

Data Sheet

NUPENTIN

100mg, 300mg & 400mg

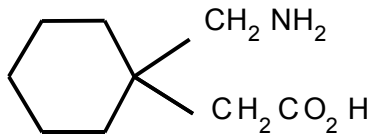
Gabapentin

Name of the Medicine

Active ingredient: Gabapentin

Chemical name: 1-(aminomethyl) cyclohexaneacetic acid

Structural formula:



Molecular formula: C₉H₁₇NO₂

Molecular weight: 171.24

CAS Registry no.: 60142-96-3

Description

Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

Each Nupentin capsule contains gabapentin 100 mg, 300 mg or 400 mg as the active ingredient. Nupentin also contains the following excipients: lactose, starch- maize, talc-purified, gelatin and Titanium dioxide. Nupentin 300 also contains Allura red AC C116035 and Quinoline yellow C147005. Nupentin 400 also contains Sunset yellow FCF C115985, Iron oxide red C177491 and Iron oxide yellow C177192. TekPrint SW-9009 Black Ink and TekPrint SW-9008 Black Ink are used as printing inks.

Pharmacology

Mechanism of Action

The mechanism by which gabapentin exerts its anticonvulsant action is unknown. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other medicines that interact with GABA synapses, including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists and GABA prodrugs. In vitro studies with radio-labelled gabapentin have characterised a novel peptide binding site in rat brain tissue, including neocortex and hippocampus, which may relate to the anticonvulsant activity of Gabapentin and its structural derivatives. However, the identification and function of the Gabapentin binding site remains to be elucidated. Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including GABA_A, GABA_B, benzodiazepine, glutamate, glycine or N-methyl-d aspartate (NMDA) receptors.

Gabapentin differs from phenytoin and carbamazepine in that it does not interact with sodium channels in vitro. Several test systems ordinarily used to assess activity at the NMDA

receptor complex have been examined. Results are contradictory, and therefore no general statement about the effects, if any, of gabapentin at the NMDA receptor can be made. 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 the 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 shows efficacy in some, but not all, seizure models. These animal models included genetic models of seizures, and seizures induced by maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis.

Pharmacokinetics

All pharmacological actions following gabapentin administration are due to the activity of the parent compound, as gabapentin is not appreciably metabolised in humans.

Absorption

Gabapentin bioavailability is not dose proportional, i.e. as the dose is increased, the bioavailability is decreased. For example, a 400 mg dose, has about 25% less bioavailability than a 100 mg dose. Over the recommended dose range of 300 to 600 mg three times a day, however, the difference in bioavailability is not large, and bioavailability is about 60%. The bioavailability of the 800 mg dose was found to be approximately 35% in single and multiple dose studies. The absolute bioavailability of gabapentin following daily doses of 1200, 2400, 3600, and 4800 mg/day averaged 47%, 34%, 33%, and 27% respectively. Food has no effect on the rate and extent of absorption of gabapentin.

Distribution

Gabapentin circulates largely unbound (< 3%) to plasma proteins. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ± 6 L (mean \pm standard deviation). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations).

Excretion

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolised in humans.

The elimination half-life of gabapentin is 4 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance and renal clearance are directly proportional to creatinine clearance. In elderly patients and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed by haemodialysis.

Dosage adjustment is recommended in patients with compromised renal function or undergoing haemodialysis (see **Dosage and Administration**).

Special Populations

Patients with Renal Insufficiency

Subjects with renal insufficiency (mean creatinine clearance ranging from 13 to 114 mL/minute) were administered an oral dose of gabapentin 400 mg. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance (CL_{cr}) > 60 mL/minute) to 52 hours (CL_{cr} < 30 mL/minute) and gabapentin renal clearance ranged from about 90 mL/minute (CL_{cr} > 60 mL/minute) to about 10 mL/minute (CL_{cr} < 30 mL/minute). Gabapentin dosage should be adjusted in patients with compromised renal function (see **Dosage and Administration**).

Patients on haemodialysis

In a study in anuric patients, the elimination half-life of gabapentin on nondialysis day was about 132 hours. Dialysis three times a week (four hour duration) lowered the apparent half-life of gabapentin by about 60%, from 132 hours to 51 hours. Gabapentin dosage should be adjusted in patients undergoing haemodialysis (see **Dosage and Administration**).

