HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEURONTIN safely and effectively. See full prescribing information for NEURONTIN.

NEURONTIN® (gabapentin) capsules, for oral use
NEURONTIN® (gabapentin) tablets, for oral use
NEURONTIN® (gabapentin) oral solution
Initial U.S. Approval: 1993

----------INDICATIONS AND USAGE----------
NEURONTIN is indicated for:
- Postherpetic neuralgia in adults (1)
- Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy (1)

----------DOSAGE AND ADMINISTRATION----------
- Postherpetic Neuralgia (2.2)
  - Dose can be titrated up as needed to a dose of 1800 mg/day
  - Day 1: Single 300 mg dose
  - Day 2: 600 mg/day (i.e., 300 mg two times a day)
  - Day 3: 900 mg/day (i.e., 300 mg three times a day)
- Epilepsy with Partial Onset Seizures (2.3)
  - Patients 12 years of age and older: starting dose is 300 mg three times daily; may be titrated up to 600 mg three times daily
  - Patients 3 to 11 years of age: starting dose range is 10 to 15 mg/kg/day, given in three divided doses; recommended dose in patients 3 to 4 years of age is 40 mg/kg/day, given in three divided doses; the recommended dose in patients 5 to 11 years of age is 25 to 35 mg/kg/day, given in three divided doses. The recommended dose is reached by upward titration over a period of approximately 3 days
- Dose should be adjusted in patients with reduced renal function (2.4, 2.5)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 100 mg, 300 mg, and 400 mg (3)
- Tablets: 600 mg, and 800 mg (3)
- Oral Solution: 250 mg/5mL (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to gabapentin or its ingredients (4)

----------WARNINGS AND PRECAUTIONS----------
- Drug Reaction with Eosinophilia and Systemic Symptoms (Multiorgan hypersensitivity): discontinue NEURONTIN if an alternative etiology cannot be established (5.1)
- Driving impairment: warn patients not to drive until they have gained sufficient experience with NEURONTIN to assess whether it will impair their ability to drive (5.2)
- Somnolence/Sedation and Dizziness: NEURONTIN may impair the patient's ability to operate complex machinery (5.3)
- Increased seizure frequency may occur in patients with seizure disorders if NEURONTIN is abruptly discontinued (5.4)
- Suicidal Behavior and Ideation: monitor for suicidal thoughts and behavior (5.5)
- Neuropsychiatric Adverse Reactions in Children 3-12 Years of Age: monitor for such events (5.6)

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

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: based on animal data, may cause fetal harm (8.1)
- Pediatric Use: effectiveness as adjunctive therapy in treatment of partial seizures in pediatric patients below the age of 3 years has not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NEURONTIN® is 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 Administration Information

Administer NEURONTIN orally with or without food.

NEURONTIN capsules should be swallowed whole with water.

Inform patients that, should they break the scored 600 mg or 800 mg NEURONTIN tablet in order to administer a half-tablet, they should take the unused half-tablet as the next dose. Half-tablets not used within 28 days of breaking the scored tablet should be discarded.

If the NEURONTIN 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).

2.2 Dosage for Postherpetic Neuralgia

In adults with postherpetic neuralgia, NEURONTIN 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 1800 mg/day (600 mg three times a day). In clinical studies, efficacy was demonstrated over a range of doses from 1800 mg/day to 3600 mg/day with comparable effects across the dose range; however, in these clinical studies, the additional benefit of using doses greater than 1800 mg/day was not demonstrated.

2.3 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 NEURONTIN is 300 mg to 600 mg three times a day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. Administer NEURONTIN three times a day using 300 mg or 400 mg capsules, or 600 mg or 800 mg tablets. The maximum time between doses should not exceed 12 hours.

Pediatric Patients Age 3 to 11 years

The starting dose range is 10 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 NEURONTIN in patients 3 to 4 years of age is 40 mg/kg/day, given in three divided doses. The recommended maintenance dose of NEURONTIN in patients 5 to 11 years of age is 25 mg/kg/day to 35 mg/kg/day, given in three divided doses. NEURONTIN 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.

2.4 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):

TABLE 1. NEURONTIN Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥ 60	900 to 3600	300 TID	400 TID	600 TID	800 TID	1200 TID
>30 to 59	400 to 1400	200 BID	300 BID	400 BID	500 BID	700 BID
>15 to 29	200 to 700	200 QD	300 QD	400 QD	500 QD	700 QD
15[a]	100 to 300	100 QD	125 QD	150 QD	200 QD	300 QD
		Post-Hemodialysis Supplemental Dose (mg)[b]				
Hemodialysis		125[b]	150[b]	200[b]	250[b]	350[b]

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

[a] 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).

