PARKE-DAVIS

NEURONTIN*

(gabapentin capsules)

100 mg, 300 mg, 400 mg Capsules
Antiepileptic Agent

ACTION AND CLINICAL PHARMACOLOGY

Gabapentin exhibits antiseizure activity in mice and rats both in the maximal electroshock and in the pentylenetetrazol seizure models.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but does not interact with GABA receptors, it is not metabolized to GABA or to GABA agonists, and it is not an inhibitor of GABA uptake or degradation. Gabapentin at concentrations up to 100 μM did not demonstrate affinity for other receptor sites such as benzodiazepine, glutamate, glycine or N-methyl-D-aspartate receptors nor does it interact with neuronal sodium channels or L-type calcium channels.

The mechanism of action of gabapentin has not yet been established, however, it is unlike that of the commonly used anticonvulsant drugs.

In vitro studies with radiolabelled gabapentin have revealed a gabapentin binding site in rat brain tissues including neocortex and hippocampus. The identity and function of this binding site remain to be elucidated.

Pharmacokinetics

Adults: Following oral administration of Neurontin (gabapentin), peak plasma concentrations are observed within 2 to 3 hours. Absolute bioavailability of a 300 mg dose of Neurontin capsules is approximately 59%. At doses of 300 and 400 mg, gabapentin bioavailability is unchanged following multiple dose administration. Gabapentin elimination from plasma is best described by linear pharmacokinetics. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours in subjects with normal renal function.

Plasma gabapentin concentrations are dose-proportional at doses of 300 to 400 mg q8h, ranging between 1 μg/mL and 10 μg/mL, but are less than dose-proportional above the clinical range (> 600 mg q8h). There is no correlation between plasma levels and efficacy. Gabapentin pharmacokinetics are not affected by repeated administration, and steady state plasma concentrations are predictable from single dose data.

Gabapentin is not appreciably metabolized in humans, is eliminated solely by renal excretion, and can be removed from plasma by hemodialysis.

Gabapentin does not induce or inhibit hepatic mixed function oxidase enzymes responsible for drug metabolism, does not interfere with the metabolism of commonly coadministered antiepileptic drugs, and is minimally bound to plasma proteins.

Food has no effect on the rate or extent of absorption of gabapentin.

Table 1 summarizes the mean steady-state pharmacokinetic parameters of Neurontin capsules.

Table 1: Summary of Neurontin (gabapentin) Mean Steady-State Pharmacokinetic Parameters in Adults Following Q8H Administration

Pharmacokinetic Parameter	300 mg (n = 7)	400 mg (n = 11)
C_{max} (μg/mL)	4.02	5.50
T_{max} (hr)	2.7	2.1
$T_{1/2}$ (hr)	5.2	6.1
AUC(0-∞) (μg•hr/mL)	24.8	33.3
AE%[1]	NA	63.6

[1]Amount excreted in urine (% of dose)
NA = Not available

In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid are approximately 20% of corresponding steady-state trough plasma concentrations.

Elderly: Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in subjects under 30 years of age to about 125 mL/min in subjects over 70 years of age. Renal clearance (CLr) of gabapentin also declined with age; however, this decrease can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age-related compromised renal function (See Dosage and Administration).

Renal Impairment: In patients with impaired renal function, gabapentin clearance is markedly reduced and dosage adjustment is necessary (See Table 5 in Dosage and Administration).

Hemodialysis: In a study in anuric subjects (n = 11), the apparent elimination half-life of gabapentin on non-dialysis days was about 132 hours; dialysis three times a week (4 hours duration) lowered the apparent half-life of gabapentin by about 60%, from 132 hours to 51 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (See Table 5 in Dosage and Administration).

Pediatric: There are no pharmacokinetic data available in children under 18 years of age.

Hepatic Impairment: Because gabapentin is not appreciably metabolized in humans, no study was performed in patients with hepatic impairment.

Clinical Trials

In placebo-controlled trials in patients not satisfactorily controlled with current antiepileptic drugs, Neurontin (gabapentin), when added to current antiepileptic therapy, was superior to placebo in reducing the frequency of both simple and complex partial seizures and secondarily generalized tonic-clonic seizures. Further analysis of data indicated a higher efficacy for complex partial seizures and secondarily generalized tonic-clonic seizures as compared to all seizure types. Doses ranged from 900 to 1800 mg/day, with a median dose of 1200 mg/day.

Long-term, open, uncontrolled studies in drug-resistant patients for periods of up to 18 months demonstrated that doses up to 2400 mg/day did not result in anything unusual in the type or frequency of adverse events.

INDICATIONS AND CLINICAL USE

Neurontin (gabapentin) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

Neurontin (gabapentin) is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

PRECAUTIONS

General

Neurontin (gabapentin) is not considered effective in the treatment of absence seizures and should therefore be used with caution in patients who have mixed seizure disorders that include absence seizures.

