

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GABAPENTIN CAPSULES safely and effectively. See full prescribing information for GABAPENTIN CAPSULES.

GABAPENTIN capsules, for oral use  
Initial U.S. Approval: 1993

RECENT MAJOR CHANGES  
Warnings and Precautions, Respiratory Depression (5.7) 04/2020

INDICATIONS AND USAGE

Gabapentin is indicated for:

- Postherpetic neuralgia in adults (1)
- Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy (1)

DOSE AND ADMINISTRATION

- Postherpetic Neuralgia (2.1)
  - Dose can be titrated up as needed to a dose of 1800 mg/day
  - Day 1: Single 300 mg dose
  - Day 2: 600 mg/day (i.e., 300 mg two times a day)
  - Day 3: 900 mg/day (i.e., 300 mg three times a day)
- Epilepsy with Partial Onset Seizures (2.2)
  - Patients 12 years of age and older: starting dose is 300 mg three times daily; may be titrated up to 600 mg three times daily
  - Patients 3 to 11 years of age: starting dose range is 10 to 15 mg/kg/day, given in three divided doses; recommended dose in patients 3 to 4 years of age is 40 mg/kg/day, given in three divided doses; the recommended dose in patients 5 to 11 years of age is 25 to 35 mg/kg/day, given in three divided doses. The recommended dose is reached by upward titration over a period of approximately 3 days

- Dose should be adjusted in patients with reduced renal function (2.3, 2.4)

DOSE FORMS AND STRENGTHS

- Capsules: 100 mg, 300 mg, and 400 mg (3)

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Known hypersensitivity to gabapentin or its ingredients (4)

WARNINGS AND PRECAUTIONS

- Drug Reaction with Eosinophilia and Systemic Symptoms (Multiorgan hypersensitivity): Discontinue if alternative etiology is not established (5.1)
- Anaphylaxis and Angioedema: Discontinue and evaluate patient immediately (5.2)
- Driving Impairment, Somnolence/Sedation and Dizziness: Warn patients not to drive until they have gained sufficient experience to assess whether their ability to drive or operate heavy machinery will be impaired (5.3, 5.4)
- Increased seizure frequency may occur in patients with seizure disorders if gabapentin is abruptly discontinued (5.5)
- Suicidal Behavior and Ideation: Monitor for suicidal thoughts/behavior (5.6)
- Respiratory Depression: May occur with gabapentin when used with concomitant central nervous system (CNS) depressants, including opioids, or in the setting of underlying respiratory impairment. Monitor patients and adjust dosage as appropriate (5.7)
- Neuropsychiatric Adverse Reactions in Children 3 to 12 Years of Age: Monitor for such events (5.8)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥8% and at least twice that for placebo) were:
  - Postherpetic neuralgia; dizziness, somnolence, and peripheral edema (6.1)
  - Epilepsy in patients >12 years of age: Somnolence, dizziness, ataxia, fatigue, and nystagmus (6.1)
  - Epilepsy in patients 3 to 12 years of age: Viral infection, fever, nausea and/or vomiting, somnolence, and hostility (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals, Inc., at 1-866-495-8330 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

DRUG INTERACTIONS

Concentrations increased by morphine; may need dose adjustment (5.4, 7.1)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

### 5.9 Tumorigenic Potential

In an oral carcinogenicity study, gabapentin increased the incidence of pancreatic acinar cell tumors in rats [see *Nonclinical Toxicology* (13.1)]. The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2,085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

### 5.10 Sudden and Unexplained Death in Patients with Epilepsy

During the course of premarketing development of gabapentin, 8 sudden and unexplained deaths were recorded among a cohort of 2203 epilepsy patients treated (2103 patient-years of exposure) with gabapentin.

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the gabapentin cohort and the accuracy of the estimates provided.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections:

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity [see *Warnings and Precautions* (5.1)]
- Anaphylaxis and Angioedema [see *Warnings and Precautions* (5.2)]
- Somnolence/Sedation and Dizziness [see *Warnings and Precautions* (5.4)]
- Withdrawal Precipitated Seizure, Status Epilepticus [see *Warnings and Precautions* (5.5)]
- Suicidal Behavior and Ideation [see *Warnings and Precautions* (5.6)]
- Respiratory Depression [see *Warnings and Precautions* (5.7)]
- Neuropsychiatric Adverse Reactions (Pediatric Patients 3 to 12 Years of Age) [see *Warnings and Precautions* (5.8)]
- Sudden and Unexplained Death in Patients with Epilepsy [see *Warnings and Precautions* (5.10)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### Postherpetic Neuralgia

The most common adverse reactions associated with the use of gabapentin in adults, not seen at an equivalent frequency among placebo-treated patients, were dizziness, somnolence, and peripheral edema.