[b] Patients 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 (CLCr) 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:

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

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

2.5 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.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 100 mg: white hard gelatin capsules printed with "PD" on the body and "Neurontin/100 mg" on the cap
- 300 mg: yellow hard gelatin capsules printed with "PD" on the body and "Neurontin/300 mg" on the cap
- 400 mg: orange hard gelatin capsules printed with "PD" on the body and "Neurontin/400 mg" on the cap

Tablets:

- 600 mg: white elliptical film-coated scored tablets debossed with "NT" and "16" on one side
- 800 mg: white elliptical film-coated scored tablets debossed with "NT" and "26" on one side

Oral solution: 250 mg per 5 mL (50 mg per mL), clear colorless to slightly yellow solution

4 CONTRAINDICATIONS

NEURONTIN is 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)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has occurred with NEURONTIN. 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 is variable in its expression, and other organ systems not noted here may be involved.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are

present, the patient should be evaluated immediately. NEURONTIN should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.2 Effects on Driving and Operating Heavy Machinery

Patients taking NEURONTIN should not drive until they have gained sufficient experience to assess whether NEURONTIN impairs their ability to drive. Driving performance studies conducted with a prodrug 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 NEURONTIN, can be imperfect. The duration of driving impairment after starting therapy with NEURONTIN is unknown. Whether the impairment is related to somnolence *[see Warnings and Precautions (5.3)]* or other effects of NEURONTIN is unknown.

Moreover, because NEURONTIN causes somnolence and dizziness *[see Warnings and Precautions (5.3)]*, patients should be advised not to operate complex machinery until they have gained sufficient experience on NEURONTIN to assess whether NEURONTIN impairs their ability to perform such tasks.

5.3 Somnolence/Sedation and Dizziness

During the controlled epilepsy trials in patients older than 12 years of age receiving doses of NEURONTIN up to 1800 mg daily, somnolence, dizziness, and ataxia were reported at a greater rate in patients receiving NEURONTIN compared to placebo: i.e., 19% in drug versus 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 NEURONTIN 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 NEURONTIN, in dosages up to 3600 mg per day: i.e., 21% in NEURONTIN-treated patients versus 5% in placebo-treated patients for somnolence and 28% in NEURONTIN-treated patients versus 8% in placebo-treated patients for dizziness. Dizziness and somnolence were among the most common adverse reactions leading to discontinuation of NEURONTIN.

5.4 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 NEURONTIN was 0.6% (3 of 543) vs. 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with NEURONTIN 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 or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with NEURONTIN is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with NEURONTIN.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including NEURONTIN, increase 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 27,863 AED-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 mechanisms 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 (5-100 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 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

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 NEURONTIN 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 be 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.

5.6 Neuropsychiatric Adverse Reactions (Pediatric Patients 3-12 Years of Age)

Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system 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 3–12 years of age, the incidence of these adverse reactions was: emotional lability 6% (gabapentin-treated patients) vs. 1.3% (placebo-treated patients); hostility 5.2% vs. 1.3%; hyperkinesia 4.7% vs. 2.9%; and thought disorder 1.7% vs. 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.

5.7 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 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following

discontinuation of NEURONTIN. Without knowledge of the background incidence and recurrence in a similar population not treated with NEURONTIN, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

5.8 Sudden and Unexplained Death in Patients with Epilepsy

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

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 NEURONTIN (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the NEURONTIN program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the NEURONTIN cohort and the accuracy of the estimates provided.

6 ADVERSE REACTIONS

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

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Somnolence/Sedation and Dizziness *[see Warnings and Precautions (5.3)]*
- Withdrawal Precipitated Seizure, Status Epilepticus *[see Warnings and Precautions (5.4)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Neuropsychiatric Adverse Reactions (Pediatric Patients 3-12 Years of Age) *[see Warnings and Precautions (5.5)]*
- Sudden and Unexplained Death in Patients with Epilepsy [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

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

Postherpetic Neuralgia

The most common adverse reactions associated with the use of NEURONTIN 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 NEURONTIN 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 NEURONTIN-treated patients were dizziness, somnolence, and nausea.

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

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

Body System/ Adverse Reaction	NEURONTIN 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	5	1
Constipation	4	2
Nausea	4	3
Vomiting	3	2
Metabolic and Nutritional Disorders		
Peripheral edema	8	2
Weight gain	2	0
Hyperglycemia	1	0
Nervous System		
Dizziness	28	8
Somnolence	21	5
Ataxia	3	0
Abnormal thinking	3	0
Abnormal gait	2	0
Incoordination	2	0
Respiratory System		
Pharyngitis	1	0
Special Senses		
Amblyopia[a]	3	1
Conjunctivitis	1	0
Diplopia	1	0
Otitis media	1	0

[a] 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 associated with the use of NEURONTIN 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 reported with the use of NEURONTIN in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility *[see Warnings and Precautions (5.4)]*.

