NEUROBA

For the use by a Registered Medical Practitioner or Hospital or a Laboratory only.

NEUROBA CAPSULES

Composition:

Each capsule contains 300mg of Gabapentin.

PHARMACOLOGICAL ACTION:

Pharmacotherapeutic groups: Other antiepileptics ATC code: N03AX12. The precise mechanism of action of gabapentin is not known. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. In vitro studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives. The binding site for gabapentin has been identified as the alpha2-delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug 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 and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems in vitro, but only at concentrations greater than 100 µM, which are not achieved in vivo. Gabapentin slightly reduces the release of monoamine neurotransmitters in vitro. Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. 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. 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).

PHARMACOKINETICS:

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.

INDICATIONS:

Epilepsy:

Gabapentin is indicated in the treatment of partial siezures with and without secondary generalization in adults and children aged 6 years and above. 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 neuropathic pain:

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

CONTRAINDICATIONS:

Hypersensitivity to active substance or to any of its excipients.

PREGNANCY AND LACTATION:

Pregnancy:

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

Lactation:

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 breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Interaction with other medicinal products

Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

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

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

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.

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SIDE EFFECTS:

The adverse effects include:

Back pain, changes in vision (double or blurred vision), clumsiness;constipation, diarrhoea, dizziness;drowsiness, dry mouth, nausea, stomach upset, tiredness, vomiting and weight gain. 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.

DRUG INTERACTIONS:

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.

Warnings/Precautions:

Gabapentin should not be discontinued abruptly after long term use. Abrupt or over rapid withdrawal may provoke a withdrawal syndrome similar to alcohol or benzodiazepine withdrawal.

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

POSOLOGY AND METHODS 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).

The below dosage is recommended for adults and adolescents aged 12 years and above.

DOSAGING CHART - INITIAL TITRATION

DAY 1	DAY 2	DAY3
300mg once daily	300mg twice daily	300mg three times a day

If gabapentin has to be discontinued, it is recommended that it 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:

The effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose. 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.

Peripheral neuropathic pain

Adults

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. 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.

Use in elderly patients (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.

Use in patients with renal impairment.

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

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.

In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

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, 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, minimize toxicity from overdoses.

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

PRESENTATION:

Blister packs of 30's in unit boxes.

STORAGE:

Do not store above 30°C. Store in a dry place. Protect from direct sunlight. Keep all medicines out of reach of children.

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