APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF MEDICINAL PRODUCT:

BINRONTIN 100 mg CAPSULES (capsule)

BINRONTIN 300 mg CAPSULES (capsule)

BINRONTIN 400 mg CAPSULES (capsule)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BINRONTIN 100 mg CAPSULES:

Each capsule contains 100 mg gabapentin.

BINRONTIN 300 mg CAPSULES:

Each capsule contains 300 mg gabapentin.

BINRONTIN 400 mg CAPSULES:

Each capsule contains 400 mg gabapentin.

Sugar free

For the full list of excipients, see section 6.1 List of excipients

3. PHARMACEUTICAL FORM

BINRONTIN 100 mg CAPSULES: White / White size '3' hard gelatin capsules imprinted with 'D' on white cap and '02' on white body with black edible ink, filled with white to off-white crystalline powder.

BINRONTIN 300 mg CAPSULES: Yellow / Yellow size '1' hard gelatin capsules imprinted with 'D' on yellow cap and '03' on yellow body with black edible ink, filled with white to off-white crystalline powder.

BINRONTIN 400 mg CAPSULES: Orange / Orange size '0' hard gelatin capsules imprinted with 'D' on orange cap and '04' on orange body with black edible ink, filled with white to off-white crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

BINRONTIN CAPSULES is indicated:

- As an adjunct to other standard anticonvulsant medications in patients who have not achieved adequate seizure control with these agents used alone or in combination.
- In controlling both simple and complex partial seizures with or without secondarily generalized tonic clonic seizures.

4.2 Posology and method of administration

Adults and children over 12 years:

- Initially 300 mg three times a day. The dosage may be gradually increased based on the clinical response. Dosages of 900 to 1 800 mg per day taken in three divided doses with not more than 12 hours between doses are effective for most patients. Dosages of up to 3 600 mg in divided doses three times a day for short periods have been well tolerated.
- 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:

900 mg/day:

Day 1	1 x 100 mg, three times a day
	or 1 x 300 mg, once a day.
Day 2	2 x 100 mg, three times a day
	or 1 x 300 mg twice a day.
Day 3	1 x 300 mg, three times a day
	or 3 x 100 mg three times a day.

1200 mg/day:

Day 1	2 x 100 mg, three times a day

	or 1 x 400 mg, once a day.
Day 2	3 x 100 mg, three times a day
	or 1 x 400 mg twice a day.
Day 3	1 x 400 mg, three times a day
	or 4 x 100 mg three times a day.

Special populations

Children under 12 years

Safety and effectiveness in children under 12 years have not been established.

Elderly patients:

Elderly patients may require dosage adjustment because of decrease in renal function with age. Dosage adjustments may be made on clinical response.

Compromised renal function:

For patients with impaired renal function or those undergoing haemodialysis the following maintenance dosage regimen are recommended.

Renal Function **Creatinine Clearance** (ml per minute)	**Total daily Dose (mg/day)**	**Dosage regimen (mg)**
>60	1200	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 **BINRONTIN CAPSULES** Following each 4 hours of haemodialysis	

- Gabapentin plasma concentrations need not to be monitored to optimise **BINRONTIN CAPSULES** therapy.
- **BINRONTIN CAPSULES** 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 antiepileptic agents.
- Withdrawal of **BINRONTIN CAPSULES** therapy or the addition of another medication to the treatment should be done gradually over a minimum of one week.

Method of administration

BINRONTIN CAPSULES may be given orally with or without food

CONTRA-INDICATIONS:

- Hypersensitivity to gabapentin or the product's excipients.
- Safety and efficacy in children under 12 years have not been established.
- Safety and efficacy in pregnancy and lactation have not been established.
- Severe impaired renal function.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

BINRONTIN CAPSULES should be used with caution in patients with a history of psychotic illness.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents 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 **BINRONTIN CAPSULES.**

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Patients who require concomitant treatment with morphine may experience increases in **BINRONTIN CAPSULES** concentrations (see section 4.5).
Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of **BINRONTIN CAPSULES** 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 **BINRONTIN CAPSULES.**
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. **BINRONTIN CAPSULES** 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, **BINRONTIN CAPSULES** 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 **BINRONTIN CAPSULES** must not be restarted in this patient at any time.

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).

If a patient develops acute pancreatitis under treatment with BINRONTIN CAPSULES discontinuation of BINRONTIN CAPSULES should be considered (see **"SIDE EFFECTS"**).

It should also be used with caution in renal impairment. See table for dosage guidelines in renal impairment and haemodialysis.

Abrupt withdrawal of **BINRONTIN CAPSULES** 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.

BINRONTIN CAPSULES 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 **BINRONTIN CAPSULES** doses to prevent breakthrough convulsions.

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.

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 **BINRONTIN CAPSULES** 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, 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 **BINRONTIN CAPSULES** 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 **BINRONTIN CAPSULES** ® misuse, abuse or dependence (development of tolerance, dose escalation, and intentional overdose, drugseeking behaviour have been reported).

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with **BINRONTIN CAPSULES**, 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 **BINRONTIN CAPSULES** 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).

