GABAPENTIN (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾CN400

Commonly used brand name(s):Neurontin.
Another commonly used name is GBP 6, 9, 16, 18, 19, 25, 26, 27.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Anticonvulsant 4, 11, 18, 19, 22, 26.

Indications

Accepted

Epilepsy (treatment adjunct)¾Gabapentin is indicated as an adjunct to other anticonvulsant medications 1, 30, 41, 42 (in the treatment of partial seizures with or without secondary generalization in adults and adolescents) * with epilepsy. 1, 42 Gabapentin is also indicated as adjunctive therapy for the treatment of partial seizures in pediatric patients 3 years of age and older with epilepsy. 44, *

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Chemical group¾Cyclohexane-acetic acid derivative. 5, 11, 13 Structural analog to gamma-aminobutyric acid (GABA) 6, 10, 11, 13, 14, 17, 20, 21, 22, 29.

Molecular weight¾171.24 1, 11, 30, 33

pKa¾3.68 and 10.70 11, 30

Mechanism of action/Effect:

The mechanism of action is unknown. 1, 2, 3, 5, 8, 11, 12, 13, 14, 15, 16, 21, 29, 30 Gabapentin does not interact with GABA receptors 1, 3, 6, 9, 11, 12, 15, 16, 21, 29, 30 , is not metabolized to a GABA agonist or to GABA 1, 30 , and does not inhibit GABA uptake 1, 5, 11, 12, 21, 29, 30 or degradation. 1, 5, 9, 12, 29, 30 In rats, gabapentin interacts with a novel binding site 3, 6, 8, 9, 29 on cortical neurons 6, 9, 21 that may be associated with the L-system amino acid transporter of brain cell membranes. 2, 21

Absorption:

Rapid. 5, 14, 16, 17 Gabapentin is absorbed in part 29, 36 by the L-amino acid transport system 29, 37 , which is a carrier-mediated 34 , saturable transport system 2, 3, 6, 21, 29, 30 ; as the dose increases, bioavailability decreases. 1, 3, 5, 9, 13, 15, 17, 21, 26, 29 Bioavailability ranges from approximately 60% for a 300-mg dose 3, 11, 21, 26, 29, 30 to approximately 35% for a 1600-mg dose. 21, 29

Absorption is unaffected by food. 1, 3, 5, 9, 17, 26, 30

Distribution:

Volume of distribution (Vol D) is approximately 50 to 60 L 1, 15, 16, 17, 21.

Gabapentin penetrates the blood-brain barrier, 7, 8, 9, 11, 12, 13, 14, 15, 17, 21, 26 yielding cerebrospinal fluid (CSF) concentrations approximately equal to 20% 1, 26 of corresponding steady-state plasma trough concentrations in patients with epilepsy 1.

Brain tissue concentrations in one patient undergoing temporal lobectomy were approximately 80% of corresponding plasma concentrations. 26, 28

Protein binding:

Very low (< 5%). 1, 2, 7, 15, 21, 30

Biotransformation:

Gabapentin is not metabolized. 1, 3, 5, 6, 7, 8, 9, 11, 14, 17, 21, 26, 29, 30, 35

Half-life:

Elimination¾

Normal renal function: 5 to 7 hours. 1, 3, 5, 6, 9, 10, 11, 13, 15, 16, 17, 21, 26, 29, 30

Impaired renal function (creatinine clearance < 30 mL/minute): 52 hours. 42

In hemodialysis: In 11 anuric patients, a single 400-mg oral dose of gabapentin had an elimination half-life of 132 hours on days when patients did not receive dialysis, 21, 23, 30 and 3.8 hours during dialysis. 21, 23

Time to peak concentration:

2 to 4 hours. 3, 5, 6, 8, 9, 11, 15, 16, 21, 26, 30

Therapeutic serum concentration

The therapeutic serum concentration range for gabapentin is not well defined. 15 However, in one study it was noted that seizure frequency decreased significantly only in patients with gabapentin

serum concentrations > 2 mg/L (11.7 micromoles/L). 3, 12, 21 After receiving gabapentin 400 mg three times per day for one week, patients maintained on phenytoin had minimum gabapentin plasma concentrations of 2 to 4.8 mg/L (11.7 to 28 micromoles/L) and maximum gabapentin plasma concentrations of 3.6 to 8.6 mg/L (21 to 50.2 micromoles/L). 15, 16 Titration of dosage is based on clinical response. 2, 15, 21

Note: Steady-state pharmacokinetics of gabapentin in patients with epilepsy were similar to those in healthy subjects 41.

