Professional Information for EPLEPTIN®

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

EPLEPTIN® 100 mg capsules

EPLEPTIN® 300 mg capsules

EPLEPTIN® 400 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPLEPTIN® 100 mg: Each capsule contains 100 mg gabapentin.

EPLEPTIN® 300 mg: Each capsule contains 300 mg gabapentin.

EPLEPTIN® 400 mg: Each capsule contains 400 mg gabapentin.

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule

EPLEPTIN® 100 mg: Hard gelatine size '3' capsules, white cap and white body, with "137" imprinted in black on cap and body, containing white crystalline powder.

EPLEPTIN® 300 mg: Hard gelatine size '1' capsules, yellow cap and yellow body, with "138" imprinted in black on cap and body, containing white crystalline powder.

EPLEPTIN® 400 mg: Hard gelatine size '0' capsules, orange cap and orange body, with "139" imprinted in black on cap and body, containing white crystalline powder.

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4. CLINICAL PARTICULARS

4.1. Therapeutic indications

EPLEPTIN® is indicated:

- As an adjunctive to therapy with standard anti-epileptic medicine in patients who have not achieved adequate seizure control with these medicines used alone or in combination.
- In controlling both simple and complex partial seizures with or without secondarily generalised tonic clonic seizures in adults and children over 12 years of age.

4.2. Posology and method of administration

General:

When in the judgment of the clinician there is a need for dose reduction, discontinuation, or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Posology

Epilepsy:

Adults and children over 12 years

Usual effective dose: 900 – 1 800 mg/day in three divided doses with not more than 12 hours between doses.

Since titration to an effective dose can progress rapidly, this may be accomplished in as few as three days using one of the following approaches:

Therapy should be initiated by titrating the dose as described in TABLE 1. Thereafter, the dose can be increased in three equally divided doses up to a maximum dose of 1 800 mg/day.

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Table 1: Dosing chart – initial titration

Dose	Day 1	Day 2	Day 3
900 mg	300 mg OD[a]	300 mg BD[b]	300 mg TDS[c]

[a] OD = once a day

[b] BD = two times a day

[c] TDS = three times a day

Special populations

Paediatric use:

Epilepsy: Safety and efficacy in children under 12 years have not been reported.

Elderly:

No significant changes in the adverse event profile have been reported in the elderly (*i.e.* over 65 years of age), an increased incidence of certain adverse events cannot be excluded. Elderly patients should be carefully monitored for adverse events. Elderly patients may require dosage adjustment because of declining renal function with age. Adjust according to creatinine clearance as in table 2 below.

4. Compromised renal function:

The elimination of gabapentin as contained in EPLEPTIN® is decreased in patients with impaired renal function.

This patient population has not been fully examined but the following guidelines are based on information derived from single doses in non-epileptic patients.

For patients with compromised renal function or those undergoing haemodialysis the following maintenance dosage regimen is recommended:

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Table 2 : Creatinine clearance – dosing chart

Renal function creatinine clearance (ml per minute)	**Total daily dose (mg/day)**	**Dose regimen (mg)**
> 60	1 200	400 three times a day
≥30 - 60	600	300 two times a day
15 - 30	300	300 once a day
< 15	150	300 once every other day
Haemodialysis [a]	-	200 - 300[b]
[a] Loading dose of 300 to 400 mg		
[b] Maintenance dose of 200 to 300 mg gabapentin following each 4 hours of haemodialysis		

Gabapentin plasma concentrations need not to be monitored to optimise EPLEPTIN® therapy.

EPLEPTIN® may be used as adjunct with phenobarbital, phenytoin, valproic acid and carbamazepine without any alteration of the plasma concentrations or serum concentrations of gabapentin or the other anti-epileptic medicines.

Withdrawal of EPLEPTIN® therapy, or the addition of another medicine to the treatment, should be done gradually over a minimum of one week.

Method of administration

EPLEPTIN® may be given orally with or without food.

4.3. Contraindications

- Hypersensitivity to gabapentin or any of the other ingredients of EPLEPTIN® (see section 6.1).
- Safety and efficacy have not been established in children under 12 years.
- Pregnancy and lactation (see section 4.6).
- Severe impaired renal function.

