

1. Name of the medicinal product:

Gabapentin Capsules USP 100 mg

2. Qualitative and quantitative composition

Each Hard Gelatin Capsule Contains:

Gabapentin USP 100 mg

S. No.	Name of the Ingredient	Specification	Qty/Tablet (mg)	Functional category
Blending				
1	Gabapentin *	USP	100.000	Active
2	Pregelatinized maize starch (Lycatab C)**	BP	24.500	Diluent
3	Purified Talc	BP	3.167	Glidant
Lubrication				
4	Magnesium Stearate	BP	2.333	Lubricant
Target fill weight per Capsule			130.000	

Note:

* Actual quantity of Gabapentin USP to be dispensed is based on actual % purity of

Gabapentin USP from the Batch formula worksheet as per subsequent calculation.

** Quantity of Pregelatinized maize starch BP (Starch 1500)**should adjust to the target weight as per the calculation shown in the Batch formula Worksheet.

\$ 2 % overages included to compensate process loss during Capsule filling.

3. Pharmaceutical form**Hard gelatin Capsule**

Hard Gelatin Capsule.

Size 3, Golden Yellow hard gelatin capsule containing white coloured powder.

4. Clinical Particular**4.1 Therapeutic Indications:**Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above (see section 5.1). Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

Treatment of peripheral neuropathic pain

Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

4.2 Posology and Method of Administration

Posology

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1		
DOSING CHART – INITIAL TITRATION		
Day 1	Day 2	Day 3
300 mg once a day	300 mg two times a day	300 mg three times a day

Discontinuation of gabapentin

In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Epilepsy

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.

Adults and adolescents:

In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

Children aged 6 years and above:

The starting dose should range from 10 to 15 mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6

years and older is 25 to 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.

Peripheral neuropathic pain:

Adults

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients.

The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

Instruction for all areas of indication

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

Elderly (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age. Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

Renal impairment

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

Table 2	
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION	
Creatinine Clearance (mL/min)	Total Daily Dose ^a (mg/day)
≥ 80	900-3600
50-79	600-1800
30-49	300-900
15-29	150 ^b -600
< 15 ^c	150 ^b -300

^a Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 mL/min).

^b The 150 mg daily dose to be administered as 300 mg every other day.

^c For patients with creatinine clearance < 15 mL/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to 300 mg of gabapentin following each 4 hours of haemodialysis, is recommended.

On dialysis-free days, there should be no treatment with gabapentin. For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

Method of administration

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid-intake (e.g. a glass of water).

4.3 Contraindications

- Hypersensitivity to Gabapentin

4.4 Special warnings and Precautions for use

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, gabapentin 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 gabapentin 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).

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with gabapentin in the post-marketing experience.

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. Discontinuation of gabapentin treatment should be considered in case of suicidal ideation and behaviour.

Acute pancreatitis

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered.

Seizures

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

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.

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.

Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a population-based, observational, nested case-control study of opioid users, co prescription of opioids and gabapentin was 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 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 conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed 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 studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Dizziness, somnolence, loss of consciousness, confusion, and mental impairment

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Misuse, Abuse potential and dependence

Gabapentin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse 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.

Patients treated with gabapentin should be monitored for symptoms of gabapentin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with gabapentin, 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 gabapentin 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.

Laboratory tests

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is 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.

Excipients with known effect

Gabapentin capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Gabapentin capsules.

4.5 Interaction with other medicinal products 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 this a particular concern with the combination of gabapentin and opioids, especially in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those with substance abuse disorders.

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Co-administration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Co-administration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid. A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.

4.6 Fertility, Pregnancy and Lactation.

Pregnancy

Risk related to epilepsy and antiepileptic drugs (AEDs) in general Specialist advice regarding the potential risk to a foetus caused by both seizures and antiepileptic treatment should be given to women of childbearing potential and especially to women planning for pregnancy and women who are pregnant. The need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, 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. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the antiepileptics used.

Risk related to gabapentin

Gabapentin crosses the human placenta.

Data from a Nordic observational study of more than 1700 pregnancies exposed to gabapentin in the first trimester showed no higher risk of major congenital malformations among the children exposed to gabapentin compared to the unexposed children and compared to the children exposed to pregabalin, lamotrigine and pregabalin or lamotrigine. Likewise, no increased risk of neurodevelopmental disorders was observed in children exposed to gabapentin during pregnancy.

There was limited evidence of a higher risk of low birth weight and preterm birth but not of stillbirth, small for gestational age, low Apgar score at 5 minutes and microcephaly in newborns of women exposed to gabapentin.

Studies in animals have shown reproductive toxicity (see section 5.3).

Gabapentin can be used during the first trimester of pregnancy if clinically needed.

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.

Breast-feeding

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breastfeeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Fertility

There is no effect on fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin 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

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (1/10); common (1/100 to < 1/10); uncommon (1/1000 to < 1/100); rare (1/10000 to < 1/1000); very rare (< 1/10000)).

Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Adverse drug reactions
Infections and infestations	
Very common	viral infection
Common	pneumonia, respiratory infection, urinary tract infection, infection, otitis media
Blood and the lymphatic system disorders	

Common	leucopenia
Not known	Thrombocytopenia
Immune system disorders	
Uncommon	allergic reactions (e.g. urticaria)
Not known	Hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis lymphadenopathy, eosinophilia and sometimes other signs and symptoms), anaphylaxis.
Metabolism and nutrition disorders	
Common	anorexia, increased appetite
Uncommon	hyperglycaemia (most often observed in patients with diabetes)
Rare	hypoglycaemia (most often observed in patients with diabetes)
Not known	<i>hyponatraemia</i>
Psychiatric disorders	
Common	hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Uncommon	agitation
Not known	Suicidal ideation, hallucinations, drug dependence
Nervous system disorders	
Very common	somnolence, dizziness, ataxia
Common	convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon	hypokinesia, mental impairment
Rare	loss of consciousness
Not known	other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)
Eye disorders	
Common	visual disturbances such as amblyopia, diplopia

Ear and labyrinth disorders	
Common	vertigo
Not known	tinnitus
Cardiac disorders	
Uncommon	palpitations
Vascular disorders	
Common	hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Rare	respiratory depression
Gastrointestinal disorders	
Common	vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Uncommon	dysphagia
Not known	pancreatitis
Hepatobiliary disorders	
Not known	hepatitis, jaundice
Skin and subcutaneous tissue disorders	
Common	facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known	Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms.
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, back pain, twitching
Not known	rhabdomyolysis, myoclonus
Renal and urinary disorders	
Not known	<i>acute renal failure, incontinence</i>

Reproductive system and breast disorders	
Common	impotence
Not known	breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)
General disorders and administration site conditions	
Very common	fatigue, fever
Common	peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	generalised oedema
Not known	withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.
Investigations	
Common	WBC (white blood cell count) decreased, weight gain
Uncommon	elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Not known	blood creatine phosphokinase increased
Injury, poisoning and procedural complications	
Common	accidental injury, fracture, abrasion
Uncommon	fall

*After discontinuation of short-term and long-term treatment with gabapentin, 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 gabapentin may indicate drug dependence. 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.

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear.

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

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 grams.

Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is not usually required. However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg.

Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic groups: Other analgesics and antipyretics, **ATC code:** N02BF01

Mechanism of action

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the $\alpha 2\delta$ (alpha-2-delta) subunit of voltagegated calcium channels and it is proposed that binding to the $\alpha 2\delta$ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than $\alpha 2\delta$.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to $\alpha 2\delta$ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the $\alpha 2\delta$ subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal

cord as well as at higher brain centers through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

Clinical efficacy and safety

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years).

The data from this additional post-hoc analysis are summarised in the table below:

Response ($\geq$ 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

5.2 Pharmacokinetic Properties

Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2 $\mu\text{g/mL}$ and 20 $\mu\text{g/mL}$ in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Table 3						
Summary of gabapentin mean (%cv) steady-state pharmacokinetic parameters following every eight hours administration						
Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C _{max} µg/mL)	4.02	(24)	5.74	(38)	8.71	(29)
t _{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T _{1/2} (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) µg•hr/mL)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Biotransformation

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced.

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).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

In a pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower C_{max} and higher clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

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. A_e%, CL/F, V_d/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CL_r and T_{1/2}), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

5.3 Preclinical safety data

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m² basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m² basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m² basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m² basis.

There are some reports of neurodegenerative changes in the brains of offspring exposed to gabapentin during pregnancy from rodent studies published in the open literature. However, limitations in study designs means the toxicological significance and clinical relevance of these findings are unclear. A GLP compliant perinatal and postnatal study in rats showed reversible behavioral changes in offspring exposed to 1000 mg/kg gabapentin (approximately 1 to 5 times the human dose of 3600 mg on a mg/m² basis) from GD15 to PND21. Overall, the available data is insufficient to determine the developmental neurotoxic potential of gabapentin.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in pregnant rabbits given 60, 300, and 1500 mg/kg/day during organogenesis.

These doses are approximately 0.3 to 8 times the daily human dose of 3600 mg on a mg/m² basis. The margins of safety are insufficient to rule out the risk of these effects in humans.

6. Pharmaceutical particulars

6.1 List of excipients

Pregelatinised Maize Starch, Purified Talc, Magnesium Stearate BP.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30°C in the Original Package in order to protect from moisture

6.5 Nature and Contents of Container

Clear PVC /Alu Blister Packing: 10 x 10's Capsules

6.6 Special precautions for disposal and other handling

No Special requirements

7. Marketing Authorization Holder

Bafna Pharmaceuticals Ltd.,

No.147, Madhavaram Redhills High Road, Grantlyon village,

Vadakarai Post,

Chennai – 600 052. India

Tel: 0091 – 44 – 26320366

8. Marketing Authorization number(s)

9. Date of first authorization/renewal of the authorization

10. Date of revision of the text

08/10/2024