In the 2 controlled trials in postherpetic neuralgia, 16% of the 336 patients who received gabapentin and 9% of the 227 patients who received placebo discontinued treatment because of an adverse reaction. The adverse reactions that most frequently led to withdrawal in gabapentin-treated patients were dizziness, somnolence, and nausea.

Table 3 lists adverse reactions that occurred in at least 1% of gabapentin-treated patients with postherpetic neuralgia participating in placebo-controlled trials and that were numerically more frequent in the gabapentin group than in the placebo group.

TABLE 3. Adverse Reactions in Pooled Placebo-Controlled Trials in Postherpetic Neuralgia

	Gabapentin N=336 %	Placebo N=227 %
<b>Body as a Whole</b>		
Asthenia	6	5
Infection	5	4
Accidental injury	3	1
<b>Digestive System</b>		
Diarrhea	6	3
Dry mouth	5	1
Constipation	4	2
Nausea	4	3
Vomiting	3	2
<b>Metabolic and Nutritional Disorders</b>		
Peripheral edema	8	2
Weight gain	2	0
Hyperglycemia	1	0
<b>Nervous System</b>		
Dizziness	28	8
Somnolence	21	5
Ataxia	3	0
Abnormal thinking	3	0
Abnormal gait	2	0
Incoordination	2	0
<b>Respiratory System</b>		
Pharyngitis	1	0
<b>Special Senses</b>		
Amblyopia <sup>a</sup>	3	1
Conjunctivitis	1	0
Diplopia	1	0
Otitis media	1	0

<sup>a</sup> Reported as blurred vision

Other reactions in more than 1% of patients but equally or more frequent in the placebo group included pain, tremor, neuralgia, back pain, dyspepsia, dyspnea, and flu syndrome.

There were no clinically important differences between men and women in the types and incidence of adverse reactions. Because there were few patients whose race was reported as other than white, there are insufficient data to support a statement regarding the distribution of adverse reactions by race.

#### Epilepsy with Partial Onset Seizures (Adjunctive Therapy)

The most common adverse reactions with gabapentin in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.

The most common adverse reactions with gabapentin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility [see *Warnings and Precautions* (5.8)].

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse reactions most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Table 4 lists adverse reactions that occurred in at least 1% of gabapentin-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy.

TABLE 4. Adverse Reactions in Pooled Placebo-Controlled Add-On Trials in Epilepsy Patients >12 years of age

	Gabapentin <sup>a</sup> N=543 %	Placebo <sup>b</sup> N=378 %
<b>Body As A Whole</b>		
Fatigue	11	5
Increased Weight	3	2
Back Pain	2	1
Peripheral Edema	2	1
<b>Cardiovascular</b>		
Vasodilatation	1	0
<b>Digestive System</b>		
Dyspepsia	2	1
Dry Mouth or Throat	2	1
Constipation	2	1
Dental Abnormalities	2	0
<b>Nervous System</b>		
Somnolence	19	9
Dizziness	17	7
Ataxia	13	6
Nystagmus	8	4
Tremor	7	3
Dysarthria	2	1
Amnesia	2	0
Depression	2	1
Abnormal thinking	2	1
Abnormal coordination	1	0
<b>Respiratory System</b>		
Pharyngitis	3	2
Coughing	2	1
<b>Skin and Appendages</b>		
Abrasion	1	0
<b>Urogenital System</b>		
Impotence	2	1
<b>Special Senses</b>		
Diplopia	6	2
Amblyopia <sup>a</sup>	4	1

<sup>a</sup> Plus background antiepileptic drug therapy

<sup>b</sup> Amblyopia was often described as blurred vision.

Among the adverse reactions occurring at an incidence of at least 10% in gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse reactions and the types of adverse reactions seen were similar among men and women treated with gabapentin. The incidence of adverse reactions increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (29/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse reactions by race.

