

Neurontin[®] (gabapentin) Capsules
Neurontin[®] (gabapentin) Tablets
Neurontin[®] (gabapentin) Oral Solution

DESCRIPTION

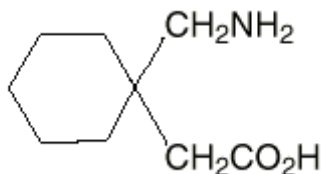
Neurontin[®] (gabapentin) Capsules, Neurontin (gabapentin) Tablets, and Neurontin (gabapentin) Oral Solution are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution containing 250 mg/5 mL of gabapentin.

The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.

The inactive ingredients for the tablets are poloxamer 407, copolyvidonum, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax and purified water.

The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor.

Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. The structural formula of gabapentin is:



Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} 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 .

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In

particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice (e.g. spinal nerve ligation models, streptozocin-induced diabetes model, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test). Gabapentin did not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase, acetic acid abdominal constriction test, footpad heat irradiation test). The relevance of these models to human pain is not known.

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify GABA_A or GABA_B radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.

Gabapentin was tested in radioligand binding assays at concentrations up to 100 μ M and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism

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_{max}).

Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 \pm 6 L (Mean \pm SD). In patients with epilepsy, steady-state predose (C_{min}) 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 (see Special Populations: Patients With Renal Insufficiency, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see DOSAGE AND ADMINISTRATION, Table 6).

Special Populations: Adult Patients With Renal Insufficiency: Subjects (N=60) with renal insufficiency (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.

Dosage adjustment in adult patients with compromised renal function is necessary (see DOSAGE AND ADMINISTRATION). 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.

Dosage adjustment in patients undergoing hemodialysis is necessary (see DOSAGE AND ADMINISTRATION).

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

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_r) and CL_r 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. Reduction of gabapentin dose may be required in patients who have age related compromised renal function. (See PRECAUTIONS, Geriatric Use, and DOSAGE AND ADMINISTRATION.)

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 TID. 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).

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.

Clinical Studies

Postherpetic Neuralgia

Neurontin was evaluated for the management of postherpetic neuralgia (PHN) in 2 randomized, double-blind, placebo-controlled, multicenter studies; N=563 patients in the intent-to-treat (ITT) population (Table 1). Patients were enrolled if they continued to have pain for more than 3 months after healing of the herpes zoster skin rash.

TABLE 1. Controlled PHN Studies: Duration, Dosages, and Number of Patients

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

^a Given in 3 divided doses (TID)

Each study included a 1-week baseline during which patients were screened for eligibility and 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. Dosages were then to be titrated in 600 to 1200 mg/day increments at 3- to 7-day intervals to target dose over 3 to 4 weeks. In Study 1, patients were continued on lower doses if not able to achieve the target dose. During baseline and treatment, 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 (baseline mean pain score for Studies 1 and 2 combined was 6.4). Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication).

Both studies showed significant differences from placebo at all doses tested.

A significant reduction in weekly mean pain scores was seen by Week 1 in both studies, and significant differences 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 these changes for Studies 1 and 2.

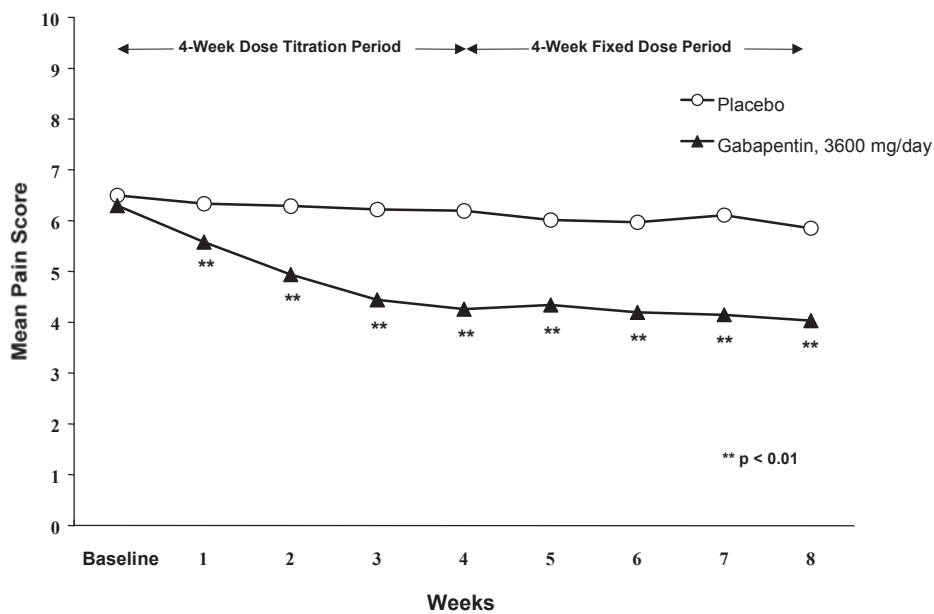


Figure 1. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 1

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