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4.4. Special warnings and precautions for use

EPLEPTIN® should be used with caution in patients with a history of psychotic illness. It should also be used with caution in renal impairment. See table for dosage guidelines in renal impairment and haemodialysis (see section 4.2).

Abrupt withdrawal of EPLEPTIN® in epileptic patients may precipitate status epilepticus. Should it be required to reduce the dosage, discontinue the treatment or substitute with another anticonvulsant medicine, it should be done gradually over a minimum of one week.
As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.
As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

EPLEPTIN® is not generally considered effective in the treatment of absence seizures and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

Do not allow more than 12 hours between EPLEPTIN® doses to prevent breakthrough convulsions.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with gabapentinoids, such as EPLEPTIN®, in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for gabapentinoids. Cases of suicidal ideation and behaviour have been reported in patients treated with gabapentin in the post-marketing experience (see section 4.8).

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Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients and caregivers should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Patients who require concomitant treatment with morphine may experience increases in EPLEPTIN® concentrations (see section 4.5).

Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of EPLEPTIN® should be reduced appropriately (see section 4.5).

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS):

Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking anti-epileptic drugs including EPLEPTIN®.

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. EPLEPTIN® should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug rash with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with gabapentin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, EPLEPTIN® should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of gabapentin, treatment with EPLEPTIN® must not be restarted in this patient at any time.

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Anaphylaxis

Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis (see section 4.8).

Acute pancreatitis

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered (see section 4.8).

Seizures

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

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Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of gabapentin, or concomitant treatment with CNS depressants including opioids, should be reduced appropriately (see section 4.5).

Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with central nervous system (CNS) depressants, including opioids, should be carefully observed for signs of CNS depression, such as somnolence, sedation, and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin, or concomitant treatment with CNS depressants including opioids, should be reduced appropriately (see section 4.5).

Caution is advised when prescribing EPLEPTIN® concomitantly with opioids due to risk of CNS depression. Co-prescription of opioids and gabapentin has been reported to be associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95 % CI, 1.18 to 1.88, p<0.001]).

Respiratory depression

Gabapentin has been reported to be associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

Elderly (over 65 years of age)

No systematic studies in patients 65 years or older have been reported with gabapentin. Somnolence, peripheral oedema and asthenia have been reported in a somewhat higher percentage in patients with neuropathic pain aged 65 years or above, than in younger patients. Apart from these reported findings,

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clinical investigations in this age group do not indicate an adverse event profile different from that reported in younger patients.

Paediatric population

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately reported. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Misuse, abuse potential or dependence:

Gabapentin as contained in EPLEPTIN® can cause drug dependence, which may occur at therapeutic doses. Cases of misuse, abuse and dependence have been reported. Patients with a history of substance abuse may be at higher risk for gabapentin misuse, abuse and dependence, and gabapentin should be used with caution in such patients. Before prescribing gabapentin, the patient's risk of misuse, abuse or dependence should be carefully evaluated. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of EPLEPTIN® misuse, abuse or dependence (development of tolerance, dose escalation, and intentional overdose, drug-seeking behaviour have been reported).

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with EPLEPTIN®, withdrawal symptoms have been observed. Withdrawal symptoms may occur shortly after discontinuation, usually within 48 hours. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise. The occurrence of withdrawal symptoms following discontinuation of EPLEPTIN® may indicate drug dependence (see section 4.8). The patient should be informed about this at the start of the treatment. If gabapentin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.2).

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4.5. Interaction with other medicines and other forms of interaction

There are spontaneous and literature case reports of respiratory depression, sedation, and death associated with gabapentin when co-administered with CNS depressants, including opioids. In some of these reports, the authors considered the combination of gabapentin with opioids to be a particular concern in frail patients, in the elderly, inpatients with serious underlying respiratory disease, with polypharmacy, and in those with substance abuse disorders.

There is no interaction between EPLEPTIN®, phenobarbitone, phenytoin, valproic acid, carbamazepine or carbamazepine-10, 11-epoxide. Gabapentin as in EPLEPTIN®, steady-state pharmacokinetics are reported to be similar for healthy subjects and patients with epilepsy receiving anti-epileptic agents.

