

MEDICATION GUIDE

Gabapentin Capsules, USP

(gab' a 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
- swollen
- 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 capsules can harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking gabapentin capsules. You and your healthcare provider will decide if you should take gabapentin capsules 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 1-888-233-2334.

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Renal Function	Total Daily Creatinine Clearance (mL/min)	Dose Regimen (mg)	1,200 mL/min	1,200 mL/min
≥60	900 to 1,600	300 TID	400 TID	600 TID
>30 to 59	400 to 1,400	200 BID	300 BID	400 BID
>15 to 29	200 to 700	200 QID	300 QID	400 QID
15*	100 to 300	100 QID	125 QID	150 QID

Post-Hemodialysis Supplemental Dose (mg) ^b	125 ^a	150 ^a	200 ^a	250 ^a	350 ^a
Hemodialysis					

TID = Three times a day; BID = Two times a day; QD = Single daily dose

*For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

^aPatients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

Creatinine clearance (CL_{Cr}) is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance can be reasonably well estimated using the equation of Cockcroft and Gault:

$$CL_{Cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

The use of gabapentin capsules in patients less than 12 years of age with compromised renal function has not been studied.

2.4 Dosage in Elderly

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 creatinine clearance values in these patients.

2.5 Administration Information

Administer gabapentin capsules orally with or without food.

Gabapentin capsules should be swallowed whole with water.

If the gabapentin capsules dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of 1 week (a longer period may be needed at the discretion of the prescriber).

3. DOSAGE FORMS AND STRENGTHS

Capsules

- 100 mg: White Opaque/White opaque size '4' hard gelatin capsules imprinted with 'LL' on cap and '100' on body with blue ink, filled with white to off-white granular powder.
- 300 mg: Yellow Opaque/Yellow opaque size '1' hard gelatin capsules imprinted with 'LL' on cap and '300' on body with blue ink, filled with white to off-white granular powder.
- 400 mg: Orange Opaque/Orange opaque size '0' hard gelatin capsules imprinted with 'LL' on cap and '400' on body with blue ink, filled with white to off-white granular powder.

4. CONTRAINDICATIONS

Gabapentin capsules are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

5. WARNINGS AND PRECAUTIONS

5.1 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multorgan Hypersensitivity

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

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Gabapentin Capsules are indicated for:

- Management of postherpetic neuralgia in adults
- 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

2. DOSAGE AND ADMINISTRATION

2.1 Dosage for Postherpetic Neuralgia

In adults with postherpetic neuralgia, gabapentin capsules may be initiated on Day 1 as a single 300 mg dose, on Day 2 as 600 mg/day (300 mg two times a day), and on Day 3 as 900 mg/day (300 mg three times a day). The dose can subsequently be titrated up as needed for pain relief to a dose of 1,800 mg/day (600 mg three times a day). In clinical studies, efficacy was demonstrated over a range of doses from 1,800 mg/day to 3,600 mg/day with comparable effects across the dose range; however, in these clinical studies, the additional benefit of using doses greater than 1,800 mg/day was not demonstrated.

2.2 Dosage for Epilepsy with Partial Onset Seizures

Patients 12 years of age and above

The starting dose is 300 mg three times a day. The recommended maintenance dose of gabapentin capsules is 300 mg to 600 mg three times a day. Dosages up to 2,400 mg/day have been well tolerated in long-term clinical studies. Doses of 3,600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. Administer gabapentin capsules three times a day using 300 mg or 400 mg capsules. The maximum time between doses should not exceed 12 hours.

Pediatric Patients Age 3 to 11 years

The starting dose is 15 mg/kg/day to 15 mg/kg/day, given in three divided doses, and the recommended maintenance dose reached by upward titration over a period of approximately 3 days. The recommended maintenance dose of gabapentin capsules in patients 3 to 4 years of age is 40 mg/kg/day, given in three divided doses. The recommended maintenance dose of gabapentin capsules in patients 5 to 11 years of age is 25 mg/kg/day to 35 mg/kg/day, given in three divided doses. Gabapentin may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

2.3 Dosage Adjustment in Patients with Renal Impairment

Dosage adjustment in patients 12 years of age and older with renal impairment or undergoing hemodialysis is recommended, as follows (see dosing recommendations above for effective doses in each indication):

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Known hypersensitivity to gabapentin or its ingredients (4)

5.2 Anaphylaxis and Angioedema

Gabapentin can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis or angioedema.