Table 5 lists adverse reactions that occurred in at least 2% of gabapentin-treated patients, age 3 to 12 years of age with epilepsy participating in placebo-controlled trials, and which were numerically more common in the gabapentin group.

TABLE 5. Adverse Reactions in a Placebo-Controlled Add-On Trial in Pediatric Epilepsy Patients Age 3 to 12 Years

	Gabapentin <sup>a</sup> N=119 %	Placebo <sup>b</sup> N=128 %
<b>Body As A Whole</b>		
Viral Infection	11	3
Fever	10	3
Increased Weight	3	1
Fatigue	3	2
<b>Digestive System</b>		
Nausea and/or Vomiting	8	7
<b>Nervous System</b>		
Somnolence	8	5
Hostility	8	2
Emotional Lability	4	2
Dizziness	3	2
Hyperkinesia	3	1
<b>Respiratory System</b>		
Bronchitis	3	1
Respiratory Infection	3	1

<sup>a</sup> Plus background antiepileptic drug therapy

Other reactions in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of gabapentin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### Hepatobiliary disorders: jaundice

Investigations: elevated creatine kinase, elevated liver function tests

Metabolic and nutrition disorders: hyponatremia

Musculoskeletal and connective tissue disorder: rhabdomyolysis

Nervous system disorders: movement disorder

Psychiatric disorders: agitation

Reproductive system and breast disorders: breast enlargement, changes in libido, ejaculation disorders and anorgasmia

Skin and subcutaneous tissue disorders: angioedema [see *Warnings and Precautions* (5.2)], bullous pemphigoid, erythema multiforme, Stevens-Johnson syndrome.

There are postmarketing reports of life-threatening or fatal respiratory depression in patients taking gabapentin with opioids or other CNS depressants, or in the setting of underlying respiratory impairment [see *Warnings and Precautions* (5.7)].

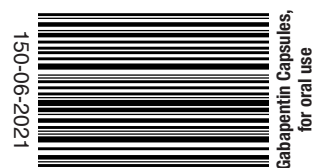
Adverse reactions following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported reactions were anxiety, insomnia, nausea, pain, and sweating.

## 7 DRUG INTERACTIONS

### 7.1 Opioids

Respiratory depression and sedation, sometimes resulting in death, have been reported following coadministration of gabapentin with opioids (e.g., morphine, hydrocodone, oxycodone, buprenorphine) [see *Warnings and Precautions* (5.7)].

#### Hydrocodone



published literature. Most of the individuals described in these reports had a history of polysubstance abuse. Some of these individuals were taking higher than recommended doses of gabapentin for unapproved uses. When prescribing gabapentin, carefully evaluate patients for a history of drug abuse and observe them for signs and symptoms of gabapentin misuse or abuse (e.g., self-dose escalation and drug-seeking behavior). The abuse potential of gabapentin has not been evaluated in human studies.

**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. There are rare postmarketing reports of individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. The dependence potential of gabapentin has not been evaluated in human studies.

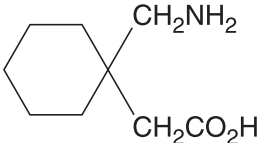
**10 OVERDOSE**  
Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

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 overdose, alone and in combination with other CNS depressants.

Gabapentin can be removed by hemodialysis.  
If overexposure occurs, call your poison control center at 1-800-222-1222.

**11 DESCRIPTION**  
The active ingredient in gabapentin capsules is gabapentin, USP which has the chemical name 1-(aminomethyl)cyclohexanecarboxylic acid.

The molecular formula of gabapentin is C<sub>8</sub>H<sub>11</sub>NO<sub>2</sub> 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<sub>a1</sub> of 3.7 and a pK<sub>a2</sub> 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 capsule contains 100 mg, 300 mg, or 400 mg of gabapentin, USP and the following inactive ingredients: mannitol, pre-gelatinized starch and talc. The 100 mg capsule shell contains titanium dioxide, gelatin and sodium lauryl sulfate. The 300 mg and 400 mg capsule shell contains FD&C Red 40, D&C Yellow 10, titanium dioxide, gelatin and sodium lauryl sulfate. The ink ingredients common for all strengths are shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide and potassium hydroxide.

