

baby. Tell your healthcare provider right away if you become pregnant while taking gabapentin tablets. You and your healthcare provider will decide if you should take gabapentin tablets while you are pregnant.

- Pregnancy Registry:** If you become pregnant while taking gabapentin tablets, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy. You can enroll in this registry by calling 1-888-233-2334 or visiting <http://www.aedpregnancyregistry.org/>.
- are breast-feeding or plan to breast-feed. Gabapentin can pass into breast milk. You and your healthcare provider should decide how you will feed your baby while you take gabapentin tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- any opioid pain medicine such as morphine, hydrocodone, oxycodone, or buprenorphine.
- any medicines for anxiety (such as lorazepam) or insomnia (such as zolpidem), or any medicines that make you sleepy. You may have a higher chance for dizziness, sleepiness, or breathing problems if these medicines are taken with gabapentin tablets.

Taking gabapentin tablets with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take gabapentin tablets?

- Take gabapentin tablets exactly as prescribed. Your healthcare provider will tell you how much gabapentin tablets to take.
- Do not change your dose of gabapentin tablets without talking to your healthcare provider.**
- Do not stop taking gabapentin tablets without talking to your healthcare provider first.** If you stop taking gabapentin tablets suddenly, you may develop side effects.
- Gabapentin tablets can be taken with or without food.
- Swallow gabapentin tablets whole with water.
- If you take gabapentin tablets and break a tablet in half, the unused half of the tablet should be taken at your next scheduled dose. Half tablets not used within 28 days of breaking should be thrown away.
- If you take an antacid containing aluminum and magnesium, such as Maalox®, Mylanta®, Gelusil®, Gavison®, or Di-Gel®, you should wait at least 2 hours before taking your next dose of gabapentin tablets.
- In case of overdose get medical help or contact a live Poison Center expert right away at 1-800-222-1222. Advice is also available online at poisonhelp.org.

What should I avoid while taking gabapentin tablets?

- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking gabapentin tablets without first talking with your healthcare provider.** Taking gabapentin tablets with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how gabapentin tablets affects you.** Gabapentin tablets can slow your thinking and motor skills.

What are the possible side effects of gabapentin tablets?

Gabapentin tablets may cause serious side effects including: See **“What is the most important information I should know about gabapentin tablets?”**

- problems driving while using gabapentin tablets. See **“What I should avoid while taking gabapentin tablets?”**
- sleepiness and dizziness, which could increase your chance of having an accidental injury, including falls

The most common side effects of gabapentin tablets include:

- lack of coordination
- viral infection
- feeling drowsy
- nausea and vomiting
- difficulty with speaking
- tremor
- swelling, usually of legs and feet
- feeling tired
- fever
- jerky movements
- difficulty with coordination
- double vision
- unusual eye movement

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of gabapentin tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store gabapentin tablets?

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Keep gabapentin tablets and all medicines out of the reach of children.

KEEP CONTAINER TIGHTLY CLOSED

Keep this and all medication out of the reach of children.

General information about the safe and effective use of gabapentin tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use gabapentin tablets for a condition for which it was not prescribed. Do not give gabapentin tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about gabapentin tablets that is written for healthcare professionals.

For more information go to www.strides.com or call 1-877-244-9825.

What are the ingredients in gabapentin tablets?

Active ingredient: gabapentin

Inactive ingredients in the tablets: Copovidone, hydroxyl propyl cellulose, magnesium stearate, mannitol, poloxamer, talc, low-substituted hydroxypropylcellulose polyvinylalcohol, polyethylene glycol, titanium dioxide, and talc. This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Although there is at least one report of neonatal withdrawal syndrome in an infant exposed to gabapentin alone during pregnancy, there are no comparative epidemiologic studies evaluating this association. Therefore, whether exposure to gabapentin alone late in pregnancy may cause withdrawal signs and symptoms is not known.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Neonatal withdrawal syndrome has been reported in newborns exposed to gabapentin in utero for an extended period of time when also exposed to opioids close to delivery. Neonatal withdrawal signs and symptoms reported have included tachypnea, vomiting, diarrhea, hypertension, irritability, sneezing, poor feeding, hyperactivity, abnormal sleep pattern, and tremor. Reported signs and symptoms that may also be related to withdrawal include tongue thrusting, wandering eye movements while awake, back arching, and continuous extremity movements. Observe neonates exposed to gabapentin and opioids for signs and symptoms of neonatal withdrawal and manage accordingly.