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

Table 4 lists adverse reactions that occurred in at least 1% of NEURONTIN-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the NEURONTIN group. In these studies, either NEURONTIN 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

Body System/ Adverse Reaction	NEURONTIN[a] N=543 %	Placebo[a] N=378 %
Body As A Whole		
Fatigue	11	5
Weight gain	3	2
Back Pain	2	1
Peripheral Edema	2	1
Cardiovascular		
Vasodilatation	1	0

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

Body System/ Adverse Reaction	NEURONTIN[a] N=543 %	Placebo[a] N=378 %
Digestive System		
Dyspepsia	2	1
Dry Mouth or Throat	2	1
Constipation	2	1
Dental Abnormalities	2	0
Nervous System		
Somnolence	19	9
Dizziness	17	7
Ataxia	13	6
Nystagmus	8	4
Tremor	7	3
Dysarthria	2	1
Amnesia	2	0
Depression	2	1
Abnormal thinking	2	1
Abnormal coordination	1	0
Respiratory System		
Pharyngitis	3	2
Coughing	2	1
Skin and Appendages		
Abrasion	1	0
Urogenital System		
Impotence	2	1
Special Senses		
Diplopia	6	2
Amblyopia[b]	4	1

[a] Plus background antiepileptic drug therapy
[b] Amblyopia was often described as blurred vision.

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

The overall incidence of adverse reactions and the types of adverse reactions seen were similar among men and women treated with NEURONTIN. The incidence of adverse reactions increased slightly with increasing age in patients treated with either NEURONTIN or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse reactions by race.

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

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

Body System/ Adverse Reaction	NEURONTIN[a] N=119 %	Placebo[a] N=128 %
Body As A Whole		
Viral Infection	11	3
Fever	10	3
Weight gain	3	1
Fatigue	3	2
Digestive System		
Nausea and/or Vomiting	8	7
Nervous System		
Somnolence	8	5
Hostility	8	2
Emotional Lability	4	2
Dizziness	3	2
Hyperkinesia	3	1
Respiratory System		
Bronchitis	3	1
Respiratory Infection	3	1

[a] Plus background antiepileptic drug therapy

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

6.2 Postmarketing Experience

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

Hepatobiliary disorders: jaundice
Investigations: blood glucose fluctuation, elevated creatine kinase, elevated liver function tests
Metabolism and nutrition disorders: hyponatremia
Nervous system disorders: movement disorder
Musculoskeletal and connective tissue disorders: rhabdomyolysis
Reproductive system and breast disorders: breast enlargement
Skin and subcutaneous tissue disorders: angioedema, erythema multiforme, Stevens-Johnson syndrome.

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

7 DRUG INTERACTIONS

7.1 Other Antiepileptic Drugs

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs *[see Clinical Pharmacology (12.3)]*.

7.2 Hydrocodone

Coadministration of NEURONTIN (125 to 500 mg) decreases hydrocodone C_{max} and AUC values in a dose-dependent manner. The C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg Neurontin and 21% to 22% lower, respectively, after administration of 500 mg NEURONTIN . Hydrocodone increases gabapentin AUC values by 14% *[see Clinical Pharmacology (12.3)]*.

7.3 Morphine

A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg NEURONTIN capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine *[see Patient Counseling Information (17)]*. Morphine pharmacokinetic parameter values were not affected by administration of NEURONTIN 2 hours after morphine. The magnitude of interaction at other doses is not known.

7.4 Maalox® (aluminum hydroxide, magnesium hydroxide)

The mean bioavailability of gabapentin was reduced by about 20% with concomitant use of an antacid (Maalox®) containing magnesium and aluminum hydroxides. It is recommended that gabapentin be taken at least 2 hours following Maalox administration *[see Clinical Pharmacology (12.3)]*.

7.5 Drug/Laboratory Test Interactions

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. In nonclinical studies in mice, rats, and rabbits, gabapentin was developmentally toxic when administered to pregnant animals at doses similar to or lower than those used clinically. NEURONTIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pregnant mice received oral doses of gabapentin (500, 1000, or 3000 mg/kg/day) during the period of organogenesis, embryo-fetal toxicity (increased incidences of skeletal variations) was observed at the two highest doses. The no-effect dose for embryo-fetal developmental toxicity in mice was 500 mg/kg/day or approximately ½ of the maximum recommended human dose (MRHD) of 3600 mg/kg on a body surface area (mg/m^2) basis.

