SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

1. NAME OF THE MEDICINAL PRODUCT

Nerveta 100/300/400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:

Gabapentin BP/Ph. Eur…100/300/400 mg

Excipients ……q. s.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard Gelatin Capsule with White opaque cap/white opaque body, printed with blue ink "GA" on cap and "04" on body, filled with white to off white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epilepsy

Nerveta 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.

Nerveta 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

Nerveta 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

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 recommended dose in adults and adolescents.

Take the number of capsules or tablets as instructed. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased as instructed by your doctor up to a maximum of 3600 mg each day and

your doctor will tell you to take this in 3 separate doses, i.e. once in the morning, once in the afternoon and once in the evening.

Children aged 6 years and above

The dose to be given to your child will be decided by your doctor as it is calculated against your child's weight. The treatment is started with a low initial dose which is gradually increased over a period of approximately 3 days. The usual dose to control epilepsy is 25-35 mg per kg per day. It is usually given in 3 separate doses, by taking the capsule(s) or tablet(s) each day, usually once in the morning, once in the afternoon and once in the evening.

It is not recommended for use in children below 6 years of age

Peripheral Neuropathic Pain

The recommended dose in adults is Take the number of capsules or tablets as instructed by your doctor. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased as instructed by your doctor up to a maximum of 3600 mg each day and your doctor will tell you to take this in 3 separate doses, i.e. once in the morning, once in the afternoon and once in the evening.

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 (see Table 2). 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 the active substance or to any of the excipients used in the formulation.

4.4 Special warnings and precautions

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has occurred with Nerveta Capsules. Some of these reactions have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved.

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

uicidal ideation and behaviour

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 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 (see section 4.8).

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

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

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 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.

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 signs and 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 (see section 4.2).

Excipients with known effect

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

Neurontin 100 mg, 300 mg and 400 mg hard capsules contain less than 1 mmol sodium (23 mg) per capsule. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium free'.

4.5 Interaction with other medicinal products and other form of interactions

Other Antiepileptic Drugs

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly co-administered antiepileptic drugs.

Opioids (hydrocodone)

Coadministration of Nerveta Capsules with hydrocodone decreases hydrocodone exposure. The potential for alteration in hydrocodone exposure and effect should be considered when Nerveta is started or discontinued in a patient taking hydrocodone.

Morphine

When gabapentin is administered with morphine, patients should be observed for signs of CNS depression, such as somnolence, sedation and respiratory depression.

Maalox® (aluminum hydroxide, magnesium hydroxide)

The mean bioavailability of gabapentin was reduced by about 20% with concomitant use of an antacid (Maalox®) containing magnesium and aluminum hydroxides. It is recommended that gabapentin be taken at least 2 hours following Maalox administration

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

4.6 Pregnancy and Lactation

There are no adequate data on the developmental risks associated with the

use of Nerveta in pregnant women. In nonclinical studies in mice, rats, and rabbits, gabapentin was developmentally toxic (increased fetal skeletal and visceral abnormalities, and increased embryofetal mortality) when administered to pregnant animals at doses similar to or lower than those used clinically.

Gabapentin is secreted in human milk following oral administration. The effects on the breastfed infant and on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nerveta and any potential adverse effects on the breastfed infant from Nerveta or from the underlying maternal condition

4.7 Effects on Ability to Drive and Use Machines

Patients taking Nerveta should not drive until they have gained sufficient experience to assess whether Nerveta impairs their ability to drive. Driving performance studies conducted with a prodrug of gabapentin (gabapentin enacarbil tablet, extended-release) indicate that gabapentin may cause significant driving impairment. Prescribers and patients should be aware that patients' ability to assess their own driving competence, as well as their ability to assess the degree of somnolence caused by Nerveta, can be imperfect. The duration of driving impairment after starting therapy with Nerveta Capsules is unknown. Whether the impairment is related to somnolence other effects of Nerveta is unknown.

Moreover, because Nerveta causes somnolence and dizziness, patients should be advised not to operate complex machinery until they have gained sufficient experience on Nerveta to assess whether it impairs their ability to perform such tasks.

4.8 Undesirable effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Contact your doctor immediately if you experience any of the following symptoms after taking this medicine as they can be serious:

- severe skin reactions that require immediate attention, swelling of the lips and face, skin rash and redness, and/or hair loss (these may be symptoms of a serious allergic reaction)

- persistent stomach pain, feeling sick and being sick as these may be symptoms of acute pancreatitis (an inflamed pancreas)
- breathing problems, which if severe you may need emergency and intensive care to continue breathing normally
- Nerveta may cause a serious or life-threatening allergic reaction that may affect your skin or other parts of your body such as your liver or blood cells. You may or may not have rash when you get this type of reaction. It may cause you to be hospitalized or to stop Nerveta. Call your doctor right away if you have any of the following symptoms:
- skin rash
- hives
- fever
- swollen glands that do not go away
- swelling of your lip and tongue
- yellowing of your skin or of the whites of the eyes
- unusual bruising or bleeding
- severe fatigue or weakness
- unexpected muscle pain
- frequent infections

These symptoms may be the first signs of a serious reaction. A doctor should examine you to decide if you should continue taking Nerveta.