4.5. Interaction with other medicines and other forms of interaction:

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

Co-administration of **BINRONTIN CAPSULES** with oral contraceptives, containing norethindrone and/or ethinyl estradiol, does not influence the steady-state plasma concentrations of either component.

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

There are spontaneous and literature case reports of respiratory depression, sedation, and death associated with gabapentin when co-administered with CNS depressants, including opioids. Concurrent use of **BINRONTIN CAPSULES** with alcohol and other CNS depressants, including opioids may increase the CNS depressant effects. 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.

Co-administration of morphine and **BINRONTIN CAPSULES** increases the gabapentin AUC significantly. 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). Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of **BINRONTIN CAPSULES** or morphine should be reduced appropriately.

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.

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.

4.6. Fertility, pregnancy and lactation

BINRONTIN CAPSULES 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 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. Coexposure 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.

Breastfeeding

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

Fertility

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

4.7 Effects on the ability to drive and operate machinery:

BINRONTIN CAPSULES acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

4.8 UNDESIRABLE EFFECTS:

Summary of the safety profile

Epilepsy

The following side effects have been reported:

The most frequent side effects are 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
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
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

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 **BINRONTIN CAPSULES** (ranging from 0,0005 for the general population of epileptics, to 0,003 for a clinical trial population similar to that in the **BINRONTIN CAPSULES** 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 **BINRONTIN CAPSULES** 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
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

		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

Symptoms of overdose include dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea (see **"SIDE EFFECTS"**). Treatment is symptomatic and supportive. Haemodialysis has been shown to be effective in eliminating **BINRONTIN CAPSULES** and may be indicated in patients with renal impairment.

Reduced absorption of **BINRONTIN CAPSULES** at higher doses may limit medicine absorption and hence minimise toxicity at the time of overdosing.

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 GABAA, GABAB, 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 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 has an apparent volume of distribution of approximately 50 to 60 l. 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 metabolized and is eliminated solely by renal excretion. Gabapentin does not induce hepatic mixed-function oxidase enzymes responsible for medicine metabolism.

In elderly patients with decrease in renal function, plasma clearance is decreased and elimination half-life is increased. The 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 nonlinearity 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 $T_{1/2}$), 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

Maize starch and talc.

The capsule shell consists of gelatine, red iron oxide, sodium lauryl sulphate, titanium dioxide and yellow iron oxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

BINRONTIN 100 mg CAPSULES:

Blister:

Capsules are packed in polyamide / aluminium foil / PVC film and printed aluminium foil with heat seal lacquer or in clear 250 mincron PVC coated blisters with 90 gsm PVdC and printed aluminium foil with heat seal lacquer. Each blister contains 10 capsules.

Pack size: 100's – Each carton contains 10 blisters of 10 capsules.

HDPE Container:

Capsules are packed in a 100 ml white opaque HDPE container with a white opaque polypropylene child resistant closure with induction seal wad.

A desiccant (silica gel sachet) is included in the container. Each container contains 100 capsules.

Pack size: 100's – One white opaque HDPE container with 100 capsules.

BINRONTIN 300 mg CAPSULES:

Blister:

Capsules are packed in polyamide / aluminium foil / PVC film and printed aluminium foil with heat seal lacquer or in clear 250 mincron PVC coated blisters with 90 gsm PVdC and printed aluminium foil with heat seal lacquer. Each blister contains 10 capsules.

Pack size: 100's – Each carton contains 10 blisters of 10 capsules.

HDPE Container:

Capsules are packed in a 120 ml white opaque HDPE container with a white opaque polypropylene child resistant closure with induction seal wad.

A desiccant (silica gel sachet) is included in the container. Each container contains 100 capsules.

Pack size: 100's – One white opaque HDPE container with 100 capsules.

BINRONTIN 400 mg CAPSULES:

Blister:

Capsules are packed in polyamide / aluminium foil / PVC film and printed aluminium foil with heat seal lacquer or in clear 250 mincron PVC coated blisters with 90 gsm PVdC and printed aluminium foil with heat seal lacquer. Each blister contains 10 capsules.

Pack size: 100's – Each carton contains 10 blisters of 10 capsules.

HDPE Container:

Capsules are packed in a 200 ml white opaque HDPE container with a white opaque polypropylene child resistant closure with induction seal wad.

A desiccant (silica gel sachet) is included in the container. Each container contains 100 capsules.

Pack size: 100's – One white opaque HDPE container with 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

STORAGE INSTRUCTIONS:

Blister:

Store at or below 25 °C. Keep blisters in the original carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

HDPE Container:

Store at or below 25 °C. Keep well closed.

KEEP OUT OF REACH OF CHILDREN.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1,

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER:

BINRONTIN 100 mg CAPSULES: 43/2.5/0288

BINRONTIN 300 mg CAPSULES: 43/2.5/0289

BINRONTIN 400 mg CAPSULES: 43/2.5/0452

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

Date of registration:

25 November 2011

10. DATE OF REVISION OF THE TEXT:

26 August 2025