**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  $\alpha_2\delta$  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 900, 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<sub>max</sub>).

**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<sub>min</sub>) 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 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 from plasma by hemodialysis.

**Specific Populations**  
**Age**  
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<sub>R</sub>) and CL<sub>R</sub> 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 the younger children. Apparent oral clearance of gabapentin was directly proportional 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 13 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 a single dose and at steady-state. Higher oral 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 highly variable in infants <1 year of age. The normalized CL/F values observed 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 range.

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 (patients with creatinine clearance >60 mL/min) to 52 hours (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 clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]. Pediatric patients with renal insufficiency have not been studied.

**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 reduced to 3.8 hours. Hemodialysis thus has 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.

**Drug Interactions**  
**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 isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL, 1 mM) was a slight degree of inhibition (14% to 30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C<sub>max</sub> 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=8) 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.

**Phenobarbital**  
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.

**Naproxen**  
Coadministration (N=18) of naproxen 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 naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

**Hydrocodone**  
Coadministration of gabapentin (125 to 500 mg, N=48) decreases hydrocodone (10 mg, N=50) C<sub>max</sub> and AUC values in a dose-dependent manner relative to administration of hydrocodone alone. C<sub>max</sub> and AUC values in a dose-dependent manner relative to administration of hydrocodone alone. C<sub>max</sub> and AUC values in a dose-dependent manner relative to administration of hydrocodone alone. C<sub>max</sub> and AUC values in a dose-dependent manner relative to administration of hydrocodone alone.

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 norethindrone and ethinyl estradiol 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<sub>max</sub> 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.

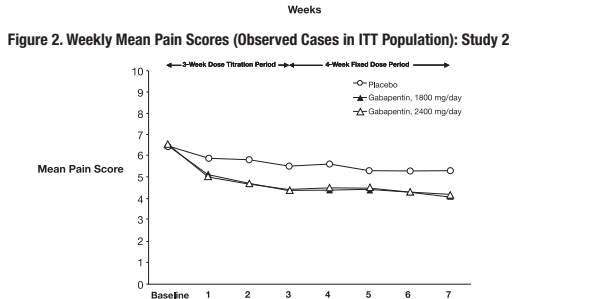
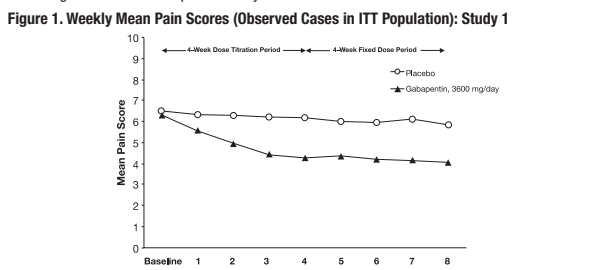
**Impairment of Fertility**  
No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg. At 2000 mg/kg, the plasma gabapentin exposure (AUC) in rats is approximately 8 times that in humans at the MRHD.

**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 pain for more than 3 months after healing of the herpes zoster skin rash (Table 6).

Study	Study Duration	Gabapentin (mg/day)* Target Dose	Patients Receiving Gabapentin	Patients Receiving Placebo
1	8 weeks	3600	113	116
2	7 weeks	1800, 2400	223	111
Total			336	227

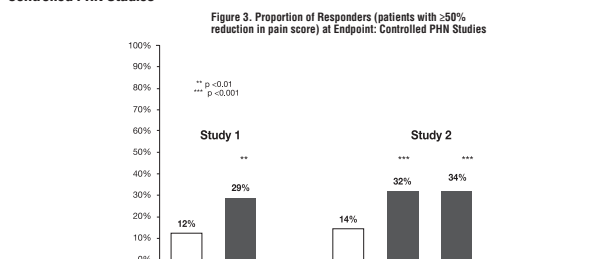
\*Given in 3 divided doses (TID)  
Each study included a 7- or 8-week double-blind phase (3 or 4 weeks of titration and 4 weeks of fixed dose). Patients initiated treatment with titration to a maximum of 900 mg/day gabapentin over 3 days. Doses were then titrated in 600 to 1200 mg/day increments at 3- to 7-day intervals to the target dose over 3 to 4 weeks. Patients recorded their pain in a daily diary using an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). A mean pain score during baseline of at least 4 was required for randomization. Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication).