Elimination:

Renal¾Entire absorbed dose 2, 3, 6, 11, 15, 16, 21, 22, 26, 29, 30 , as unchanged drug. 1, 3, 7, 11, 16, 17, 24 Gabapentin clearance is directly proportional to creatinine clearance. 1, 3, 9, 15

In dialysis¾Gabapentin can be removed from plasma by hemodialysis. 1, 23, 30

Precautions to Consider

Carcinogenicity/Tumorigenicity

In two-year carcinogenicity studies, a statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats 1, 5, 9, 16, 21, 30 receiving doses of gabapentin that produced plasma concentrations 10 times higher than those seen in humans receiving 3600 mg per day. 1 Tumors were noninvasive, did not metastasize, did not affect survival, and did not occur in female rats or in mice. 1 The significance to humans is unknown. 1, 21, 30

Mutagenicity

No evidence of mutagenicity was found in appropriate in vitro and in vivo testing. 1, 11, 30 Gabapentin was negative in the Ames test, and negative in the in vitro HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the in vitro Chinese hamster lung cell assay; it was negative in the in vivo chromosomal aberration assay and in the in vivo micronucleus test in Chinese hamster bone marrow. 42

Pregnancy/Reproduction

Fertility¾No adverse effect on fertility was seen in rats given up to 5 times an equivalent human dose of 3600 mg on a mg per square meter of body surface area (mg/m 2) basis. 1

Pregnancy¾Gabapentin should be used during pregnancy only if the benefit justifies the potential risk to the fetus. 1

Adequate and well-controlled studies have not been done in humans. 1, 30, 41, 42

Gabapentin has been shown to be fetotoxic in rodents 42.

Pregnant mice given 1 to 4 times an equivalent human dose of 3600 mg on a mg/m 2 basis during organogenesis produced offspring with delayed ossification of several bones in the skull, vertebrae, and limbs. 1, 42 Rats given approximately 1 to 5 times an equivalent human dose of 3600 mg on a mg/m 2 basis produced offspring with an increased incidence of hydroureter and hydronephrosis. 1 In rabbits given < 1/4 to 8 times an equivalent human dose of 3600 mg on a mg/m 2 basis, an increased incidence of postimplantation fetal loss occurred. 1, 42

FDA Pregnancy Category C. 1, 42

Breast-feeding

It is not known whether gabapentin is distributed into breast milk. 1, 30

Pediatrics

Appropriate studies performed to date have not demonstrated pediatrics specific problems that would limit the usefulness of gabapentin in children ages 3-12. 44

Adolescents

Appropriate studies on the relationship of age to the effects of gabapentin have not been performed in the adolescent population. However, clinical trials that included a limited number of patients aged 12 to 18 years revealed no adolescence-specific problems. 30

Geriatrics

Plasma clearance of gabapentin is reduced in the elderly 1, 21, 22, 30 , probably due to age-related renal function decline. 1, 21, 22, 30 Dosage reduction 1, 21, 30 based on creatinine clearance 1, 21 is recommended. Further dosage adjustments should be based on clinical response. 36

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Gabapentin does not induce or inhibit the hepatic mixed oxidase enzymes responsible for drug metabolism 41.

Also, it does not interfere with the metabolism of commonly coadministered antiepileptic agents 41.