In studies in which rats received oral doses of gabapentin (500 to 2000 mg/kg/day), during pregnancy, adverse effect on offspring development (increased incidences of hydroureter and/or hydronephrosis) were observed at all doses. The lowest effect dose for developmental toxicity in rats is approximately equal to the MRHD on a mg/m^2 basis.

When pregnant rabbits were treated with gabapentin during the period of organogenesis, an increase in embryo-fetal mortality was observed at all doses tested (60, 300, or 1500 mg/kg). The lowest effect dose for embryo-fetal developmental toxicity in rabbits is less than the MRHD on a mg/m^2 basis.

In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere with activity of the α2δ subunit of voltage-activated calcium channels, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.

To provide information regarding the effects of *in utero* exposure to NEURONTIN, physicians are advised to recommend that pregnant patients taking NEURONTIN enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.3 Nursing Mothers

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, NEURONTIN should be used in women who are nursing only if the benefits clearly outweigh the risks.

8.4 Pediatric Use

Safety and effectiveness of NEURONTIN in the management of postherpetic neuralgia in pediatric patients have not been established.

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established *[see Clinical Studies (14.2)]*.

8.5 Geriatric Use

The total number of patients treated with NEURONTIN in controlled clinical trials in patients with postherpetic neuralgia was 336, of which 102 (30%) were 65 to 74 years of age, and 168 (50%) were 75 years of age and older. There was a larger treatment effect in patients 75 years of age and older compared with younger patients who received the same dosage. Since gabapentin is almost exclusively eliminated by renal excretion, the larger treatment effect observed in patients ≥75 years may be a consequence of increased gabapentin exposure for a given dose that results from an age-related decrease in renal function. However, other factors cannot be excluded. The types and incidence of adverse reactions were similar across age groups except for peripheral edema and ataxia, which tended to increase in incidence with age.

Clinical studies of NEURONTIN in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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 *[see Dosage and Administration (2.4), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Dosage adjustment in adult patients with compromised renal function is necessary *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. Pediatric patients with renal insufficiency have not been studied.

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

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse and abuse. These individuals were taking higher than recommended doses of gabapentin for unapproved uses. Most of the individuals described in these reports had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances. 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. development of tolerance, self-dose escalation, and drug-seeking behavior).

9.3 Dependence

There are rare postmarketing reports of individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances. The dependence and abuse potential of gabapentin has not been evaluated in human studies.

10 OVERDOSAGE

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

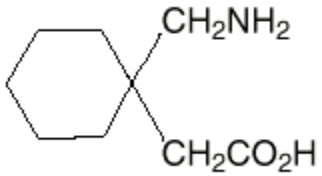
Acute oral overdoses of NEURONTIN up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea, were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

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

11 DESCRIPTION

The active ingredient in NEURONTIN capsules, tablets, and oral solution is gabapentin, which has the chemical name 1-(aminomethyl)cyclohexaneacetic acid.
The molecular formula of gabapentin is $C_9H_{17}NO_2$ and the molecular weight is 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.

Each Neurontin capsule contains 100 mg, 300 mg, or 400 mg of gabapentin and the following inactive ingredients: lactose, cornstarch, talc, gelatin, titanium dioxide, FD&C Blue No. 2, yellow iron oxide (300 mg and 400 mg only), and red iron oxide (400 mg only).

Each Neurontin tablet contains 600 mg or 800 mg of gabapentin and the following inactive ingredients: poloxamer 407, copovidone, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, and candelilla wax

Neurontin oral solution contains 250 mg of gabapentin per 5 mL (50 mg per mL) and the following inactive ingredients: glycerin, xylitol, purified water, and artificial cool strawberry anise flavor.

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 α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown.

12.3 Pharmacokinetics

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability

Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{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±6 L (mean ±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. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Special Populations

Adult Patients with Renal Impairment

Subjects (N=60) with renal impairment (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*. Pediatric patients with renal insufficiency have not been studied.

Hemodialysis

In a study in anuric adult subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

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 (CLr) and CLr adjusted for

body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function *[see Dosage and Administration (2.4) and Use in Specific Populations (8.5)]*.

Pediatric

Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day given three times a day. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day *[see Dosage and Administration (2.3)]*.

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.