5.3 Effects on Driving and Operating Heavy Machinery

Patients taking gabapentin should not drive until they have gained sufficient experience to assess whether gabapentin impairs their ability to drive. Driving performance studies conducted with a product of gabapentin (gabapentin enacarbil tablet, extended-release) indicate that gabapentin may cause significant driving impairment. Prescribers and patients should be aware that patients' ability to assess their own driving competence, as well as their ability to assess the degree of somnolence caused by gabapentin, can be imperfect. The duration of effect of morphine may experience when gabapentin is unknown. Whether the impairment is related to somnolence [see Warnings and Precautions (5.4)] or other effects of gabapentin is unknown.

5.4 Somnolence/Sedation and Dizziness

During the controlled epilepsy studies in patients older than 12 years of age receiving doses of gabapentin up to 1,800 mg/day, somnolence, dizziness, and ataxia were reported at a rate in patients receiving placebo (1.4%, 1.9%, and 1.9%, respectively) compared to 9% in placebo for somnolence, 17% in drug versus 7% in placebo for dizziness, and 13% in drug versus 6% in placebo for ataxia. In these trials somnolence, ataxia and fatigue were common adverse reactions leading to discontinuation of gabapentin in patients older than 12 years of age, with 1.2%, 0.8% and 0.6% discontinuing for these events, respectively.

During the controlled trials in patients with post-herpetic neuralgia, somnolence, and dizziness were reported at a greater rate compared to placebo in patients receiving gabapentin, in dosages up to 3,600 mg per day: i.e., 21% in gabapentin-treated patients versus 5% in placebo-treated patients for somnolence and 28% in gabapentin-treated patients versus 8% in placebo-treated patients for dizziness. Dizziness and somnolence were among the most common adverse reactions leading to discontinuation of gabapentin.

Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence and sedation, when gabapentin is used with other drugs with sedative properties because of potential synergy. In addition, patients who require concomitant treatment with morphine may experience increased gabapentin concentrations and may require dose adjustment [see Drug Interactions (7.1)].

5.5 Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled epilepsy studies in patients >12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.43% compared to 0.51% in patients receiving placebo (2 of 378). Among the 2,074 patients >12 years of age treated with gabapentin across all epilepsy studies (controlled and uncontrolled), 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment with gabapentin or while on other medications. Because historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

5.6 Suicidal Behavior and Ideation

Patients taking gabapentin capsules should be monitored for the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying degrees of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

TABLE 2 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	6.5	1.5	0.9
Other	1.0	1.0	1.0	0.0
Total	2.4	4.3	1.8	2.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing gabapentin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.7 Respiratory Depression

There is evidence from case reports, human studies, and animal studies associating gabapentin with serious, life-threatening, or fatal respiratory depression when coadministered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment. When the decision is made to co-prescribe gabapentin with another CNS depressant, particularly an opioid, or to prescribe gabapentin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating gabapentin at a low dose. The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants (including gabapentin).

5.8 Neuropsychiatric Adverse Reactions (Pediatric Patients 3 to 12 Years of Age)

Gabapentin use in pediatric patients with epilepsy 3 to 12 years of age is associated with the occurrence of CNS related adverse reactions. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the reactions were mild to moderate in intensity.

In controlled clinical epilepsy trials in pediatric patients 3 to 12 years of age, the incidence of these adverse reactions was: emotional lability 6% (gabapentin-treated patients) versus 1.3% (placebo-treated patients); hostility 5.2% versus 1.3%; hyperkinesia 4.7% versus 2.9%; and thought disorder 1.7% versus 0%. One of these reactions, a report of hostility, was considered serious. Discontinuation 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 prostatic 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 2,203 epilepsy patients treated (2,103 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 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)/Multorgan 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 trial 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 patients receiving gabapentin than in the placebo group.