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Alcohol 24, 30 or

Central nervous system (CNS) depression-producing medications, other 24, 32 (see Appendix II)

(increased CNS depression may occur)

>> Antacids, especially aluminum- and magnesium-containing 1, 5, 20, 21, 30

(antacid taken with or within 2 hours after gabapentin reduces gabapentin"s bioavailability by 20% 1, 5, 20, 21 ; gabapentin should be taken at least 2 hours after antacid 1, 5, 42)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Dipstick tests for urinary protein (e.g., Ames N-Multistix SG, Chemstrip 3) 1, 31

(gabapentin causes a false positive result; the sulfosalicylic acid precipitation procedure should be used to detect urinary protein in patients taking gabapentin 1, 30)

With physiology/laboratory test values

White blood cell counts 1, 11, 14, 21, 30

(may be decreased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

>> Renal function impairment

(elimination may be prolonged in patients not receiving hemodialysis, 1, 4, 21, 26, 35 and shortened in patients during hemodialysis 21, 23 ; dosage adjustment based on creatinine clearance 35 is recommended 1, 3, 5, 9, 21, 26)

Sensitivity to gabapentin or any ingredients in the formulation 44, 1, 30

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Note: Adverse effects from gabapentin therapy are generally mild 9, 14, 30, 41 to moderate 14, 18, 19, 30, 41 in severity, and tend to diminish with continued use 6, 8, 12, 14, 21, 30.

Those indicating need for medical attention

Incidence more frequent

Ataxia 1, 2, 3, 5, 8, 9, 11, 13, 16, 21, 25, 30 (clumsiness or unsteadiness)¾may be dose-related 41, 42; nystagmus 1, 5, 8, 9, 11, 12, 15, 16, 21, 25, 27, 30 (continuous, uncontrolled, back-and-forth and/or rolling eye movements)

In pediatric patients 3 to 12 years of age

Neuropsychiatric problems, including emotional lability 44 (anxiety; behavior problems; crying ; false sense of well-being; mental depression ; reacting too quickly, too emotionally, or overreacting ; rapidly changing moods); hostility 44 (aggressive behavior; suspiciousness or distrust); hyperkinesia 44 (hyperactivity or increase in body movements; restlessness); and thought disorders 44 (concentration problems and change in school performance)
Incidence less frequent

Amnesia 1, 13, 14, 30 (loss of memory); depression, irritability, or other mood or mental changes 1, 13, 14, 30
Incidence rare

Leukopenia 1, 30 (usually asymptomatic ; rarely, fever or chills; cough or hoarseness ; lower back or side pain; painful or difficult urination)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Dizziness 1, 2, 3, 5, 6, 8, 9, 11, 12, 13, 14, 15, 16, 18, 21, 25, 27; fatigue 1, 2, 3, 5, 6, 8, 9, 11, 14, 16, 18, 21, 25, 30 (unusual tiredness or weakness); myalgia 1, 30 (muscle ache or pain); peripheral edema 1, 30 (swelling of hands, feet, or lower legs); somnolence 1, 2, 3, 5, 6, 8, 9, 11, 12, 13, 14, 16, 18, 21, 25, 27, 30 (drowsiness)¾may be dose-related 41, 42; tremor 1, 8, 9, 12, 13, 21, 30 (trembling or shaking); vision abnormalities, including blurred vision 1, 11, 12 and diplopia 1, 8, 9, 11, 13, 16, 21, 30 (double vision)
Incidence less frequent or rare

Asthenia 1, 11, 16 (weakness or loss of strength); back pain 41, 42; dryness of mouth or throat 1, 11, 16, 30; dysarthria 1, 11 (slurred speech); frequent urination 1, 8; gastrointestinal effects, including constipation 41, 42 , diarrhea 11, 13, 16 , dyspepsia 1, 12, 30 (indigestion); nausea 1, 6, 9, 11, 13, 16, 21 , and vomiting 1, 9, 14, 21; headache 6, 8, 9, 13, 15, 16, 21, 27; hypotension 1, 11, 16 (low blood pressure); impotence 41, 42 (decrease in sexual desire or ability); insomnia 11, 13, 16 (trouble in sleeping); rhinitis 1, 8, 9, 15, 21, 27, 30 (runny nose); tinnitus 1, 8 (noise in ears); trouble in thinking 1, 11, 13, 30; twitching 41, 42; weight gain 1, 3, 11, 14, 16, 30

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

Note: Some of the effects of gabapentin overdose may be similar to adverse effects seen at therapeutic doses; they may be more severe, or several adverse effects may occur together. Saturation of the carrier-mediated absorption pathway at higher gabapentin doses may limit drug absorption at the time of overdose and subsequently reduce the toxicity from overdose 34, 41.

