

May 17, 2004

Food and Drug Administration
Dockets Management Branch
Room 1061
5630 Fishers Lane
Rockville, MD 20852

**Re: Citizen Petition to Request Addition of Postmarketing Suicide Reports to the
Neurontin (Pfizer/Parke-Davis) Labeling**

Dear Sir/Madam,

Pursuant to 21 CFR 10.30, the enclosed Citizen Petition has been prepared to request the amplification of the current Neurontin labeling to properly reflect the significant number of postmarketing reports of completed suicides, suicidal attempts and suicidal ideations. The current Neurontin labeling provides no information relating to these postmarketing reports in the section entitled Postmarketing and Other Experience. The enclosed submission includes three copies of the Citizen Petition.

Please contact the undersigned if you have any questions or require additional information.

Very Truly Yours,



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2004P-0235

CP 1

**THE UNITED STATES DEPARTMENT OF
HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

May 17, 2004

**Petition to Require Pfizer, Inc. (and its
Subsidiaries Including Parke-Davis and
The Warner-Lambert Co.) to Revise the
Labeling of Neurontin® and Add Warnings,
Precautions, and Adverse Event Information
Relating to the Escalating Numbers of
Postmarketing Reports of Completed
Suicides and other Suicide-Related Events**

Docket No.

**Submitted by: Keith Altman
Director of Adverse Event Analyses
Finkelstein and Partners
436 Robinson Avenue
Newburgh, NY 12550**

CITIZEN PETITION

Keith Altman and Finkelstein and Partners submit this petition to request action by the Food and Drug Administration (FDA) relating to the drug product, Neurontin (gabapentin). The petitioners request that FDA require the manufacturer of Neurontin, Pfizer, Inc. and its subsidiaries including Parke-Davis and the Warner Lambert Co. (Pfizer) to amplify the Neurontin labeling to specifically warn prescribers and health care professionals of the escalating number of postmarketing reports of completed suicides by patients receiving Neurontin for both its labeled and unlabeled indications. The proposed actions include the addition of a Black Box Warning, amplified Precautions and Adverse Event information and dissemination of "Dear Doctor" and "Dear Healthcare Professional" letters. This Petition is submitted pursuant to 21 CFR 10.35, and relating to 21 CFR 201.5, 201.128, and Sections 201(n), 502(a), 502(f)(1) and 505 of the Federal Food, Drug and Cosmetic Act.

I. Introduction and Action Requested

Pfizer, Inc. manufactures and markets oral dosage forms of Neurontin (gabapentin). The current FDA approved labeling for Neurontin provides for its use in patients with Postherpetic Neuralgia and Epilepsy. However, recent reports have noted that a large percentage (approximately 80-90%) of Neurontin's U.S. sales is actually derived from sales for non-FDA approved uses. Pfizer has recently agreed to plead guilty to criminal wrongdoing in their illegal marketing practices designed to promote these unapproved uses. Neurontin enjoys wide use in the U.S. with annual sales exceeding two billion dollars.

The current FDA-approved labeling does not warn prescribers and patients to the increasing dangers of completed suicide and suicide-related events associated with Neurontin, as evidenced by the escalating numbers of postmarketing reports. For example, the current labeling provides no information to warn of completed suicides, although FDA's postmarketing Adverse Event Reporting System (A.E.R.S) database recorded a substantial increase in these fatalities during the first six months of 2003. Eight completed suicides were reported from 1998 through 2002. Seventeen additional suicides have been recorded for the period between January – June, 2003.

The petitioners request that the FDA Commissioner act immediately to require the labeling additions noted below. This action is especially critical because of Neurontin's wide use for nonlabeled indications and for which proper medical monitoring instructions have not been established by FDA.

- **Bolded Black Box Warning:**

<p style="text-align: center;">Psychiatric Disorders</p> <p>Neurontin has been associated with completed suicides, suicide attempts and suicidal ideations, in postmarketing reports. Prescribers should carefully monitor patients prior to initiation of Neurontin therapy and throughout its period of use. (See Precautions and Adverse Reactions)</p>
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- **PRECAUTIONS**

Suicide-Related Events:

Neurontin use has been associated with completed suicides, suicide attempts and suicidal ideations in postmarketing reports. Patients should be prospectively cautioned regarding the possibility of these events and advised to report any symptomatology immediately. Patients should also be carefully observed throughout therapy for signs of suicide-related symptoms.