Tumorigenic Potential

Gabapentin produced an increased incidence of acinar cell adenomas and carcinomas in the pancreas of male rats, but not female rats or in mice, in oncogenic studies with doses of 2000 mg/kg which resulted in plasma concentrations 14 times higher than those occurring in humans at the maximum recommended dose of 2400 mg/day. The relevance of these pancreatic acinar cell tumours in male rats to humans in unknown, particularly since tumours of ductal rather than acinar cell origin are the predominant form of human pancreatic cancer.

Drug Discontinuation

As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. When in the judgement of the clinician there is a need for dose reduction, discontinuation or substitution with alternative medication, this should be done gradually over a minimum of one week.

Occupational Hazards

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were somnolence, ataxia, fatigue and nystagmus. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that Neurontin does not affect them adversely.

Drug Interactions

Antiepileptic Agents: **There is no interaction between Neurontin and phenytoin, valproic acid, carbamazepine, or phenobarbital. Consequently, Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the plasma concentrations of gabapentin or the other antiepileptic drugs.**

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

Oral Contraceptives: Coadministration of Neurontin with the oral contraceptive Norlestrin* does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Antacids: Coadministration of Neurontin with an aluminum and magnesium-based antacid reduces gabapentin bioavailability by up to 24%. Although the clinical significance of this decrease is not known, coadministration of similar antacids and gabapentin is not recommended.

Probenecid: Renal excretion of gabapentin is unaltered by probenecid.

Cimetidine: A slight decrease in renal excretion of gabapentin observed when it is coadministered with cimetidine is not expected to be of clinical importance.

Use in Pregnancy

No evidence of impaired fertility or harm to the fetus due to gabapentin administration was revealed in reproduction studies in mice at doses up to 62 times, and in rats and rabbits at doses up to 31 times the human dose of 2400 mg/day. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.

Use in Lactation

It is not known if gabapentin is excreted in human milk, and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from gabapentin, breast-feeding is only recommended if the potential benefit outweighs the potential risks.

Use in Children

Systematic studies to establish safety and efficacy in children have not been performed. Data in 39 patients between the ages of 12 and 18 years included in the double-blind, placebo-controlled trials showed that gabapentin was superior to placebo in reducing seizure frequency. Safety data showed that the incidence of adverse events in this group of patients were similar to those observed in older individuals.

Use in the Elderly

Systematic studies in geriatric patients have not been conducted. Adverse clinical events reported among 59 patients over the age of 65 years treated with Neurontin did not differ from those reported for younger individuals. The small number of individuals evaluated and the limited duration of exposure limits the strength of any conclusions reached about the influence of age, if any, on the kind and incidence of adverse events associated with the use of Neurontin.

As Neurontin is eliminated primarily by renal excretion, dosage adjustment may be required in elderly patients because of declining renal function (See Dosage and Administration).

Use in Renal Impairment

Gabapentin clearance is markedly reduced in this patient population and dosage reduction is necessary (See Table 5 in Dosage and Administration).

Laboratory Test

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin. Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or other antiepileptic drugs.

For urinary protein determination the sulfosalicylic acid precipitation procedure is recommended, as false positive readings were reported with the Ames N-Multistix SG® dipstick test, when gabapentin or placebo was added to other anticonvulsant drugs.

ADVERSE REACTIONS

Incidence in Controlled Clinical Trials

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 1% of patients with partial seizures participating in placebo-controlled studies. In these studies, either Neurontin (at doses of 600, 900, 1200 or 1800 mg/day) or placebo were added to the patient's current antiepileptic drug therapy.

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

Among the treatment-emergent adverse events occurring in Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n = 54, from one controlled study) experienced approximately a two-fold increase, as compared to patients on lower doses of 600 to 1200 mg/day (n = 489, from several controlled studies), in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Adverse events were usually mild to moderate in intensity, with a median time to resolution of 2 weeks.

Since Neurontin was administered most often in combination with other antiepileptic agents, it was not possible to determine which agent(s) was associated with adverse events.

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Table 2: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Add-On Trials (Events in a Least 1% of Neurontin Patients and Numerically More Frequent than in the Placebo Group)

BODY SYSTEM/ ADVERSE EVENT (AE)	NEURONTIN[a] n = 543 %	Placebo[a] n = 378 %
BODY AS A WHOLE:		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
CARDIOVASCULAR:		
Vasodilatation	1.1	0.3
DIGESTIVE SYSTEM:		
Dyspepsia	2.2	0.5
Dry Mouth or Throat	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
HEMATOLOGIC AND LYMPHATIC SYSTEMS:		
Leukopenia	1.1	0.5
MUSCULOSKELETAL SYSTEM:		
Myalgia	2.0	1.9
Fracture	1.1	0.8
NERVOUS SYSTEM:		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.8
Abnormal Thinking	1.7	1.3
Twitching	1.3	0.5
Abnormal Coordination	1.1	0.3
RESPIRATORY SYSTEM:		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
SKIN AND APPENDAGES:		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
UROGENITAL SYSTEM:		
Impotence	1.5	1.1
SPECIAL SENSES:		
Diplopia	5.9	1.9
Amblyopia	4.2	1.1
LABORATORY DEVIATIONS:		
WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy

Data from long-term, open, uncontrolled studies shows that Neurontin treatment does not result in any new or unusual adverse events.