Drug Interactions

In Vitro Studies

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

In Vivo Studies

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin

In a single (400 mg) and multiple dose (400 mg three times a day) study of NEURONTIN 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 NEURONTIN (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 NEURONTIN (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 NEURONTIN and 21% to 22% lower, respectively, after administration of 500 mg NEURONTIN. 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 NEURONTIN 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 NEURONTIN 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine

In the presence of cimetidine at 300 mg QID (N=12), the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus, cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive

Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg three times a day; N=13). The C_{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

Gabapentin was administered orally to mice and rats in 2-year carcinogenicity studies. No evidence of drug-related carcinogenicity was observed in mice treated at doses up to 2000 mg/kg/day. At 2000 mg/kg, the plasma gabapentin exposure (AUC) in mice is approximately 2 times that in humans at the MRHD of 3600 mg/day. In rats, increases in the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving the highest dose (2000 mg/kg), but not at doses of 250 or 1000 mg/kg/day. At 1000 mg/kg, the plasma gabapentin exposure (AUC) in rats is approximately 5 times that in humans at the MRHD.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and 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; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

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

14 CLINICAL STUDIES

14.1 Postherpetic Neuralgia

NEURONTIN was evaluated for the management of postherpetic neuralgia (PHN) in two randomized, double-blind, placebo-controlled, multicenter studies. The intent-to-treat (ITT) population consisted of a total of 563 patients with pain for more than 3 months after healing of the herpes zoster skin rash (Table 6).

TABLE 6. 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 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 the target dose over 3 to 4 weeks. Patients recorded their pain in a daily diary using an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). A mean pain score during baseline of at least 4 was required for randomization. Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication).

Both studies demonstrated efficacy compared to placebo at all doses tested.