Co-administration of EPLEPTIN® with oral contraceptives, containing norethindrone and/or ethinyl oestradiol, does not influence the steady-state plasma concentrations of either component.

Concomitant use of EPLEPTIN® with a magnesium- and aluminium-containing antacid reduces gabapentin bioavailability by approximately 20 %. It is recommended that gabapentin be taken about two hours following antacid administration.

Concurrent use of EPLEPTIN® with alcohol and other CNS depressants may increase the CNS depressant effects.

False positive tests for proteinuria may occur with Ames Multistix-SG.
Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin has been reported when it is co-administered with cimetidine is not expected to be of clinical importance.

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Morphine:

In a reported study involving healthy volunteers, when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, the mean gabapentin AUC increased by 44 % compared to gabapentin administered without morphine. The clinical significance of such changes has not been defined. Morphine pharmacokinetic parameter values have not been reported to be affected by administration of gabapentin 2 hours after morphine. The reported opioid-mediated side effects associated with morphine plus gabapentin in the volunteers did not differ significantly from morphine plus placebo. The magnitude of interaction at other doses is not known (see section 4.4).

Patients who require concomitant treatment with morphine may experience increases in EPLEPTIN® concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of EPLEPTIN® should be reduced appropriately (see section 4.4).

Laboratory tests

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. Itis therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

4.6. Fertility, pregnancy and lactation

Pregnancy:

EPLEPTIN® is contraindicated in Pregnancy (see section 4.3).

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is reported to be increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a

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higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child.
Developmental delay in children of mothers with epilepsy has been reported rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Neonatal withdrawal syndrome has been reported in newborns exposed in utero to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk of neonatal withdrawal syndrome. Newborns should be monitored carefully.

Risk related to gabapentin

Gabapentin crosses the human placenta.

Breast-feeding

EPLEPTIN® is contraindicated in Pregnancy and lactation (see section 4.3). EPLEPTIN® is excreted in human milk. Because the effect on the nursing infant is unknown, EPLEPTIN® should not be used in breastfeeding mothers.

Fertility

There is no reported effect on fertility in animals (see section 5.3).

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4.7 Effects on ability to drive and use machines

Special care should be taken by patients driving, operating machinery or performing any hazardous tasks.

EPLEPTIN® frequently causes dizziness and somnolence. Head and body injuries and road traffic incidents have also been reported with EPLEPTIN®. Therefore, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether EPLEPTIN® affects their ability to perform these activities.

4.8. Undesirable effects

The following side effects have been reported:

The most frequent clinical adverse events reported were: somnolence, dizziness, ataxia, headache, nystagmus, tremor, fatigue, diplopia, nausea and/or vomiting and rhinitis.

From data drawn from reported studies, adverse events are listed in descending order of frequency both by bodily system and by associated adverse events:

MedDRA System Organ Class	**Frequency**	**Undesirable effect**
Infections and infestations	Frequent	Viral infection, respiratory infection, pneumonia, urinary tract infection, infection, otitis media
Blood and lymphatic system disorders	Frequent	Leukopenia, purpura, white blood cells decreased
Metabolism and nutrition disorders	Frequent	Increased appetite resulting in weight gain, anorexia
	Less frequent	Hyperglycaemia (most often observed in patients with diabetes), hypoglycaemia (most often observed in patients with diabetes), hyponatraemia

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Psychiatric disorders	Frequent	Confusion, depression, emotional lability, nervousness, thinking abnormal, hostility, anxiety
	Less frequent	Suicidal ideation and behaviour, agitation, drug dependence
Nervous system disorders	Frequent	Fatigue, ataxia, dizziness, somnolence, amnesia, coordination abnormal, dysarthria, insomnia, headache, nystagmus, tremor, vertigo convulsions, hyperkinesias, sensations such as paresthesia, hypaesthesia, increased, decreased, or absent reflexes
	Less frequent	Headache, dysarthria, amnesia, confusion, insomnia, twitching, abnormal co-ordination, paraesthesia, nervousness, hypokinesia, mental impairment, loss of consciousness, other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)
Eye disorders	Frequent	Amblyopia, diplopia, nystagmus
Ear and labyrinth disorders	Frequent	Vertigo
Vascular disorders	Frequent	Peripheral oedema Vasodilation, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	Coughing, pharyngitis, rhinitis, respiratory tract infection, dyspnoea, bronchitis
	Less frequent	Respiratory depression