Elderly patients

In a study examining the effect of age on the elimination of gabapentin, apparent oral clearance of gabapentin decreased as age increased, from about 225 mL/minute in those under 30 years of age to about 125 mL/minute in those over 70 years of age. Renal clearance also declined with age, however the decline in the renal clearance of gabapentin can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function.

Paediatric patients

Gabapentin pharmacokinetics were determined in 24 healthy paediatric subjects between the ages of four and twelve years. In general, plasma gabapentin concentrations in these children are similar to those in adults.

Clinical Trials

Epilepsy

The effectiveness of gabapentin as adjunctive therapy was established in three multicentre, placebo controlled, double blind, parallel group, clinical trials in 705 adults with refractory partial seizures. The patients enrolled had a history of at least four partial seizures per month in spite of receiving one or more antiepileptic medicines at therapeutic levels and were observed on their established antiepileptic medicine regimen during a twelve week baseline period. In patients continuing to have at least two (or four in some studies) seizures per month, gabapentin or placebo was then added on to the existing therapy during a twelve week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as $(T - B)/(T + B)$, where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1. Increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent to treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared gabapentin 1200 mg/day three times daily with placebo. Responder rate was 23% (14/61) in the gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the gabapentin group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study primarily compared 1200 mg/day three times daily gabapentin (N = 101) with placebo (N = 98). Additional smaller gabapentin dosage groups (600 mg/day, N = 53; 1800 mg/day, N = 54) were also studied for information regarding dose response. Responder rate was higher in the gabapentin 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the gabapentin 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant (p = 0.224). A better response was seen in the gabapentin 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared gabapentin 900 mg/day three times daily (N = 111) and placebo (N = 109). An additional gabapentin 1200 mg/day dosage group (N = 52) provided dose response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the gabapentin 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day gabapentin (-0.184) compared to placebo.

A one week, prospective, multicentre, randomised, double blind, placebo lead-in, parallel group study compared the tolerability of gabapentin administered as an initial dosage of 900 mg/day versus a dosage titrated to 900 mg/day over three days (i.e. 300 mg on Day 1, 600 mg on Day 2, 900 mg on Day 3). 781 patients (titrated = 383, non-titrated = 388) involved in the study had partial seizures which were not adequately controlled with one or two other antiepileptic medicines. For the MITT population, on both the first day of active medication, and all five days of active medication, there were no clinically meaningful treatment group differences in the incidences of fatigue, ataxia and somnolence (i.e. the upper 95% confidence limit for the difference < 7.5%). Only the difference in dizziness exceeded this upper confidence limit (upper confidence limit = 10.7% for the first day and 11.3% for all five days), with the non-titrated group reporting the higher incidence, however, it did not lead to increased discontinuation in this group.

The safety and efficacy of gabapentin administered as adjunctive therapy for the treatment of partial seizures in paediatric patients aged three to twelve years were assessed in two randomised, double blind, parallel group, placebo controlled, multicentre clinical studies. The studies were conducted in 247 children who had refractory partial seizures and were receiving one to three standard antiepileptic medicines. After a six week baseline phase, during which patients received their prescribed antiepileptic medicines, there was a twelve week double blind treatment phase. Patients who had experienced a minimum of four seizures during baseline were randomised and had either gabapentin (25 to 35 mg/kg/day) or placebo added to their baseline AEDs. The primary analysis of RRatio (MITT population) demonstrated that gabapentin was significantly better than placebo in controlling partial seizures ($p = 0.04$). Results for the ITT population did not show a significant difference in RRatio between the treatment groups. Further analysis using rank transformed data was performed as the data showed evidence of non-normality of distribution. Results of this analysis showed that mean RRatio was significantly lower (better) for the gabapentin treatment group than for the placebo group in both the MITT ($p = 0.01$) and ITT ($p = 0.03$) populations.