Other side effects include:

Very common: (may affect more than 1 in 10 people)

- Viral infection
- Feeling drowsy, dizziness, lack of coordination
- Feeling tired, fever

Common: (may affect up to 1 in 10 people)

- Pneumonia, respiratory infections, urinary tract infection, inflammation of the ear or other infections
- Low white blood cell counts
- Anorexia, increased appetite
- Anger towards others, confusion, mood changes, depression, anxiety, nervousness, difficulty with thinking
- Convulsions, jerky movements, difficulty with speaking, loss of

memory, tremor, difficulty sleeping, headache, sensitive skin, decreased sensation (numbness), difficulty with coordination, unusual eye movement, increased, decreased or absent reflexes

- Blurred vision, double vision
- Vertigo
- High blood pressure, flushing or dilation of blood vessels
- Difficulty breathing, bronchitis, sore throat, cough, dry nose
- Vomiting (being sick), nausea (feeling sick), problems with teeth, inflamed gums, diarrhoea, stomach pain, indigestion, constipation, dry mouth or throat, flatulence
- Facial swelling, bruises, rash, itch, acne
- Joint pain, muscle pain, back pain, twitching
- Difficulties with erection (impotence)
- Swelling in the legs and arms, difficulty with walking, weakness, pain, feeling unwell, flu-like symptoms
- Decrease in white blood cells, increase in weight
- Accidental injury, fracture, abrasion

Additionally in clinical studies in children, aggressive behaviour and jerky movements were reported commonly.

Uncommon: (may affect up to 1 in 100 people)

- Agitation (a state of chronic restlessness and unintentional and purposeless motions)
- Allergic reaction such as hives
- Decreased movement
- Racing heartbeat
- Difficulty swallowing
- Swelling that may involve the face, trunk and limbs
- Abnormal blood test results suggesting problems with the liver
- Mental impairment
- Fall
- Increase in blood glucose levels (most often observed in

patients with diabetes) Rare: (may affect up to 1 in 1,000 people)

- Decrease in blood glucose levels (most often observed in patients with diabetes)
- Loss of consciousness
- Trouble breathing, shallow breaths (respiratory depression)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting Systems (PVERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of Nerveta up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy, and diarrhea were observed. All patients recovered with supportive care. Coma, resolving with dialysis, has been reported in patients with chronic renal failure who were treated with Nerveta.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Gabapentin:

Antiepileptic 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 α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than α2δ.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ 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 α2δ 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 (≥ 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 µg/mL and 20 µg/mL in clinical studies, such concentrations were not predictive of safety or efficacy.

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.

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12years. 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 approximately30% lower exposure (AUC), lower Cmax and higher clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

5.3 Preclinical safety data

Carcinogenesis

Gabapentin was administered orally to mice and rats in 2-year carcinogenicity studies. No evidence of drug-related carcinogenicity was observed in mice treated at doses up to 2000 mg/kg/day. At 2000 mg/kg, the plasma gabapentin exposure (AUC) in mice was approximately 2 times that in humans at the MRHD of 3600 mg/day. In rats, increases in the incidence of

pancreatic acinar cell adenoma and carcinoma were found in male rats receiving the highest dose (2000 mg/kg), but not at doses of 250 or 1000 mg/kg/day. At 1000 mg/kg, the plasma gabapentin exposure (AUC) in rats was approximately 5 times that in humans at the MRHD. Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells in vitro and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Mutagenesis

Gabapentin did not demonstrate mutagenic or genotoxic potential in in vitro (Ames test, HGPRT forward mutation assay in Chinese hamster lung cells) and in vivo (chromosomal aberration and micronucleus test in Chinese hamster bone marrow, mouse micronucleus, unscheduled DNA synthesis in rat hepatocytes) assays.

Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg. At 2000 mg/kg, the plasma gabapentin exposure (AUC) in rats is approximately 8 times that in humans at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule shell (Size 3),
Mannitol,
Pregelatinized
Starch
Talc

6.2 Incompatibilities

Not known

6.3 Shelf Life

24 months

6.4 Special precaution for storage

Store below 25°C.

6.5 Nature and content of container

10 capsules packed in blister of Clear PVC/PVdC foil and Aluminium foil, 10 blister of 10 capsules packed in a monocarton along with pack insert.

6.6 Special instructions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

BLISS GVS PHARMA LTD.
102, Hyde Park, Saki-Vihar
road Andheri (East) Mumbai
400 072, INDIA

8. MARKETING AUTHORIZATION NUMBER

CTD 11499

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

30/05/2024

10. DATE OF REVISION OF THE TEXT

11/05/2025