- **ADVERSE REACTIONS (addition to existing section)**

Postmarketing and Other Experience:

“In the postmarketing period, there have been multiple reports of completed suicides, suicide attempts and suicidal ideations in patients receiving Neurontin for a variety of uses” (continuation of existing text).

- **Dear Doctor and Dear Healthcare Professional Letters**

The Petitioners believe the gravity of the reported events of completed suicides dictate health care providers be alerted to this information as soon as possible. These letters should be provided to all U.S. prescribers because of the high use of Neurontin for unlabeled indications encompassing several disciplines of medicine. Letters should also be sent to pharmacists, medical associations and hospitals to allow the most rapid and most extensive dissemination of this critical safety information. These letters should also provide guidance to prescribers in the proper screening of potential patients for the use of Neurontin. Advice should also be given to prescribers for the monitoring of suicide-related events in patients following the initiation of Neurontin and throughout its period of use.

II. Statement of Factual Grounds

A. The Current Neurontin Labeling Fails to Comply with Labeling Requirements

Under Sections 201(n), 502(a), 502(F)(1), and 505 of the Federal Food, Drug and Cosmetic Act and 21 CFR Sections 201.5 and 201.128, it is mandated that prescription drug product labeling must include all materials and facts necessary for their safe and effective use and must not be false and misleading in any particular including the failure to state material facts.

The current Neurontin labeling is provided with Attachment 1. This labeling does not address, in any manner, the postmarketing reports of completed suicides, suicide attempts and suicidal ideations. As such, the current labeling violates the applicable regulations by failure to state material facts. The Neurontin labeling does note that suicide gestures were rarely reported in the Neurontin premarketing clinical trials and that suicidal(*sic*) was infrequently reported in the clinical trials. It is important to note that completed suicides are not included, in any manner, in the Neurontin labeling. Pfizer acknowledges that postmarketing reports of completed suicides are currently unlabeled events when providing these as expedited reports to FDA's A.E.R.S. database (Attachment 2).

Given the recent sharp increase in the number of completed suicides reported in 2003, and the continued reporting of postmarketing attempted suicides and suicidal ideations, it is imperative that this postmarketing information be included in the Neurontin professional labeling as quickly as possible. Pfizer recognizes the need to emphasize postmarketing experience because the current Neurontin labeling includes a specific section for postmarketing experience. This information currently alerts prescribers to the following events: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder such as dyskinesia and Stevens-Johnson syndrome. Obviously, it is as important for prescribers and patients to be made aware of increasing numbers of completed suicides, as it is to possible changes in clinical laboratory parameters.

B. The FDA's A.E.R.S. Database Indicates an Escalating Number of Completed Suicides, Suicide Attempts and Suicidal Ideations Received by Pfizer and FDA.

The Petitioners have evaluated FDA's A.E.R.S. database (provided by N.T.I.S.) and have summarized, below, the number of suicide-related events reported by Pfizer and others to FDA for the period 1998-2003. To date,

only the events reported for the first six months of 2003 have been released by FDA.

The following Tables provide both the number of events reported by Pfizer to FDA (Pfizer Count) and the total number of events received by FDA (Total Count). Because of the possibility of duplicate reports submitted by multiple manufacturers to FDA, the Petitioners will focus on the reports prepared and submitted by Pfizer. The suicide related events include the Preferred Terms of completed suicide, suicide attempt and suicidal ideation. The listed events adopt FDA's procedures and include the "last best case" data in order to consider the data from the latest follow-up of an individual report. If there are no follow-up reports, then the initial report data are used. The drug names employed in the search procedure were Neurontin and gabapentin.