Neuropathic Pain

The efficacy and safety of gabapentin for the treatment of neuropathic pain in adults over 18 years of age were assessed in two randomised, double blind, parallel group, placebo controlled, multicentre studies. One study examined the efficacy and safety of gabapentin in the treatment of painful diabetic peripheral neuropathy and the other study was conducted in patients with postherpetic neuralgia. The studies were of a similar design. Following a baseline screening week and randomisation, gabapentin was titrated from 900 mg/day to 1800 mg, 2400 mg and 3600 mg/day divided into three times a day dosing consecutively over the first four weeks of the study. Patients were then maintained at the maximum dose that was tolerated for the remaining four weeks. The primary efficacy measure used in both studies was change from baseline to the final week in mean pain score obtained from daily pain diaries (pain was measured using an eleven point Likert scale). Several secondary outcomes were also assessed, including the Short Form McGill Pain Questionnaire (SF-MPQ) (sensory, affective and total pain scores), SF-MPQ visual analogue scale (VAS) and present pain intensity scale (PPI), mean sleep interference score, Patient and Clinical Global Impression of Change (PGIC and CGIC) and the quality of life measures SF-36 Quality of Life Questionnaire (QOL) and Profile of Mood States (POMS).

Results from both studies demonstrated that gabapentin provided statistically significantly greater improvement in relief of neuropathic pain than placebo. In patients with painful diabetic peripheral neuropathy, mean pain score decreased by 2.6 in patients receiving gabapentin and 1.4 in patients receiving placebo ($p < 0.001$). In the postherpetic neuralgia

study, mean pain score decreased by 2.1 in patients receiving gabapentin and 0.5 in patients receiving placebo ($p < 0.001$). Gabapentin was significantly better than placebo in controlling pain from week 2 of both studies ($p < 0.001$). Sleep interference scores, Short Form McGill sensory, affective and total pain scores, VAS and PPI scale as well as PGIC, CGIC and some of the quality of life measures showed significant differences in favour of gabapentin.

Indications

Treatment of partial seizures, including secondarily generalised tonic-clonic seizures, initially as add-on therapy in adults and children age 3 years and above who have not achieved adequate control with standard antiepileptic drugs.

Treatment of neuropathic pain.

Contraindications

Hypersensitivity to gabapentin or the inactive ingredients.

Precautions

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, there is a need for dose reduction, discontinuation, or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Gabapentin is not generally considered effective in the treatment of absence seizures and may exacerbate these seizures in some patients. Consequently, gabapentin should be used with caution in patients who have mixed seizure disorders that include absence seizures.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see **Interactions with Other Medicines**).

An analysis of reports of suicidality (suicidal behaviour or ideation) from placebo-controlled clinical studies of eleven medicines used to treat epilepsy as well as psychiatric disorders, and other conditions revealed that patients receiving anti-epileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behaviour and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine and continued through 24 weeks. The results were generally consistent among the eleven medicines. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for suicidality was higher in the patients with epilepsy compared to the patients who were given one of the medicines in the class for psychiatric or other conditions.

All patients who are currently taking or starting on any anti-epileptic drug should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

Health Care Professionals should inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

Information for Patients

To ensure safe and effective use of gabapentin, the following information and instructions should be given to patients:

- Patients should inform their doctor about any prescription or nonprescription medications, alcohol or medicines they are now taking or plan to take during their treatment with gabapentin.
- No teratogenic effects have been found in animals, however the risk to the human fetus cannot be dismissed. Therefore female patients should inform their doctor if they are pregnant, are planning to become pregnant, or become pregnant while taking gabapentin.
- Gabapentin is excreted in human breast milk, and the effect on the breastfeeding infant is unknown. Women should inform their doctor if they are breastfeeding an infant.
- Gabapentin may impair the ability to drive a car or operate potentially dangerous machinery. Until patients have experienced how they are affected by this medication, they should not engage in these activities.
- More than twelve hours should not be allowed between gabapentin doses. If a dose is missed by not more than four hours, the dose should be taken as soon as it is remembered. However, if a dose is missed by more than four hours, the dose should be skipped and the following doses taken as usual.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Gabapentin was given in the diet to mice at 200, 600 and 2000 mg/kg/day and to rats at 250, 1000 and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell adenoma and carcinoma was found only in male rats at the highest dose. Peak plasma drug concentrations and areas under the concentration time curve in rats at 2000 mg/kg/day are 14 times higher than plasma concentrations in humans given the recommended maximum tolerated dose of 2400 mg/day. The pancreatic acinar cell tumours in male rats are low grade malignancies, did not metastasise or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is unclear.