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Gastrointestinal disorders	Frequent	Abdominal pain, constipation, dental abnormalities, diarrhoea, dyspepsia, mouth or throat dry, nausea and/or vomiting, gingivitis, flatulence
	Less frequent	Dysphagia
Skin and subcutaneous tissue disorders	Frequent	Acne, pruritus, rash, maculopapular rash, facial oedema, purpura most often described as bruises resulting from physical trauma
Musculoskeletal and connective tissue disorders	Frequent	Back pain, myalgia, twitching, fracture, arthralgia
Reproductive system and breast disorders	Frequent	Impotence
General disorders and administration site conditions	Frequent	Fatigue, fever, peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
	Less frequent	Generalized oedema
Investigations	Frequent	WBC (white blood cell count) decreased, weight increase
	Less frequent	Elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Injury, poisoning and procedural complications	Frequent	Abrasion, fracture, accidental injury
	Less frequent	Fall

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Some of these could represent seizure-related deaths in which the seizure was not observed e.g. at night. This represents an incidence of 0,0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving EPLEPTIN® (ranging from 0,0005 for the general population of epileptics, to 0,003 for a clinical trial population similar to that in the EPLEPTIN® program, to 0,005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the EPLEPTIN® cohort and the accuracy of the estimates provided.

Post-marketing experience:

The following cases have been reported:

MedDRA System Organ Class	**Frequency**	**Undesirable effect**
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	Allergic reaction including urticaria, anaphylactic, anaphylactoid reaction and hypersensitivity including systemic reactions with eosinophilia, fever, rash, hepatitis, lymphadenopathy, and systemic DRESS symptoms. (see section 4.4)
Metabolism and nutrition disorders	Frequency unknown	Hyponatraemia
Psychiatric disorders	Frequency unknown	Hallucinations
Nervous system disorders	Frequency unknown	Movement disorders such as choreoathetosis, dyskinesia, and dystonia, spastic torticollis and myoclonus

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Ear and labyrinth disorders	Frequency unknown	Tinnitus
Cardiac disorders	Frequency unknown	Palpitation, chest pain
Gastrointestinal disorders	Frequency unknown	Pancreatitis
Hepatobiliary disorders	Frequency unknown	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Alopecia, angioedema, erythema multiforme, Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (see section 4.4)
	Less frequent	Toxic epidermal necrolysis (TEN) (see section 4.4)
Musculoskeletal and connective tissue disorders	Frequency unknown	Rhabdomyolysis, myoclonus
Renal and urinary disorders	Frequency unknown	Acute kidney failure, urinary incontinence
Reproductive system and breast disorders	Frequency unknown	Breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)
General disorders and administration site conditions	Frequency unknown	Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, and sweating, sudden unexplained

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		deaths, depression, headache, pain, tremor, agitation, panic attacks, diarrhoea, dizziness, tachycardia, confusion and generalized oedema
Investigations	Frequent	Blood glucose fluctuations in patients with diabetes, elevated liver function tests (LFTs), increased blood creatine phosphokinase

c. Description of selected adverse reactions

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Aggressive behaviour and hyperkinesias were reported in children.

Reporting of suspected adverse reactions:

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9. Overdose

No specific information is available on the treatment of overdose with gabapentin, although haemodialysis has been reported to be effective in eliminating gabapentin. Treatment is symptomatic and supportive, consistent with established medical care.

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Overdoses of gabapentin up to 49 g ingested at one time have been reported in four people, all of whom recovered fully.

Symptoms of overdose include dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea (see section 4.8).

Treatment is symptomatic and supportive. Haemodialysis has been shown to be effective in eliminating EPLEPTIN® and may be indicated in patients with renal impairment.

Reduced absorption of EPLEPTIN® at higher doses may limit absorption and hence minimise toxicity at the time of overdosing.