Petitioners' Summary of Neurontin A.E.R.S. Events

Table 1. Completed Suicides

Preferred Term	Date	Total Count	Pfizer Count
COMPLETED SUICIDE	1998Q1	0	0
COMPLETED SUICIDE	1998Q2	0	0
COMPLETED SUICIDE	1998Q3	0	0
COMPLETED SUICIDE	1998Q4	0	0
COMPLETED SUICIDE	1999Q1	1	0
COMPLETED SUICIDE	1999Q2	0	0
COMPLETED SUICIDE	1999Q3	2	0
COMPLETED SUICIDE	1999Q4	0	0
COMPLETED SUICIDE	2000Q1	0	0
COMPLETED SUICIDE	2000Q2	3	1
COMPLETED SUICIDE	2000Q3	1	0
COMPLETED SUICIDE	2000Q4	1	0
COMPLETED SUICIDE	2001Q1	1	1
COMPLETED SUICIDE	2001Q2	1	0
COMPLETED SUICIDE	2001Q3	5	0
COMPLETED SUICIDE	2001Q4	7	0
COMPLETED SUICIDE	2002Q1	2	0
COMPLETED SUICIDE	2002Q2	3	2
COMPLETED SUICIDE	2002Q3	7	1
COMPLETED SUICIDE	2002Q4	8	3
COMPLETED SUICIDE	2003Q1	12	6
COMPLETED SUICIDE	2003Q2	16	11

Petitioners' Summary of Neurontin A.E.R.S. Events

Table 2. Suicide Attempts

Preferred Term	Date	Total Count	Pfizer Count
SUICIDE ATTEMPT	1998Q1	0	0
SUICIDE ATTEMPT	1998Q2	0	0
SUICIDE ATTEMPT	1998Q3	2	0
SUICIDE ATTEMPT	1998Q4	0	0
SUICIDE ATTEMPT	1999Q1	2	1
SUICIDE ATTEMPT	1999Q2	2	0
SUICIDE ATTEMPT	1999Q3	7	0
SUICIDE ATTEMPT	1999Q4	2	1
SUICIDE ATTEMPT	2000Q1	4	3
SUICIDE ATTEMPT	2000Q2	2	0
SUICIDE ATTEMPT	2000Q3	7	2
SUICIDE ATTEMPT	2000Q4	6	2
SUICIDE ATTEMPT	2001Q1	7	3
SUICIDE ATTEMPT	2001Q2	7	4
SUICIDE ATTEMPT	2001Q3	2	1
SUICIDE ATTEMPT	2001Q4	4	0
SUICIDE ATTEMPT	2002Q1	6	2
SUICIDE ATTEMPT	2002Q2	5	2
SUICIDE ATTEMPT	2002Q3	4	1
SUICIDE ATTEMPT	2002Q4	6	0
SUICIDE ATTEMPT	2003Q1	6	3
SUICIDE ATTEMPT	2003Q2	8	1

Petitioners' Summary of Neurontin A.E.R.S. Events
Table 3. Suicidal Ideation

Preferred Term	Date	Total Count	Pfizer Count
SUICIDAL IDEATION	1998Q1	0	0
SUICIDAL IDEATION	1998Q2	0	0
SUICIDAL IDEATION	1998Q3	0	0
SUICIDAL IDEATION	1998Q4	2	1
SUICIDAL IDEATION	1999Q1	4	4
SUICIDAL IDEATION	1999Q2	3	1
SUICIDAL IDEATION	1999Q3	2	0
SUICIDAL IDEATION	1999Q4	4	1
SUICIDAL IDEATION	2000Q1	4	4
SUICIDAL IDEATION	2000Q2	3	1
SUICIDAL IDEATION	2000Q3	3	0
SUICIDAL IDEATION	2000Q4	4	0
SUICIDAL IDEATION	2001Q1	3	1
SUICIDAL IDEATION	2001Q2	3	2
SUICIDAL IDEATION	2001Q3	4	1
SUICIDAL IDEATION	2001Q4	5	1
SUICIDAL IDEATION	2002Q1	7	5
SUICIDAL IDEATION	2002Q2	8	2
SUICIDAL IDEATION	2002Q3	6	0
SUICIDAL IDEATION	2002Q4	13	3
SUICIDAL IDEATION	2003Q1	8	3
SUICIDAL IDEATION	2003Q2	8	0

C. The Petitioners' Review of the Completed Suicide Reports and Other Related Events Submitted to FDA's A.E.R.S. Database Confirms the Necessity and Urgency of the Proposed Labeling Additions.

In the first six months of 2003, Pfizer reported 17 new events of completed suicide. These events represent approximately 6% of all the expedited adverse events reported by Pfizer for Neurontin in this same period. These 17 new events of completed suicide also represent a sharp and startling increase in the number of reported postmarketing suicides. Obviously, any event representing these contributions to the total numbers of serious and fatal events must be specifically listed in all product labeling. Fatality-associated events also require highlighted positioning in all Neurontin labeling and promotional pieces.