There is no evidence that gabapentin has genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg/day.

Use in Pregnancy (Category B1)

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic medicines receive pre-pregnancy counseling with regard to the risk of fetal abnormalities;
- antiepileptic medicines should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Reproduction studies in mice at doses up to 3000 mg/kg/day and in rats at doses up to 2000 mg/kg/day revealed no evidence of impaired fertility or harm to the fetus due to gabapentin administration. In these studies, exposure to gabapentin (based on areas under the concentration-time curve) was up to five times higher in the mouse and up to 14 times higher in the rat than in humans at the recommended maximum tolerated dose of 2400 mg/day. In rabbits given gabapentin 60, 300 or 1500 mg/kg/day during the period of organogenesis, maternal toxicity and abortion were observed at the high dose, but at the low and mid-doses no evidence of impaired fertility or harm to the fetus was observed.

There are, however, no adequate and well controlled studies in pregnant women. Therefore, this medicine should be used during pregnancy only if clearly needed.

Use in Lactation

Gabapentin is excreted in human breast milk. In a perinatal/ postnatal study in rats at doses of 500, 1000 and 2000 mg/kg/day, there was a dose related increase in the incidence of hydronephrosis in 21 day-old pups. Because the effect on the breastfeeding infant is unknown, and because of the potential for serious adverse reactions in breastfed infants from gabapentin, a decision should be made whether to discontinue breastfeeding or to discontinue the medicine, taking into account the importance of the medicine to the mother. Gabapentin should be used in breastfeeding mothers only if the benefits clearly outweigh the risks.

Use in Children

Epilepsy: Safety and effectiveness in children below the age of 3 years have not been established.

Neuropathic pain: Safety and effectiveness in children below the age of 18 years have not been established.

Impaired Renal Function

Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see *Pharmacokinetics* and **Dosage and Administration**).

Use in the Elderly

Reduction of gabapentin dosage may be required in patients with age related compromised renal function (see *Pharmacokinetics*).

Interactions with Other Medicines

In pharmacokinetic studies, no interactions were observed between gabapentin and phenobarbitone (number of subjects, n = 12), phenytoin (n = 8), valproic acid (n = 17) or carbamazepine (n = 12).

Gabapentin did not influence the steady-state pharmacokinetics of norethisterone and ethinyloestradiol when administered concomitantly with an oral contraceptive containing these two drugs (n = 13).

Coadministration of gabapentin with antacid reduced gabapentin bioavailability by about 20% (n = 16).

In the presence of cimetidine 300 mg four times daily, the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance by 10% (n = 12). Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. Renal excretion of gabapentin was unaltered by probenecid, a blocker of renal tubular secretion.

Morphine. A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine

(see Precautions). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

Effect on the Ability to Drive and Use Machines

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

Effects on Laboratory Tests

False positive readings were reported with the Ames N-Multistix SG dipstick test when gabapentin was added to other anticonvulsant medicine. To determine urinary protein, the more specific sulfosalicylic acid precipitation procedure is recommended.

Adverse Effects

Epilepsy

Adults and children over 12 years

Gabapentin has been evaluated for safety in approximately 2000 subjects and patients and was well tolerated. Of these, 543 patients participated in controlled clinical trials.

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic medicines, not seen in an equivalent frequency among placebo treated patients, were somnolence, dizziness, ataxia, fatigue and nystagmus.

Approximately 7% of the 2074 individuals who received gabapentin in the premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence, ataxia, fatigue, nausea and/ or vomiting and dizziness.

Incidence in controlled clinical trials

Table 1 lists the treatment emergent signs and symptoms that occurred in at least 1% of gabapentin treated patients with epilepsy participating in gabapentin placebo-controlled trials. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic medicine therapy. Adverse events were usually mild to moderate in intensity.