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

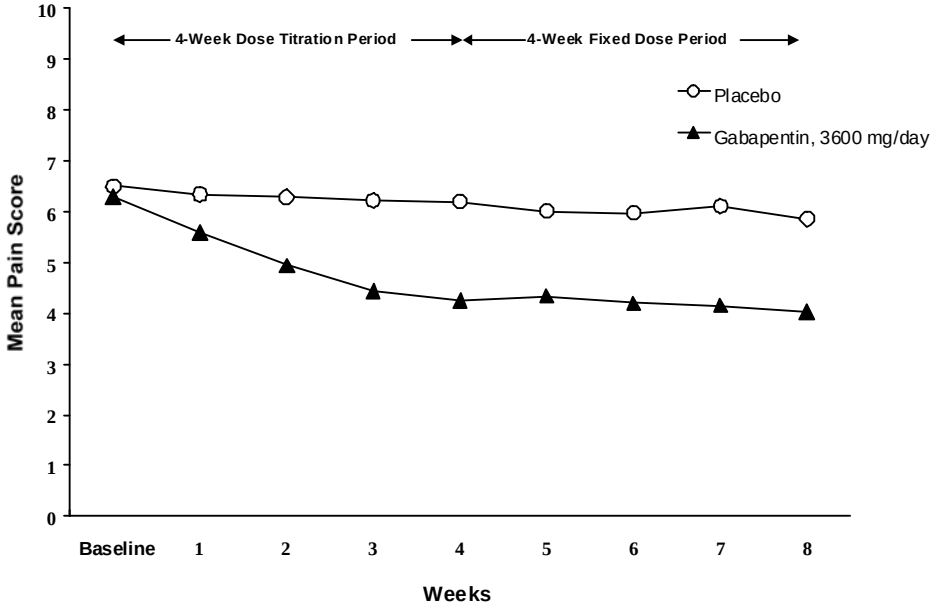


Figure 1. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 1

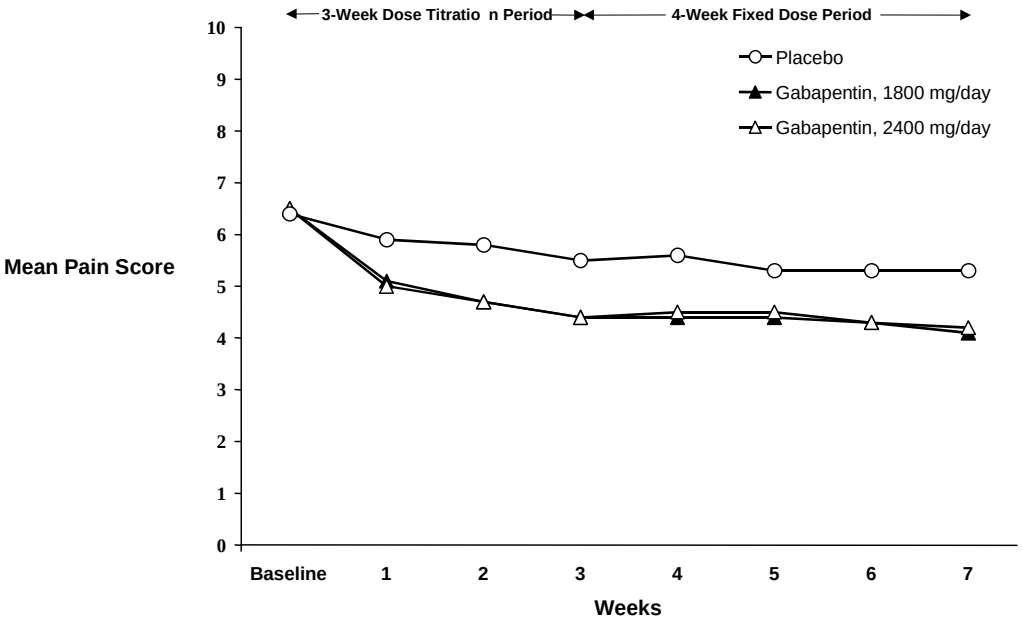


Figure 2. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 2

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

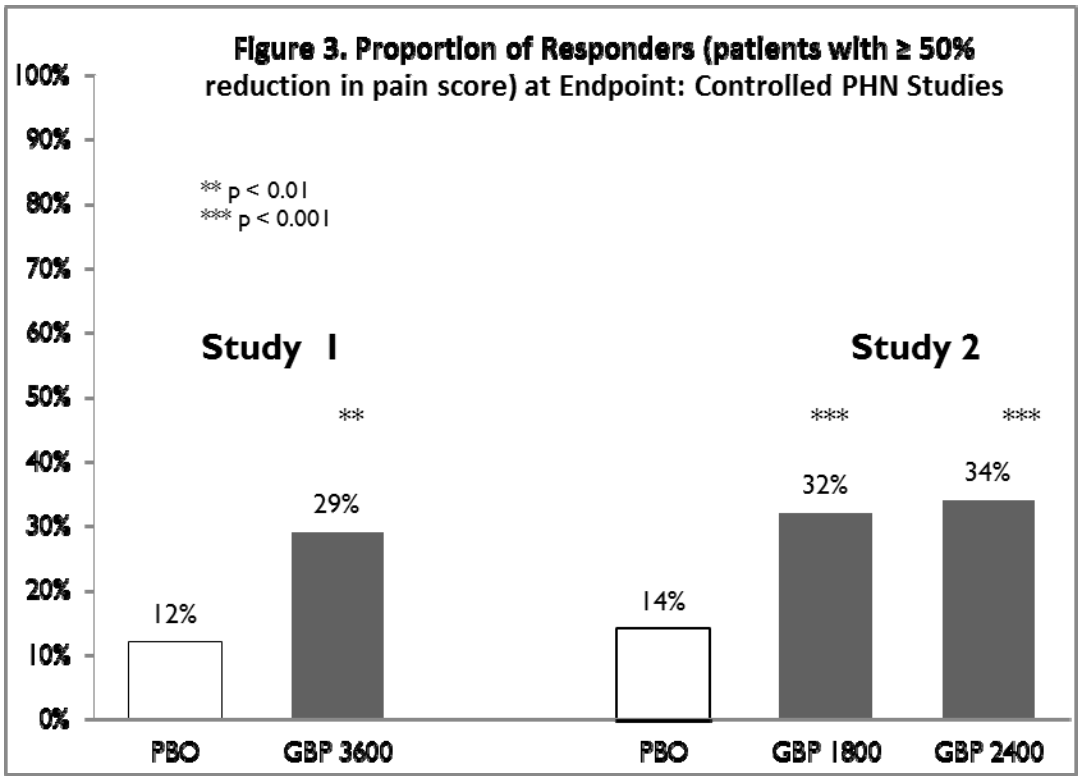


Figure 3. Proportion of Responders (patients with ≥50% reduction in pain score) at Endpoint: Controlled PHN Studies

14.2 Epilepsy for Partial Onset Seizures (Adjunctive Therapy)

The effectiveness of NEURONTIN as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, NEURONTIN or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), in which B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared NEURONTIN 1200 mg/day, in three divided doses, with placebo. Responder rate was 23% (14/61) in the NEURONTIN group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the NEURONTIN group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily NEURONTIN 1200 mg/day, in three divided doses (N=101), with placebo (N=98). Additional smaller NEURONTIN dosage groups (600 mg/day, N=53; 1800 mg/day, N=54) were also studied for information regarding dose response. Responder rate was higher in the NEURONTIN 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the NEURONTIN 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ($p = 0.224$). A better response was seen in the NEURONTIN 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared NEURONTIN 900 mg/day, in three divided doses (N=111), and placebo (N=109). An additional NEURONTIN 1200 mg/day dosage group (N=52) provided dose-response data. A statistically significant difference in responder rate was seen in the NEURONTIN 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the NEURONTIN 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day NEURONTIN (-0.184) compared to placebo.