The Petitioners have appended summaries of the completed suicide reports provided to A.E.R.S. in Attachment 2. These reports have been designated by Pfizer as expedited reports and are derived from healthcare professionals, consumers, and the scientific literature. When provided, the indications note the unlabeled uses of peripheral neuropathy, bipolar disorders and pain. Neurontin is considered the primary suspect agent in all but one of these suicide fatality reports. Neurontin is listed as sole therapy in approximately twenty-five percent of these reports.

Suicide attempts and suicidal ideations have been steadily noted in postmarketing reports submitted between 1998 and 2003. To date, Pfizer has reported a total of 26 reports of suicide attempts and 30 reports of suicidal ideations.

Given the frequency, magnitude and critical nature of these reports, it is readily apparent that postmarketing reports of completed suicide, as well as suicide attempts and ideations must be immediately added to the Neurontin insert. This information must be highlighted in all three labeling sections related to drug product safety. Given the critical safety issues evidenced in completed suicide reports, a Black Box Warning is also required to increase the prescribers' focus on these potentially fatal events.

The new labeling information must also be disseminated as expeditiously as possible to healthcare providers. The Petitioners believe all U.S. prescribers and healthcare associated professionals must be provided with immediate Dear Doctor and Dear Healthcare Professional letters outlining the escalating number of fatal suicide events. Additional methods and venues of communication with prescribers and patients may also be warranted because of Neurontin's significant commercialization for non-labeled indications by a wide variety of prescribers.

III. Environmental Impact Statement

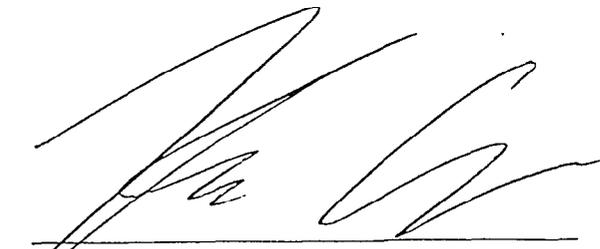
The Petitioners believe the actions requested in this Petition provide no significant environmental impact. The requested actions will not introduce any substance into the environment and is categorically excluded pursuant to 21 CFR 25.30.

IV. Economic Impact Statement

This information is only to be submitted when requested by the Commissioner following a review of this petition.

V. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioners which are unfavorable to the petition.



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May 17, 2004

Attachment 1

Current Neurontin Labeling

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

DESCRIPTION

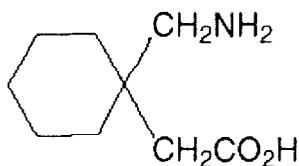
Neurontin[®] (gabapentin) Capsules, Neurontin[®] (gabapentin) Tablets, and Neurontin[®] (gabapentin) Oral Solution are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution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

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

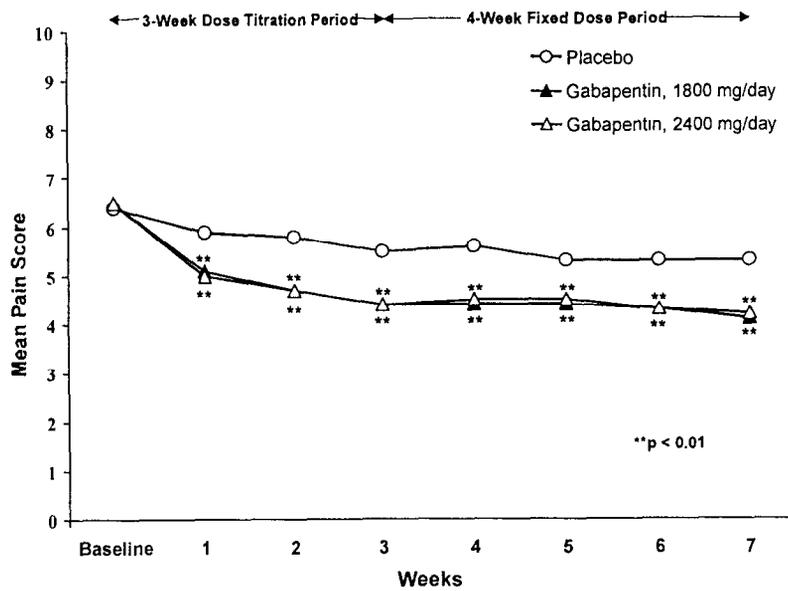


Figure 2. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 2

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).