Withdrawal From Treatment Due to Adverse Events

Approximately 6.4% of the 543 patients who received Neurontin in the placebo-controlled studies withdrew due to adverse events. In comparison, approximately 4.5% of the 378 placebo-controlled participants withdrew due to adverse events during these studies. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue, nausea and/or vomiting and dizziness (all at 0.6%).

Other Adverse Events Observed in All Clinical Trials

Adverse events that occurred in at least 1% of the 2074 individuals who participated in all clinical trials are described below, except those already listed in the previous table:

Body As a Whole : aesthenia, malaise, facial edema
Cardiovascular System : hypertension
Digestive System : anorexia, flatulence, gingivitis
Hematologic and Lymphatic System : purpura; most often described as bruises resulting from physical trauma
Musculoskeletal System : arthralgia
Nervous System : vertigo, hyperkinesia, parasthesia, anxiety, hostility, decreased or absent reflexes
Respiratory System : pneumonia
Special Senses : abnormal vision

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute, life-threatening toxicity has not been observed with Neurontin (gabapentin) overdoses of up to 49 grams ingested at one time. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patients clinical state or in patients with significant renal impairment. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, reduce toxicity from overdoses.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

DOSAGE AND ADMINISTRATION

Adults

The usual effective maintenance dose is 900 to 1200 mg/day. Treatment should be initiated with 300 to 400 mg/day. Titration to an effective dose, in increments of 300 mg or 400 mg/day, can progress rapidly and can be accomplished over three days (see Table 3). Neurontin is given orally with or without food.

Table 3: Titration Schedule

DOSE	Day 1	Day 2	400 mg
900 mg/day	300 mg OD	300 mg BID	300 mg TID
1200 mg/day	400 mg OD	400 mg BID	400 mg TID

Data from clinical trials suggest that doses higher than 1200 mg/day may have increased efficacy in some patients; however, higher doses may also increase the incidence of adverse events (See Adverse Reactions).

Daily maintenance doses should be given in three equally divided doses (See Table 4), and the maximum time between doses in a three times daily schedule should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations in order to optimize Neurontin therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, Neurontin may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

Table 4: Maintenance Dosage Schedule

Total Daily Dose (mg/day)	Schedule
900	300 mg TID
1200	400 mg TID
1800	2 X 300 mg TID
2400	2 x 400 mg TID

Dosage adjustment in elderly patients due to declining renal function and in patients with renal impairment or undergoing hemodialysis is recommended as follows:

Table 5: Maintenance Dosage of Neurontin in Adults With Reduced Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose	Dose Regimen (mg)
> 60	1200 mg	400 Three times a day
30-60	600 mg	300 Twice a day
15-30	300 mg	300 Once a Day
< 15	150 mg	300 Once Daily Every Other Day
Hemodialysis[a]	—	200-300[b]

[a] Loading dose of 300 to 400 mg
[b] Maintenance dose of 200 to 300 mg Neurontin following each 4 hours of hemodialysis

Children Over 12 Years of Age

The dosage used in a limited number of patients in this age group was 900-1200 mg/day. Doses above 1200 mg/day have not been investigated.

AVAILABILITY OF DOSAGE FORMS

Neurontin (gabapentin) capsules are supplied as follows:

100 mg capsules; Hard gelatin SUPRO® capsules with white opaque body and cap printed with "PD" on one side and "Neurontin 100 mg" on the other. Bottles of 100 capsules.

300 mg capsules; Hard gelatin SUPRO® capsules with yellow opaque body and cap printed with "PD" on one side and "Neurontin 300 mg" on the other. Bottles of 100 capsules.

400 mg capsules; Hard gelatin SUPRO® capsules with orange opaque body and cap printed with "PD" on one side and "Neurontin 400 mg" on the other. Bottles of 100 capsules.

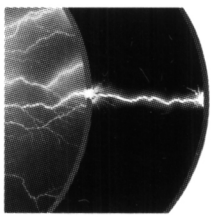
Composition

Capsules contain gabapentin, lactose, corn starch, and talc. Capsule shells may contain gelatin, titanium dioxide, silicon dioxide, sodium lauryl sulfate, yellow iron oxide, red iron oxide, and FD&C Blue No. 2.

Stability and Storage Recommendations

Store at controlled room temperature 15-30°C.

Product Monograph available upon request.



NEURONTIN* (gabapentin capsules)

Easy to add-on

PARKE-DAVIS

Scarborough, Ontario M1L 2N3

*T.M. Warner-Lambert Company, Parke-Davis Division, Warner-Lambert Canada Inc., auth. user.

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See pages ix, xix.

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