Both studies demonstrated efficacy compared to placebo at all doses tested. The reduction in weekly mean pain scores was seen by Week 1 in both studies, and were maintained to the end of treatment. Comparable treatment effects were observed in all active treatment arms. Pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses. Figures 1 and 2 show pain intensity scores over time for Studies 1 and 2.



The proportion of responders (those patients reporting at least 50% improvement in endpoint pain score compared to baseline) was calculated for each study (Figure 3).

**Figure 3. Proportion of Responders (patients with >50% reduction in pain score) at Endpoint: Controlled PHN Studies**



**14.2 Epilepsy for Partial Onset Seizures (Adjunctive Therapy)**  
The effectiveness of gabapentin as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in 4 months studies) seizures per month, gabapentin or placebo was then added on to the existing therapy during a 12-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 the "responder rate" and a derived measure called responder rate, a measure of change defined as (T - B)/(T + B), in which B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Responder rate 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 responder rate 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, in three divided doses 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. Responder rate 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 compared primarily gabapentin 1200 mg/day, in three divided doses (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. Responder rate 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.

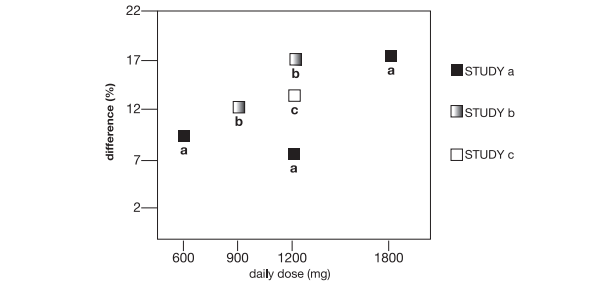
A third study compared gabapentin 900 mg/day, in three divided doses (N=111), and placebo (N=109). An additional gabapentin 1200 mg/day dosage group (N=52) provided dose-response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Responder rate 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 responder rate in 1200 mg/day gabapentin (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of gabapentin on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for gabapentin compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N=162, gabapentin; N=89, placebo) also showed a significant advantage for gabapentin over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of gabapentin was used. Within each study, the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 4).

**Figure 4. Responder Rate in Patients Receiving Gabapentin Expressed as a Difference from Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age with Partial Seizures**



In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo-assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to gabapentin. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25-35 mg/kg/day gabapentin (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the responder rate was statistically significantly better for the gabapentin group (-0.16) than for the placebo group (-0.079). For the same population, the responder rate for gabapentin (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day gabapentin (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response rate or responder rate.

**16 HOW SUPPLIED/STORAGE AND HANDLING**  
Gabapentin capsules, USP are supplied as follows:

- 100 mg capsules:  
Hard Gelatin Capsule Shell Size "3" White Opaque cap and White Opaque body printed with "A" on Cap and "469" on body in black ink filled with White to Off-white powder; supplied in Bottles of 100: NDC 31722-148-01  
Bottles of 500: NDC 31722-148-05  
Bottles of 1000: NDC 31722-148-10
- 300 mg capsules:  
Hard Gelatin Capsule Shell Size "1" Yellow Opaque cap and Yellow Opaque body printed with "A" on Cap and "470" on body in black ink filled with White to Off-white powder; supplied in Bottles of 100: NDC 31722-149-01  
Bottles of 500: NDC 31722-149-05  
Bottles of 1000: NDC 31722-149-10
- 400 mg capsules:  
Hard Gelatin Capsule Shell Size "0" Orange Opaque cap and Orange Opaque body printed with "A" on Cap and "471" on body in black ink filled with White to Off-white powder; supplied in Bottles of 100: NDC 31722-150-01  
Bottles of 500: NDC 31722-150-05

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

**17 PATIENT COUNSELING INFORMATION**  
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

**Administration Information**  
Inform patients that gabapentin is taken orally with or without food.

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity**  
Prior to initiation of treatment with gabapentin, instruct patients that a rash or other signs or symptoms of hypersensitivity (such as fever or lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately [see Warnings and Precautions (5.1)].

**Anaphylaxis and Angioedema**  
Advise patients to discontinue gabapentin and seek medical care if they develop signs or symptoms of anaphylaxis or angioedema [see Warnings and Precautions (5.2)].