Table 1: Adverse Events Reported in At Least 1% of Participants in Gabapentin Placebo-Controlled Trials

Body System	Adverse Event	Gabapentin ^a N=543 (%)	Placebo ^a N=378 (%)
Body As A Whole	Fatigue	11.0	5.0
	Weight Increase	2.9	1.6
	Back Pain	1.8	0.5
	Peripheral Oedema	1.7	0.5
	Viral Infection	1.3	2.1
	Fever	1.3	1.3
Cardiovascular	Vasodilatation	1.1	0.3
Digestive System	Nausea and/or Vomiting	6.1	7.1
	Dyspepsia	2.2	0.5

Body System	Adverse Event	Gabapentin ^a N=543 (%)	Placebo ^a N=378 (%)
	Abdominal Pain	1.8	2.4
	Mouth or Throat Dry	1.7	0.5
	Constipation	1.5	0.8
	Dental Abnormalities	1.5	0.3
	Diarrhoea	1.3	2.1
	Increased Appetite	1.1	0.8
Haematologic and Lymphatic Systems	Leukopenia	1.1	0.5
Musculoskeletal System	Myalgia	2.0	1.9
	Fracture	1.1	0.8
Nervous System	Somnolence	19.3	8.7
	Dizziness	17.1	6.9
	Ataxia	12.5	5.6
	Nystagmus	8.3	4.0
	Headache	8.1	9.0
	Tremor	6.8	3.2
	Nervousness	2.4	1.9
	Dysarthria	2.4	0.5
	Amnesia	2.2	0.0
	Depression	1.8	1.1
	Thinking Abnormal	1.7	1.3
	Confusion	1.7	1.9
	Twitching	1.3	0.5
	Coordination Abnormal	1.1	0.3
	Insomnia	1.1	1.9
	Emotional Lability	1.1	1.3
Respiratory System	Rhinitis	4.1	3.7
	Pharyngitis	2.8	1.6
	Coughing	1.8	1.3
Skin and Appendages	Rash	1.5	1.6
	Abrasion	1.3	0.0
	Pruritus	1.3	0.5
	Acne	1.1	1.3
Urogenital System	Impotence	1.5	1.1
Special Senses	Diplopia	5.9	1.9
	Amblyopia ^b	4.2	1.1
Laboratory Deviations	WBC Decreased	1.1	0.5

^a Plus background antiepileptic medicine therapy

^b Amblyopia was often described as blurred vision.

Other adverse events observed during all clinical studies

Those events that occurred in at least 1% of the study participants with epilepsy who received gabapentin as adjunctive therapy in any clinical study and that are not described in the previous section as frequently occurring treatment emergent signs and symptoms during placebo controlled studies are summarised below.

Body as a whole. Asthenia, malaise, facial oedema.

Cardiovascular. Hypertension.

Digestive System. Flatulence, anorexia, gingivitis.

Haemic, Lymphatic System. Purpura (most often described as bruises resulting from physical trauma).

Musculoskeletal. Arthralgia.

Nervous system. Vertigo, hyperkinesia, increased, decreased or absent reflexes, paraesthesia, anxiety, hostility.

Respiratory. Pneumonia.

Genitourinary. Urinary tract infection.

Special senses. Abnormal vision.

Other possible effects include suicidal behaviour, suicidal ideation and emergence or worsening of existing depression.

Children 3 to 12 years

The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic medicines in children 3 to 12 years of age, not seen in equal frequency among placebo treated patients, were viral infection, fever, nausea and/ or vomiting, and somnolence.

Approximately 8% of the 292 children age 3 to 12 years who received gabapentin in pre-approval clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in children were somnolence (1.4%), hyperkinesia (1.0%), and hostility (1.0%) (see Table 2).

Table 2: Treatment Emergent Adverse Event Incidence in Children Age 3 to 12 Years in Controlled Add-On Trials (Events in at least 2% of gabapentin patients and numerically more frequent than in the placebo group)

Body System	Adverse Event	Gabapentin ^a N = 119 (%)	Placebo ^a N = 128 (%)
Body As A Whole	Viral Infection	10.9	3.1
	Fever	10.1	3.1
	Weight Increase	3.4	0.8
	Fatigue	3.4	1.6
Digestive System	Nausea and/or Vomiting	8.4	7.0

Body System	Adverse Event	Gabapentin ^a N = 119 (%)	Placebo ^a N = 128 (%)
Nervous System	Somnolence	8.4	4.7
	Hostility	7.6	2.3
	Emotional Lability	4.2	1.6
	Dizziness	2.5	1.6
	Hyperkinesia	2.5	0.8
Respiratory System	Bronchitis	3.4	0.8
	Respiratory Infection	2.5	0.8

^a Plus background antiepileptic medicine therapy

Other events in more than 2% of children but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhoea, anorexia, coughing, and otitis media.