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

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

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

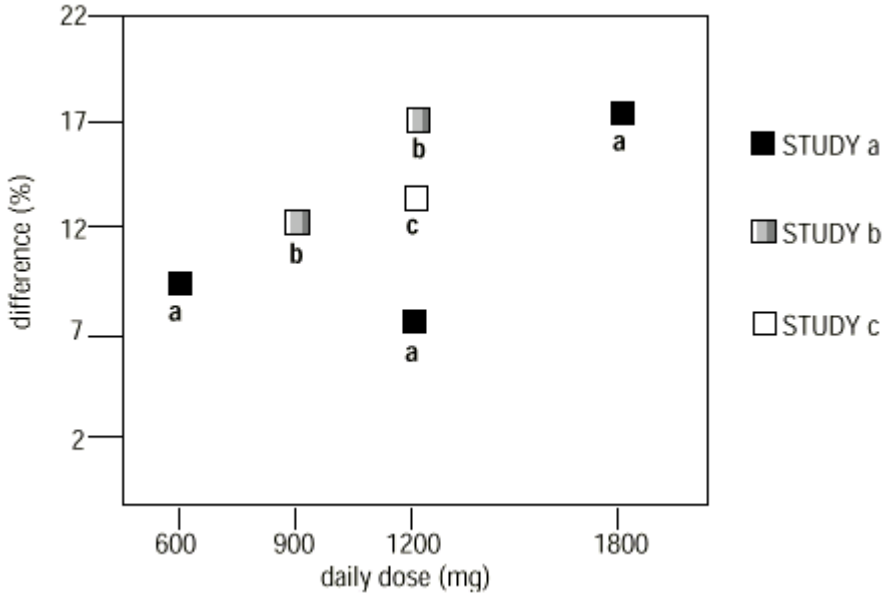


Figure 4. Responder Rate in Patients Receiving NEURONTIN Expressed as a Difference from Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age with Partial Seizures

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo-assigned patients attaining a 50% or greater reduction in

seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

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

A fourth study in pediatric patients age 3 to 12 years compared 25 – 35 mg/kg/day NEURONTIN (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the NEURONTIN group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for NEURONTIN (21%) was not significantly different from placebo (18%).

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

16 HOW SUPPLIED/STORAGE AND HANDLING

NEURONTIN (gabapentin) capsules, tablets, and oral solution are supplied as follows:

100 mg capsules:

White hard gelatin capsules printed with “PD” on the body and “Neurontin/100 mg” on the cap; available in:
Bottles of 100: NDC 0071-0803-24

300 mg capsules:

Yellow hard gelatin capsules printed with “PD” on the body and “Neurontin/300 mg” on the cap; available in:
Bottles of 100: NDC 0071-0805-24
Unit dose 50’s: NDC 0071-0805-40

400 mg capsules:

Orange hard gelatin capsules printed with “PD” on the body and “Neurontin/400 mg” on the cap; available in:
Bottles of 100: NDC 0071-0806-24
Unit dose 50’s: NDC 0071-0806-40

600 mg tablets:

White elliptical film-coated scored tablets debossed with “NT” and “16” on one side; available in:
Bottles of 100: NDC 0071-0513-24

800 mg tablets:

White elliptical film-coated scored tablets debossed with “NT” and “26” on one side; available in:
Bottles of 100: NDC 0071-0401-24

250 mg per 5 mL oral solution:

Clear colorless to slightly yellow solution; each 5 mL of oral solution contains 250 mg of gabapentin; available in:
Bottles containing 470 mL: NDC 0071-2012-23

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

Store NEURONTIN Oral Solution refrigerated, 2°C to 8°C (36°F to 46°F)

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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

Effects on Driving and Operating Heavy Machinery
Inform patients that NEURONTIN may cause a significant driving impairment. Accordingly, advise them not to drive a car until they have gained sufficient experience on NEURONTIN to assess whether NEURONTIN impairs their ability to drive, although patients’ ability to determine their level of impairment can be unreliable. Inform patients that it is not known how long this effect lasts. They should be told the same thing regarding the operation of heavy machinery.

Dizziness and Somnolence
Advise patients that NEURONTIN may cause dizziness, somnolence, and other symptoms and signs of CNS depression. Accordingly, advise them neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on NEURONTIN to gauge whether or not it affects their mental and/or motor performance adversely.