**Dizziness and Somnolence and Effects on Driving and Operating Heavy Machinery**  
Advise patients that gabapentin may cause dizziness, somnolence, and other symptoms and signs of CNS depression. Other drugs with sedative properties may increase these symptoms. Accordingly, although patients' ability to determine their level of impairment can be unreliable, advise them neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely. Inform patients that it is not known how long this effect lasts [see Warnings and Precautions (5.3) and Warnings and Precautions (5.4)].

**Risk of Suicidal Thoughts and Behavior**  
Counsel the patient, their caregivers, and families that AEDs, including gabapentin, may increase the risk of suicidal thoughts and behavior. Advise patients of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients to report behaviors of concern immediately to healthcare providers [see Warnings and Precautions (5.6)].

**Respiratory Depression**  
Inform patients about the risk of respiratory depression. Include information that the risk is greatest for those using concomitant CNS depressants (such as opioid analgesics) or those with underlying respiratory impairment. Teach patients how to recognize respiratory depression and advise them to seek medical attention immediately if it occurs [see Warnings and Precautions (5.7)].

**Use in Pregnancy**  
Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see Use in Specific Populations (8.1) and (8.2)].

Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see Use in Specific Populations (8.1)].

**Manufactured by:**  
Ascent Pharmaceuticals, Inc.  
Central Islip, NY 11722

**Manufactured for:**  
Camber Pharmaceuticals, Inc.  
Piscataway, NJ 08854

Rev: 06/21

**MEDICATION GUIDE**  
**Gabapentin Capsules, USP**  
(gab-ah-PEN-tin)

**What is the most important information I should know about gabapentin capsules?**  
Do not stop taking gabapentin capsules without first talking to your healthcare provider. Stopping gabapentin capsules suddenly can cause serious problems.

**Gabapentin capsules can cause serious side effects including:**

**1. Suicidal Thoughts. Like other antiepileptic drugs, gabapentin capsules may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

**Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**How can I watch for early symptoms of suicidal thoughts and actions?**

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms. **Do not stop taking gabapentin capsules without first talking to a healthcare provider.**

- Stopping gabapentin capsules suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

**2. Changes in behavior and thinking** - Using gabapentin capsules in children 3 to 12 years of age can cause emotional changes, aggressive behavior, problems with concentration, restlessness, changes in school performance, and hyperactivity.

**3. Gabapentin capsules may cause serious or life-threatening allergic reactions that may affect your skin or other parts of your body such as your liver or blood cells.** This may cause you to be hospitalized or to stop gabapentin capsules. You may or may not have a rash with an allergic reaction caused by gabapentin capsules. Call a healthcare provider right away if you have any of the following symptoms:

- skin rash
- hives
- difficulty breathing
- fever
- swollen glands that do not go away
- swelling of your face, lips, throat, or 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 healthcare provider should examine you to decide if you should continue taking gabapentin capsules.

**4. Serious breathing problems.** Serious breathing problems can occur when gabapentin capsules are taken with other medicines that can cause severe sleepiness or decreased awareness, or when it is taken by someone who already has breathing problems. Watch for increased sleepiness or decreased breathing when starting gabapentin capsules or when the dose is increased. Get help right away if breathing problems occur.

**What are gabapentin capsules?**  
Gabapentin capsules are a prescription medicine used to treat:

- Pain from damaged nerves (postherpetic pain) that follows healing of shingles (a painful rash that comes after a herpes zoster infection) in adults.
- Partial seizures when taken together with other medicines in adults and children 3 years of age and older with seizures.

**Who should not take gabapentin capsules?**  
Do not take gabapentin capsules if you are allergic to gabapentin or any of the other ingredients in gabapentin capsules. See the end of this Medication Guide for a complete list of ingredients in gabapentin capsules.

**What should I tell my healthcare provider before taking gabapentin capsules?**  
Before taking gabapentin capsules, tell your healthcare provider if you:

- have or have had kidney problems or are on hemodialysis
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have diabetes
- have breathing problems
- are pregnant or plan to become pregnant. It is not known if gabapentin can harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking gabapentin. You and your healthcare provider will decide if you should take gabapentin while you are pregnant.
- Pregnancy Registry:** If you become pregnant while taking gabapentin capsules, 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 1-88