Adverse events occurring during clinical trials in children treated with gabapentin that were not reported in adjunctive therapy trials in adults included:

Body as a Whole. Dehydration, infectious mononucleosis.

Digestive System. Hepatitis, oral moniliasis.

Haemic and Lymphatic System. Coagulation defect.

Nervous System. Aura disappeared, occipital neuralgia.

Psychobiologic Function. Sleepwalking.

Respiratory System. Pseudo croup, hoarseness.

Neuropathic Pain

Adults over 18 years of age with neuropathic pain.

The most commonly observed adverse events reported with the use of gabapentin in adults over 18 years of age with neuropathic pain, seen in at least twice the frequency among placebo treated patients, were dry mouth, peripheral oedema, weight gain, abnormal gait, amnesia, ataxia, confusion, dizziness, hypoaesthesia, somnolence, thinking abnormal, vertigo, rash and amblyopia.

In the painful diabetic peripheral neuropathy and post-herpetic neuralgia trials, 13.2% of the 821 adults who received gabapentin discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were dizziness (4.4%), somnolence (2.9%) and nausea (1.3%). (See Table 3.)

Table 3: Summary of Treatment-Emergent Signs and Symptoms in ≥1% of Gabapentin-Treated Patients in Neuropathic Pain Placebo-Controlled Studies

COSTART Body System	Adverse Event	Gabapentin N = 821		Placebo N = 537	
		Number	%	Number	%
Body As A Whole	Abdominal pain	23	2.8	17	3.2
	Accidental injury	32	3.9	17	3.2

COSTART Body System	Adverse Event	Gabapentin N = 821		Placebo N = 537	
		Number	%	Number	%
	Asthenia	41	5.0	25	4.7
	Back pain	19	2.3	8	1.5
	Flu syndrome	21	2.6	14	2.6
	Headache	45	5.5	33	6.1
	Infection	38	4.6	40	7.4
	Pain	30	3.7	36	6.7
Digestive System	Constipation	19	2.3	9	1.7
	Diarrhoea	46	5.6	24	4.5
	Dry Mouth	27	3.3	5	0.9
	Dyspepsia	16	1.9	10	1.9
	Flatulence	14	1.7	6	1.1
	Nausea	45	5.5	29	5.4
	Vomiting	16	1.9	13	2.4
Metabolic and Nutritional	Peripheral oedema	44	5.4	14	2.6
	Weight gain	14	1.7	0	0.0
Nervous System	Abnormal gait	9	1.1	0	0.0
	Amnesia	15	1.8	3	0.6
	Ataxia	19	2.3	0	0.0
	Confusion	15	1.8	5	0.9
	Dizziness	173	21.1	35	6.5
	Hypoaesthesia	11	1.3	3	0.6
	Somnolence	132	16.1	27	5.0
	Thinking Abnormal	12	1.5	0	0.0
	Tremor	9	1.1	6	1.1
	Vertigo	8	1.0	2	0.4
Respiratory System	Dyspnoea	9	1.1	3	0.6
	Pharyngitis	15	1.8	7	1.3
Skin and Appendages	Rash	14	1.7	4	0.7
Special Senses	Amblyopia	15	1.8	2	0.4

Post-marketing experience

The following adverse events have been reported in patients receiving gabapentin post-marketing, however, the data are insufficient to support an estimate of their incidence or to establish causation.

Sudden, unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established. Additional post-marketing adverse events reported include: jaundice, abnormal liver function, acute kidney failure, allergic reactions including urticaria, alopecia, anaemia, angioedema, blood glucose fluctuations in patients with

diabetes, breast hypertrophy, gynaecomastia, cardiac arrest, chest pain, convulsions, depersonalisation, erythema multiforme, movement disorders such as choreoathetosis, dyskinesia and dystonia, myoclonus, palpitation, pancreatitis, renal impairment, speech disorder, sexual dysfunction, Stevens-Johnson syndrome, tachycardia, thrombocytopenia, tinnitus, urinary incontinence, and symptoms of psychosis such as delusions, hallucinations and thinking abnormal.