In patients with renal impairment, haemodialysis may be indicated.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants, including anti-epileptics, ATC code: N03AX12

Gabapentin is an analogue of the neurotransmitter GABA (gamma-aminobutyric acid). It is neither a GABA agonist nor antagonist and its mechanism of action as an anti-epileptic medicine remains unclear. The reported *in vitro* animal studies with radiolabelled gabapentin have characterized a peptide binding site in brain tissues including neocortex and hippocampus that may relate to anticonvulsant activity of gabapentin and its structural derivatives. However, the mechanism of action remains unclear.

Gabapentin at relevant clinical concentrations does not bind to other common medicines or neurotransmitter receptors of the brain including $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*. Gabapentin administration to rats increases GABA turnover in several brain regions. The relevance of these various actions of gabapentin to the anticonvulsant effects

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remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

5.2 Pharmacokinetic properties:

Gabapentin is absorbed after oral administration in part by the L-amino acid transport system, which is a carrier-mediated, saturable transport system. As the dose increases, bioavailability decreases.
Peak plasma concentrations are reached within 2 to 3 hours after administration. Absorption is unaffected by food and plasma protein binding is very low.
Absolute bioavailability of 300 mg and 400 mg gabapentin capsules is approximately 55 %. Gabapentin elimination parameters are independent of dose.
Gabapentin is not bound to plasma proteins and has an apparent volume of distribution of 57,7 litres. Gabapentin penetrates the blood-brain barrier, yielding cerebrospinal fluid (CSF) concentrations in the range of 7– 35 % of corresponding steady-state plasma trough concentrations in patients with epilepsy. Gabapentin is not metabolised and is eliminated solely by renal excretion. Gabapentin does not induce hepatic mixed-function oxidase enzymes responsible for metabolism.

In elderly patients with a decreased renal function, plasma clearance is decreased and elimination half-life is increased. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Linearity/non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and

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$T_{1/2}$), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Calcium sulfate dihydrate
- pregelatinised starch
- calcium carbonate
- glyceryl behenate

Composition of capsule EPLEPTIN® 100 mg:

- gelatin
- water
- sodium lauryl sulphate
- titanium dioxide

Composition of capsule EPLEPTIN® 300 mg

- gelatin
- water
- sodium lauryl sulphate
- titanium dioxide
- Iron oxide yellow

Composition of capsule: EPLEPTIN® 400 mg

- gelatin
- water
- sodium lauryl sulphate
- titanium dioxide
- Iron oxide yellow

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- Iron oxide red

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

EPLEPTIN® 100 mg are packed into 75 cc white round HDPE bottles with 33 mm polypropylene white ribbed caps. 100 Capsules per bottle.

EPLEPTIN® 300 mg are packed into 150 cc white round HDPE bottles with 38 mm polypropylene white ribbed caps. 100 Capsules per bottle.

EPLEPTIN® 400 mg are packed into 150 cc white round HDPE bottles with 38 mm polypropylene white ribbed caps. 100 Capsules per bottle.

Blister Pack 100's: 10 blisters of 10 Capsules each packed in the silver Aluminum/clear PVC/PVDC blister. Ten blisters of ten Capsules each are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Protect from light and moisture.

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Keep bottle tightly closed until required for use.

KEEP OUT OF REACH OF CHILDREN.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Ranbaxy Pharmaceuticals (Pty) Ltd.

14 Lautre Road, Stormill, Ext. 1,

Roodepoort, Johannesburg 1724

8. REGISTRATION NUMBERS:

EPLEPTIN® 100 mg (capsules): A40/2.5/0158

EPLEPTIN® 300 mg (capsules): A40/2.5/0159

EPLEPTIN® 400 mg (capsules): A40/2.5/0160

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

Date of registration: 6 October 2006

10. DATE OF REVISION OF THE TEXT:

09 September 2024

Namibia

Scheduling: NS2

EPLEPTIN® 100 mg capsules: 07/2.5/0090

EPLEPTIN® 300 mg capsules: 07/2.5/0089

EPLEPTIN® 400 mg capsules: 07/2.5/0088

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