastfeeding has not been established. Levetiracetam is excreted in human breast milk. Patients using KEPPRA should not breastfeed their babies (see section 4.3).

Fertility:

No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines:

Levetiracetam has minor or moderate influence on the ability to drive and use machines. Patients might experience somnolence or other central nervous system related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g., driving vehicles or operating machinery.

4.8 Undesirable effects:

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).

MedDRA SOC	Frequency category				
	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	Nasopharyngitis			Infection	

Blood and lymphatic system disorders			Thrombocytopenia, leukopenia	Pancytopenia, neutropenia, agranulocytosis	
Immune system disorders				Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis)	
Metabolism and nutrition disorders		Anorexia	Weight decreased, weight increase	Hyponatraemia	
Psychiatric disorders		Depression, hostility/ aggression, anxiety, insomnia, nervousness/ irritability	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	Obsessive compulsive disorder**
Nervous system disorders	Somnolence, headache	Convulsion, balance disorder, dizziness, lethargy, tremor	Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia,	Choreoathetosis, dyskinesia, hyperkinesia, gait disturbance, encephalopathy, seizures aggravated	

			disturbance in attention	Neuroleptic malignant syndrome*	
Eye disorders			Diplopia, vision blurred		
Ear and labyrinth disorders		Vertigo			
Cardiac disorders				electrocardiogram QT prolonged	
Respiratory, thoracic and mediastinal disorders		Cough			
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea		Pancreatitis	
Hepatobiliary disorders		Liver function test abnormal		Hepatic failure, hepatitis	
Renal and Urinary Disorders				acute kidney injury	

Skin and subcutaneous tissue disorders		Rash	Alopecia, eczema, pruritus,	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme	
Musculoskeletal and connective tissue disorders			Muscular weakness, myalgia	Rhabdomyolysis and blood creatine phosphokinase increased*	
General disorders and administration site conditions		Asthenia/ fatigue			
Injury, poisoning and procedural complications			Injury		
* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients **Very rare cases of development of obsessive-compulsive disorders (OCD) in patients with underlying history of OCD or psychiatric disorders have been observed in post-marketing surveillance.					

Description of selected adverse reactions:

The risk of anorexia is higher when KEPPRA 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 have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Paediatric population:

Safety profile in paediatric patients in placebo-controlled trials were consistent with safety profile of KEPPRA in adults, except for behavioural and psychiatric side effects which were more common in children than in adults.

In children and adolescents aged 4 to 16 years, the following adverse events were reported more frequently:

Psychiatric disorders:

Common: agitation, mood swings, lability, aggression, abnormal behaviour

Nervous system disorders:

Common: lethargy

Gastrointestinal disorders:

Very common: vomiting.

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, 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: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases).

Reporting of side effects:

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

4.9 Overdose:

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. 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.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES:

A 2.5 Anticonvulsants, including anti-epileptics.

5.1 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 anti-epileptic active substances.

The precise mechanism of action by which levetiracetam induces seizure protection is unknown. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

The mechanism of action may relate to an interaction with a specific and stereoselective binding site that is only found within the central nervous system.

5.2 Pharmacokinetic properties:

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 section 4.2).

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 section 4.2).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

The oral solution also contains sodium citrate, citric acid monohydrate, ammonium glycyrrhizate, glycerol, maltitol, acesulfame potassium, grape flavour, purified water, methyl parahydroxybenzoate and propyl parahydroxybenzoate.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

36 months.

6.4 Special precautions for storage:

Store at or below 30 °C.

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

6.5 Nature and contents of container:

KEPPRA 100 mg/mL 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.

6.6 Special precautions for disposal:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

A40/2.5/0587

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Registration date: 09 October 2009

10 DATE OF REVISION OF THE TEXT

12 April 2024

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