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Diarrhea 1, 30, 34; diplopia 1, 30 (double vision); dysarthria 1, 30 (slurred speech); lethargy 1, 30, 34 (sluggishness); somnolence 1, 30 (drowsiness)
Treatment of overdose

Note: There is no specific antidote for gabapentin overdose.
Specific treatment¾Hemodialysis 1, 30 (may be indicated by clinical state or in patients with significant renal impairment) 30

Supportive care 1, 30 ¾Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Gabapentin (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to gabapentin
Use in the elderly¾Elderly patients may excrete gabapentin more slowly; dosage reduction based on creatinine clearance and dosage adjustment based on clinical response are recommended
Other medications, especially antacids
Other medical problems, especially renal function impairment
Proper use of this medication

>> Compliance with therapy; not taking more or less medicine than prescribed; not missing any doses

Importance of not exceeding 12-hour interval between any 2 doses while on 3-times-a-day dosing schedule

>> Importance of dissolving each dose as needed when a liquid dosage form is required; not dissolving any doses to save for later use

Missed dose: Taking as soon as possible; if less than 2 hours until next dose, taking missed dose immediately and taking next dose 1 to 2 hours later, then resuming regular dosing schedule; not doubling doses
>> Proper storage
Precautions while using this medication

>> Importance of regular visits to physician to check progress of therapy

>> Discussing alcohol use or use of other CNS depressants with physician

>> Possible blurred or double vision, dizziness, drowsiness, impairment of thinking or motor skills; caution when driving or doing jobs requiring alertness

Possible false positive results with dipstick tests for urinary protein; using the sulfosalicylic acid precipitation procedure to determine presence of urinary protein

>> Not discontinuing gabapentin abruptly; consulting physician about gradually reducing dosage

Side/adverse effects

Ataxia; nystagmus; amnesia; depression, irritability, or other mood or mental changes; leukopenia

General Dosing Information

Gabapentin dosage is titrated to clinical effect 2, 15, 21 , not to plasma concentration. 2

Adverse effects are generally mild 9, 30 to moderate 18, 19, 30 in severity, and tend to diminish with continued use of gabapentin. 6, 8, 12, 14, 21, 30

Anticonvulsant medications should not be discontinued abruptly because of the possibility of increased seizure frequency. 1, 30 If gabapentin is to be discontinued, or if another anticonvulsant medication is to be added to the patient's therapy, the change should be made gradually, 1, 2, 21, 30 over a minimum period of one week, 1, 21, 30 to avoid loss of seizure control. 21

Diet/Nutrition

Gabapentin may be taken with or without food. 41, 42

Oral Dosage Forms

GABAPENTIN CAPSULES

Usual adult and adolescent dose

Anticonvulsant¾
Oral, initially 300 mg three times a day 42, 43.

The dosage may be gradually increased 1, 2, 3 based on clinical response. 2, 3, 15, 21 Dosages of 900 to 1800 mg per day are effective for most patients 1, 42.

However, dosages as high as 2400 to 3600 mg per day have been well tolerated. 1

Note: Dosage may be increased more slowly to avoid CNS adverse effects. 37

When taking gabapentin three times a day, the maximum time between doses should not exceed twelve hours. 1, 30

For patients with renal function impairment: See Usual geriatric dose .
For patients undergoing hemodialysis: Oral, 300 to 400 mg initially 1, 30, 42 for patients who have never received gabapentin 1 , then 200 to 300 mg following each four hours of hemodialysis. 1, 30, 42

Usual adult and adolescent prescribing limits

3600 mg per day. 37, 38

Usual pediatric dose

Anticonvulsant¾
Children 3 years to 12 years¾ The starting dose should range from 10 to 15 mg per kg per day, divided into three doses. The effective dose should be reached by upward titration over a period of approximately 3 days. 44

· Ages 5 years and older¾The effective dose is 25 to 35 mg per kg per day given in divided doses (three times a day) 44

· Ages 3 years and 4 years¾ The effective dose is 40 mg per kg per day given in divided doses (three times a day) 44