Data

Human Data

An observational study based on routinely collected data from administrative and medical registers in Denmark, Finland, Norway, and Sweden, compared the prevalence of major congenital malformations in approximately 1,500 pregnancies exposed to gabapentin monotherapy in the first trimester to pregnancies unexposed to antiepileptics (n=295,816) and pregnancies exposed to lamotrigine monotherapy in the first trimester (n=7,582). The adjusted prevalence rates in a pooled analysis were 1.00 (95% CI: 0.80-1.24) compared to pregnancies unexposed to antiepileptics and 1.29 (95% CI: 1.00-1.67) compared to pregnancies exposed to lamotrigine monotherapy in the first trimester.

Data from another observational study in the US based on Medicaid data, which compared the risk for major congenital malformations in more than 4,600 pregnancies exposed to gabapentin during the first trimester to pregnancies unexposed (n=1,753,865), estimated an adjusted relative risk of 1.07 (95% CI: 0.94-1.21).

Data from a cohort study of over 200,000 Medicaid-eligible pregnancies with prescription opioid exposure in the last 45 days of pregnancy found that the risk of neonatal drug withdrawal was greater in pregnancies with combined exposure to gabapentin and opioids compared to pregnancies with exposure to opioids alone.

The data from these observational studies should be interpreted with caution due to the potential for exposure misclassification, outcome misclassification, and residual confounding, including by underlying disease.

Animal Data

When pregnant mice received oral doses of gabapentin (500, 1000, or 3000 mg/kg/day) during the period of organogenesis, embryofetal toxicity (increased incidences of skeletal variations) was observed at the two highest doses. The no-effect dose for embryofetal developmental toxicity in mice (500 mg/kg/day) is less than the maximum recommended human dose (MRHD) of 3600 mg on a body surface area (mg/m²) basis.

In studies in which rats received oral doses of gabapentin (500 to 2000 mg/kg/day), during pregnancy, adverse effect on offspring development (increased incidences of hydrocephalus and hydronephrosis) were observed at all doses. The lowest dose tested is similar to the MRHD on a mg/m² basis.

When pregnant rabbits were treated with gabapentin during the period of organogenesis, an increase in embryofetal mortality was observed at all doses (60, 300, or 1500 mg/kg). The lowest dose tested is less than the MRHD on a mg/m² basis.

In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown to interfere with actin polymerization in cultured neurons. In addition, a channel, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.

8.2 Lactation

Risk Summary

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 gabapentin and any potential adverse effects on the breastfed infant from gabapentin or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of gabapentin in the management of postherpetic neuralgia in pediatric patients have not been established.

Safety and effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established [see Clinical Studies (14.2)].

8.5 Geriatric Use

The total number of patients treated with gabapentin in controlled clinical trials in patients with postherpetic neuralgia was 336, of which 102 (30%) were 65 to 74 years of age, and 168 (50%) were 75 years of age and older. There was a larger treatment effect in patients 75 years of age and older compared to younger patients who received the same dosage. Since gabapentin is almost exclusively eliminated by renal excretion, the larger treatment effect observed in patients > 75 years may be a consequence of increased gabapentin exposure for a given dose that results from an age-related decrease in renal function. However, other factors cannot be excluded. The types and incidence of adverse reactions were similar across age groups except for peripheral edema and ataxia, which tended to increase in incidence with age.

Clinical studies of gabapentin in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Drug Interactions

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on renal function. Decreased renal clearance values in patients with renal insufficiency have been observed [see Dosage and Administration (2.4), Adverse Reactions (6), and Clinical Pharmacology (12.3)].

8.6 Renal Impairment

Dosage adjustment in adult patients with compromised renal function is necessary [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. Pediatric patients with renal insufficiency have not been studied. Dosage adjustment in patients undergoing hemodialysis is necessary [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Gabapentin is not a controlled substance

9.2 Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed.

Gabapentin does not exhibit affinity for benzodiazepine, opioid (mu, delta or kappa), or cannabinoid 1 receptor sites. Gabapentin misuse and abuse have been reported in the postmarketing setting and published literature. Most of the individuals described in these reports had no history of identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed in some patients. Withdrawal symptoms may occur shortly after discontinuation, usually within 48 hours. In the postmarketing setting, reported adverse reactions have included, but not been limited to, seizures, depression, suicidal ideation and behavior, agitation, confusion, disorientation, psychotic symptoms, anxiety, insomnia, nausea, pain, sweating, tremor, headache, dizziness, and malaise. The dependence potential of gabapentin has not been evaluated in human studies.

10 OVERDOSAGE

Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, excitation, hyporeactivity, or excitation.

Acute oral overdoses of gabapentin have been reported. Symptoms have included double vision, tremor, slurred speech, drowsiness, altered mental status, dizziness, lethargy, and diarrhea. Fatal respiratory depression has been reported with gabapentin overdoses alone and in combination with other CNS depressants.