Suicidal Thinking and Behavior

Counsel the patient, their caregivers, and families that AEDs, including NEURONTIN, may increase the risk of suicidal thoughts and behavior. Advise patients of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients to report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.3)]*.

Use in Pregnancy

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy *[see Use in Specific Populations (8.1) and (8.3)]*.

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

This product's label may have been updated. For full prescribing information, please visit www.pfizer.com.

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MEDICATION GUIDE

NEURONTIN (Neu rŏn' tĭn)
(Gabapentin)

Capsules, Tablets, and Oral Solution

Read the Medication Guide before you start taking NEURONTIN and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

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

NEURONTIN can cause serious side effects including:

1. **Suicidal Thoughts. Like other antiepileptic drugs, NEURONTIN 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 NEURONTIN without first talking to a healthcare provider.

- Stopping NEURONTIN 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 NEURONTIN 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. NEURONTIN may cause a serious or life-threatening allergic reaction that may affect your skin or other parts of your body such as your liver or blood cells. You may or may not have rash when you get this type of reaction. It may cause you to be hospitalized or to stop NEURONTIN. Call a healthcare provider right away if you have any of the following symptoms:

- skin rash
- hives
- fever
- swollen glands that do not go away
- swelling of your lip and 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 NEURONTIN.

What is NEURONTIN?

NEURONTIN is 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 NEURONTIN?

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

What should I tell my healthcare provider before taking NEURONTIN?

Before taking NEURONTIN, 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
- are pregnant or plan to become pregnant. It is not known if NEURONTIN can harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking NEURONTIN. You and your healthcare provider will decide if you should take NEURONTIN while you are pregnant.
    - If you become pregnant while taking NEURONTIN, 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.
- are breast-feeding or plan to breast-feed. NEURONTIN can pass into breast milk. You and your healthcare provider should decide how you will feed your baby while you take NEURONTIN.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking NEURONTIN with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take NEURONTIN?

- Take NEURONTIN exactly as prescribed. Your healthcare provider will tell you how much NEURONTIN to take.
    - Do not change your dose of NEURONTIN without talking to your healthcare provider.

- If you take NEURONTIN tablets and break a tablet in half, the unused half of the tablet should be taken at your next scheduled dose. Half tablets not used within 28 days of breaking should be thrown away
- Take NEURONTIN capsules with water.

- NEURONTIN tablets can be taken with or without food. If you take an antacid containing aluminum and magnesium, such as Maalox®, Mylanta®, Gelusil®, Gaviscon®, or Di-Gel®, you should wait at least 2 hours before taking your next dose of NEURONTIN.

If you take too much NEURONTIN, call your healthcare provider or your local Poison Control Center right away at 1-800-222-1222.

What should I avoid while taking NEURONTIN?

- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking NEURONTIN without first talking with your healthcare provider. Taking NEURONTIN with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how NEURONTIN affects you. NEURONTIN can slow your thinking and motor skills.

What are the possible side effects of NEURONTIN?

NEURONTIN may cause serious side effects including:

See "What is the most important information I should know about NEURONTIN?"

- problems driving while using NEURONTIN. See "What I should avoid while taking Neurontin?"
- sleepiness and dizziness
- **The most common side effects of NEURONTIN include:**
  - lack of coordination
  - viral infection
  - feeling drowsy
  - nausea and vomiting
  - difficulty with speaking
  - tremor
  - swelling, usually of legs and feet
  - feeling tired
  - fever
  - jerky movements
  - difficulty with coordination
  - double vision
  - unusual eye movement

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of NEURONTIN. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NEURONTIN?

- Store NEURONTIN Capsules and Tablets between 68°F to 77°F (20°C to 25°C).
- Store NEURONTIN Oral Solution in the refrigerator between 36°F to 46°F (2°C to 8°C).

Keep NEURONTIN and all medicines out of the reach of children.

General information about the safe and effective use of NEURONTIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NEURONTIN for a condition for which it was not prescribed. Do not give NEURONTIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about NEURONTIN. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NEURONTIN that was written for healthcare professionals.

For more information go to http://www.pfizer.com. or call 1-800-438-1985.

What are the ingredients in NEURONTIN?

Active ingredient: gabapentin

Inactive ingredients in the capsules: lactose, cornstarch, talc, gelatin, titanium dioxide and FD&C Blue No. 2.

The 300-mg capsule shell also contains: yellow iron oxide.

The 400-mg capsule shell also contains: red iron oxide, and yellow iron oxide.

Inactive ingredients in the tablets: poloxamer 407, copovidone, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, and candelilla wax

Inactive ingredients in the oral solution: glycerin, xylitol, purified water, and artificial flavor.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

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