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

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

* 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 patients 3 to 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 were 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* N=433	Placebo* N=373
Body As A Whole		
Fatigue	11	5
Increased Weight	3	2
Back Pain	2	1
Peripheral Edema	2	0
Cardiovascular		
Vasodilation	1	0
Digestive System		
Dyspepsia	2	1
Dry Mouth or Throat	2	1
Constipation	2	1
Dental Abnormalities	2	0
Nervous System		
Somnolence	19	9
Dizziness	13	6
Ataxia	13	4
Nystagmus	8	7
Tremor	7	3
Dysarthria	2	1
Amnesia	2	0
Depression	2	1
Ab		

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 scheduled drug.

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 (μ , δ , or κ), 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 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 linesses for which the drug is not approved. Such symptoms include 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. OVERDOSAGE

Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hyporeflexia, or excretion.

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.

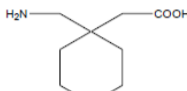
Gabapentin can be removed by hemodialysis.

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

11. DESCRIPTION

The active ingredient in gabapentin capsules, USP is gabapentin USP, which has the chemical name 1-(Amino methyl)-cyclohexane acetic acid.

The molecular formula of gabapentin is $C_8H_{15}NO_2$ and the molecular weight is 171.24. The structural formula of gabapentin is:



Gabapentin USP is a white to off-white powder. It is freely soluble in water, 0.1 N sodium hydroxide and glacial acetic acid, slightly soluble in ethanol and insoluble in toluene. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25. Each gabapentin capsules, USP contain 100 mg, 300 mg, or 400 mg of gabapentin USP and the following inactive ingredients: mannitol, pregelatinized starch and talc.

The empty hard gelatin capsule shell consists of gelatin, sodium lauryl sulfate, and titanium dioxide. In addition 300 mg also contains yellow iron oxide and 400 mg also contains yellow iron oxide and red iron oxide. The capsules are printed with edible ink containing FD&C Blue No. 2 and shellac.

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 pharmacokinetic 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 500, 1,200, 2,400, 3,600, and 4,800 mg/day given in 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 150 mg intravenous administration is 55aL (mean \pm SD). In patients with epilepsy, steady-state plasma (C_{ss}) 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 to 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) CL_R adjusted for body surface area also declined with age; however, age had little effect 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 the 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 to 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 (2.2) and Use in Specific Populations (8.6)]. Pediatric patients with renal insufficiency have not been studied.

Hemodialysis

In a study in anuric adult patients (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 Vivo 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 isoflur selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 μ g/mL, 1 mM) was a slight degree of inhibition (14% to 30%) of isoflur CYP2A6 observed. No inhibition of any of the other isoflur tested was observed at gabapentin concentrations up to 171 μ g/mL (approximately 15 times the C_{max} at 3,600 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.

Pharmacokinetics

Pharmacokinetics 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_{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 norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 μ g 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 2,000 mg/kg/day. At 2,000 mg/kg, the plasma gabapentin exposure (AUC) in mice was approximately 2 times that in humans at the MFRD of 3,600 mg/day. In rats, increases in the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving the highest dose (2,000 mg/kg), but not at doses of 250 or 1,000 mg/kg/day. At 1,000 mg/kg, the plasma gabapentin exposure (AUC) in rats was approximately 5 times that in humans at the MFRD.

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 2,000 mg/kg. At 2,000 mg/kg, the plasma gabapentin exposure (AUC) in rats is approximately 8 times that in humans at the MFRD.

14. CLINICAL STUDIES

14.1 Postherpetic Neuralgia

Gabapentin (fixed dose), Patient 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) ^a Target Dose	Patients Receiving Gabapentin	Patients Receiving Placebo
1	8 weeks	3,600	113	116
2	7 weeks	1,800, 2,400	223	111
		Total	336	227

^a 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 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).

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day, N=53; 1,800 mg/day, N=54) were also studied for information regarding dose response. Response rate was higher in the gabapentin 1,200 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 1,800 mg group (26%) was statistically significantly superior to the placebo rate. Response rate was better in the gabapentin 1,200 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 1,800 mg/day group (<0.222) than in the 1,200 mg/day group, with the 1,800 mg/day group achieving statistical significance compared to the placebo group.