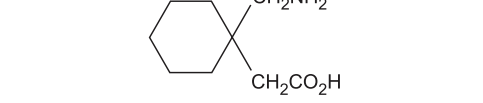
Gabapentin can be removed by hemodialysis.

If overdosage occurs, call your poison control center at 1-800-222-1222.

11 DESCRIPTION

The active ingredient in gabapentin tablets, USP is gabapentin, which has the chemical name 1-(aminomethyl)pyrrolidine-2-carboxylic acid.

The molecular formula of gabapentin is C₈H₁₅N₂O₃ and the molecular weight is 171.24. The structural formula of gabapentin is



Gabapentin, USP is a white to off-white crystalline solid with a pK_a of 3.7 and a pK_a of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25.

Each gabapentin tablet contains 600 mg or 800 mg of gabapentin and the following inactive ingredients: copovidone, hydroxyl propyl cellulose,

magnesium stearate, mannitol, poloxamer, talc, low-substituted hydroxypropyl cellulose, polyvinyl alcohol, polyethylene glycol, titanium dioxide, and talc

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms by which gabapentin produces its analgesic and antiepileptic actions are unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. *In vitro* studies have shown that gabapentin binds with high-affinity to the α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown.

12.3 Pharmacokinetics

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

Oral Bioavailability

Gabapentin bioavailability is not dose proportional, i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 300, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution

Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (mean±SD). In patients with epilepsy, steady-state predose (C_{tr}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination

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

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma half-life, 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 from plasma by hemodialysis.

Specific Populations

The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CL_R) and CL/F adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. [see Dosage and Administration (2.4) and Use in Specific Populations (8.5)].

Gender

Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race

Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Pediatric

Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in younger children. Apparent oral clearance of gabapentin decreased proportionally to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 12 years of age. Patients received 10 to 65 mg/kg/day given three times a day. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following steady-state and non-steady-state dosing. Higher clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was also variable in the age <1 year age group. The normalized CL/F was higher in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age group.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day [see Dosage and Administration (2.2)].

Adult Patients with Renal Impairment

Subjects (N=60) with renal impairment (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours in patients with creatinine clearance >60 mL/min to 12 hours in patients with creatinine clearance <30 mL/min and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma half-life decreased from approximately 190 to 100 minutes with increasing creatinine clearance. Mean plasma half-life was similar in patients with creatinine clearance >60 mL/min [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].

Hemodialysis

In a study in anuric adult subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was about 2.8 hours. Hemodialysis had a significant effect on gabapentin elimination in anuric subjects [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].

Hepatic Disease

Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

• In Vitro Studies

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoflurane selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mg/mL, 1 mM) was a slight degree of inhibition (14% to 30%) of isoflurane CYP2A6 observed. No inhibition of any of the other isoflurane was observed at gabapentin concentrations up to 171 mg/mL (approximately 15 times the C_{max} at 3600 mg/day).

• In Vivo Studies

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin

In a single (400 mg) and multiple dose (400 mg three times a day) study of gabapentin in epileptic patients (N=48) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine

Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg three times a day, N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid

The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg three times a day, N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg three times a day, N=12) are identical whether the drugs are administered alone or together.

Nazogel

Coadministration (N=18) of Nazogel sodium capsules (250 mg) with gabapentin (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on Nazogel pharmacokinetic parameters. These data are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose range of either drug is not known.

Hydrocodone

Coadministration of gabapentin (125 to 500 mg; N=48) decreases hydrocodone (10 mg, N=50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone. C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

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. 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.

Cimetidine

In the presence of cimetidine at 300 mg four times a day (N=12), the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus, cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive

Based on AUC and half-life, multiple-dose pharmacokinetic profiles of ethinyl estradiol and norethindrone following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg three times a day, N=13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®) (aluminum hydroxide, magnesium hydroxide)

Antacid (Maalox®) containing magnesium and aluminum hydroxides reduced the mean bioavailability of gabapentin (N=16) by about 20%. This decrease

in bioavailability was about 10% when gabapentin was administered 2 hours after Maalox.

Probenecid

Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

14 CLINICAL STUDIES

14.1 Postherpetic Neuralgia

Gabapentin was evaluated for the management of postherpetic neuralgia (PHN) in two randomized, double-blind, placebo-controlled, multicenter studies. The intent-to-treat (ITT) population consisted of a total of 563 patients with PHN for more than 3 months after healing of the herpes zoster skin rash (Table 6).

TABLE 6. Controlled PHN Studies: Duration, Dosages, and Number of Patients

Study	Duration	Target Dose	Gabapentin	Placebo
1	8 weeks	3600	113	116
2	7 weeks	1800, 2400	223	111
Total			336	227