Generalised oedema, hepatitis, hypotension, neuropathy/peripheral neuropathy and syncope have been rarely reported.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

Some cases of hypomania have been reported after commencement of gabapentin. In each case, other anticonvulsants had been used concurrently, and symptoms of hypomania resolved following a reduction in dosage or cessation of the medicine.

Dosage and Administration

Epilepsy in adults and children over 12 years of age

Initiation of treatment should be as add-on therapy. Gabapentin can be given orally with or without food.

In controlled clinical trials, the effective dose range was 900 to 1800 mg/day given in divided doses (three times a day).

Therapy may be initiated by administering 300 mg capsules three times a day on Day 1 or by titrating the dose as described: titration to an effective dose can take place rapidly, over a few days by giving 300 mg on day 1, 300 mg twice a day on day 2, then 300 mg three times a day on day 3. Titration may be preferable for patients with renal impairment, patients with encephalopathy, patients on more than two other antiepileptic medicines and patients with multiple other medical problems.

To minimise potential side effects, especially somnolence, dizziness, fatigue and ataxia, the first dose on Day 1 may be administered at bedtime. If necessary, the dose may be increased by 300 or 400 mg three times a day up to 2400 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term open-label clinical studies. The maximum time between doses in the three times a day (TID) schedule should not exceed 12 hours.

Neuropathic Pain in Adults (over 18 years of age)

The starting dose is 900 mg/day given as three daily divided doses, and titrated if necessary, based on response, up to a maximum dose of 3600 mg/day.

Impaired Renal function in patients with Neuropathic Pain or Epilepsy

Dosage adjustment is recommended in patients with compromised renal function or those undergoing haemodialysis. (See Table 4.)

Table 4. Maintenance Dosage of Gabapentin in Adults with Reduced Renal Function

Renal function Creatinine Clearance (mL/min)	Total Daily Dose ^a (mg/day)			
≥80	900	1200	2400	3600
50-79	600	600	1200	1800
30-49	300	300	600	900

15-29	150 ^b	300	300	600
<15	150 ^b	150 ^b	150 ^b	300

^a Total daily dose should be administered as a three times daily (tid) regimen. Doses used to treat patients with normal renal function (creatinine clearance >80 mL/min) range from 900 to 3600 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79 mL/min).

^b To be administered as 300 mg every other day.

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

Children aged 3 to 12 years of age

The effective dose of gabapentin is 25 to 35 mg/kg/day given in divided doses (3 times a day). Titration to an effective dose can take place over 3 days by giving 10 mg/kg/day on Day 1, 20 mg/kg/day on Day 2, and 30 mg/kg/day on Day 3. Dosages up to 40 to 50 mg/kg/day have been well tolerated in a long-term clinical study. Doses of 60 mg/kg/day have also been administered to a small number of children.

Unlike other agents in this class, it is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicines without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicines.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of one week.

Overdosage

Symptoms

Symptoms of an overdose included somnolence, ataxia, dizziness, double vision, nystagmus, slurred speech, drowsiness, lethargy, mild hypotension and gastrointestinal symptoms including diarrhoea. Gabapentin overdose alone has not been reported to produce significant cardiotoxicity.

Overdoses as high as 108 g have been reported with full recovery following symptomatic therapy. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise toxicity from overdoses.

Treatment

There is no specific antidote for gabapentin; treatment is symptomatic. The patient should be monitored closely and given supportive care where necessary to maintain vital functions.

Activated charcoal may reduce absorption of the medicine if given within one hour after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Gabapentin can be removed by haemodialysis. Although haemodialysis 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.

Ipecac-induced emesis is not recommended because of the potential for CNS depression.

Presentation

Nupentin 100: size 3 capsule with white body and white cap, "GP100" printed in black ink on the body and "G" on the cap. Blister packs containing 100 capsules.

Nupentin 300: size 1 capsule with yellow body and yellow cap, "GP300" printed in black ink on the body and "G" on the cap. Blister packs containing 100 capsules.

Nupentin 400: size 0 capsule with orange body and orange cap, "GP400" printed in black ink on the body and "G" on the cap. Blister packs containing 100 capsules.

Storage Conditions

Store below 25°C.

Further Information

Nil.

Medicine Classification

Prescription Medicine

Name and Address

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2 February 2009