Children 12 years of age and over: See Usual adult and adolescent dose. 1

Usual pediatric prescribing limits

Dosages of up to 50 mg per kg per day have been well tolerated in long-term clinical studies. 44

Usual geriatric dose

Anticonvulsant¾
Oral, initial dosage recommendations, based on creatinine clearance, are 1, 30, 35 as follows. Dosage adjustments may be made based on clinical response. 36

Creatinine Clearance	Total Daily Dose	Dosage Regimen (mg)

(mL per minute)	(mg per day)	
> 60	1200	400 three times a day
30 to 60	600	300 two times a day
15 to 30	300	300 once a day
<15	150	300 once every other day

Strength(s) usually available

U.S.¾100 mg (Rx)[Neurontin (lactose)]

300 mg (Rx)[Neurontin (lactose)]

400 mg (Rx)[Neurontin (lactose)] 44

Canada¾100 mg (Rx)[Neurontin (lactose) 30]

300 mg (Rx)[Neurontin (lactose) 30]

400 mg (Rx)[Neurontin (lactose) 30]

Note: Capsule shells may contain gelatin, titanium dioxide, silicon dioxide, sodium lauryl sulfate, yellow iron oxide, red iron oxide, and FD&C Blue No. 2. 30

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C 1, 30 (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Preparation of dosage form:

For patients who cannot take oral solids¾Individual doses may be dissolved in juice or sprinkled over soft foods, such as applesauce, immediately before use. However, gabapentin solutions degrade over time and should be freshly prepared and taken immediately after preparation. 24, 39, 40

Auxiliary labeling:

- May cause blurred vision.
- May cause dizziness.
- May cause drowsiness. Alcohol may intensify this effect.

GABAPENTIN ORAL SOLUTION

Usual adult and adolescent dose

SeeGabapentin Capsules

Usual adult and adolescent prescribing limits

SeeGabapentin Capsules

Usual pediatric dose

SeeGabapentin Capsules

Children 12 years of age and over: See Usual adult and adolescent dose. 1

Usual pediatric prescribing limits

See Gabapentin Capsules

Usual geriatric dose

SeeGabapentin Capsules

Strength(s) usually available

U.S.¾ 50 mg per mL (Rx)[Neurontin (glycerin) (xylitol) (purified water) (artificial cool strawberry anise flavor)]

Canada¾Not commercially available.

Packaging and storage:

Store refrigerated, 2 °- 8 °C (36°-46 °F) 44

Auxiliary labeling:

· May cause blurred vision.
· May cause dizziness.
· May cause drowsiness. Alcohol may intensify this effect.

GABAPENTIN TABLETS

Usual adult and adolescent dose

SeeGabapentin Capsules

Usual adult and adolescent prescribing limits

SeeGabapentin Capsules

Usual pediatric dose

SeeGabapentin Capsules

Children 12 years of age and over: See Usual adult and adolescent dose. 1

Usual pediatric prescribing limits

See Gabapentin Capsules

Usual geriatric dose

SeeGabapentin Capsules

Strength(s) usually available

U.S.¾600 mg (Rx)[Neurontin (poloxamer 407) (copolyvidonum) (cornstarch) (magnesium stearate) (hydroxypropyl cellulose) (talc) (candellila wax) (purified water) (synthetic black iron oxide) (pharmaceutical shellac) (pharmaceutical glaze) (propylene glycol) (ammonium hydroxide) (isopropyl alcohol) (n-butyl alcohol)]

800 mg (Rx)[Neurontin (poloxamer 407) (copolyvidonum) (cornstarch) (magnesium stearate) (hydroxypropyl cellulose) (talc) (candellila wax) (purified water) (synthetic yellow iron oxide) (synthetic red iron oxide) (hydroxypropyl methylcellulose) (propylene glycol) (methanol) (isopropyl alcohol) (deionized water)]

Canada¾Not commercially available.

Packaging and storage:

Store at 25 °C (77 °F); excursions permitted to 15° and 30 °C (59° and 86 °F) 44

Auxiliary labeling:

- May cause blurred vision.
- May cause dizziness.
- May cause drowsiness. Alcohol may intensify this effect.