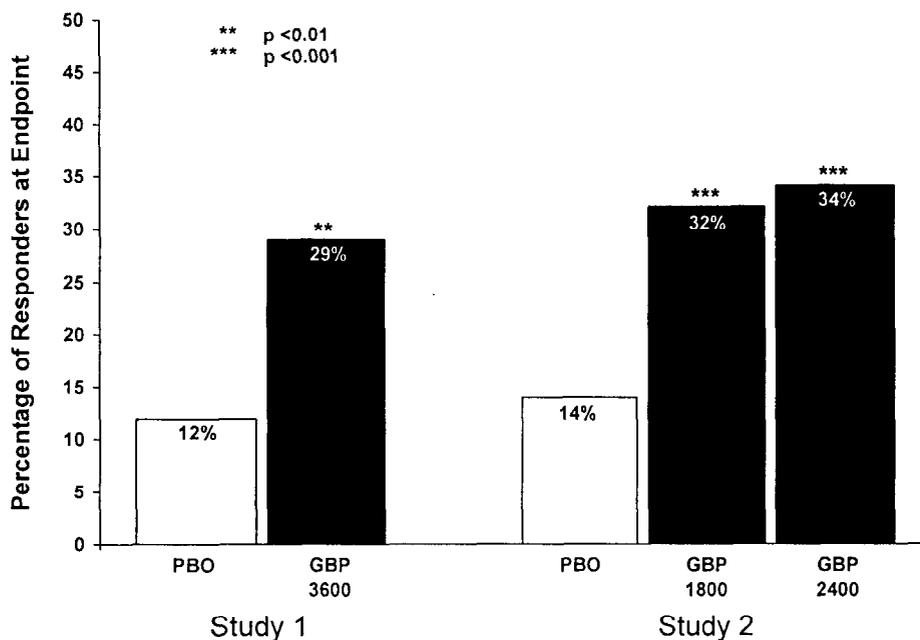


Figure 3. Proportion of Responders (patients with $\geq 50\%$ reduction in pain score) at Endpoint: Controlled PHN Studies

Epilepsy

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 $(T - B)/(T + B)$, where 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 divided TID 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 1200 mg/day divided TID Neurontin[®] (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 divided TID (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).

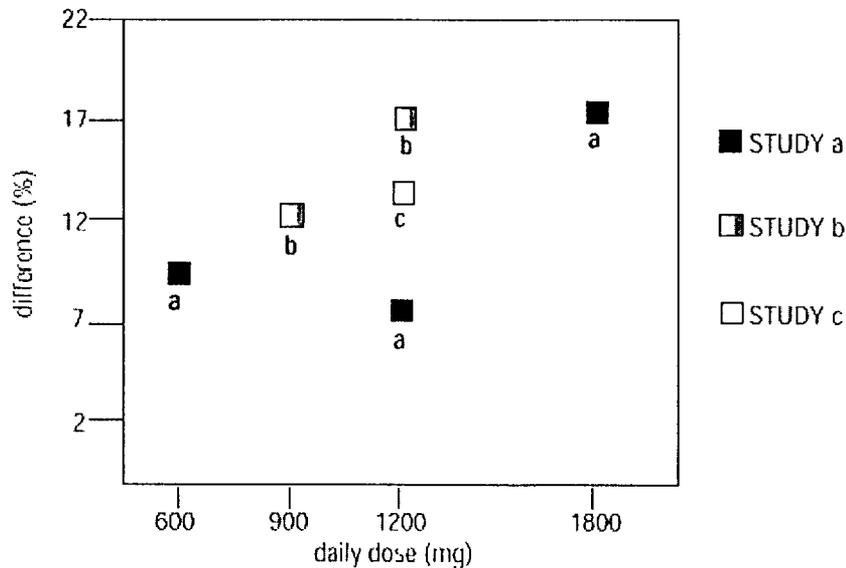


Figure 4. Responder Rate in Patients Receiving Neurontin[®] Expressed as a Difference from Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥ 12 Years of Age with Partial Seizures

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.

INDICATIONS AND USAGE

Postherpetic Neuralgia

Neurontin[®] (gabapentin) is indicated for the management of postherpetic neuralgia in adults.

Epilepsy

Neurontin[®] (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Neurontin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 – 12 years.

CONTRAINDICATIONS

Neurontin[®] is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events—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 events. 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 events were mild to moderate in intensity.

In controlled trials in pediatric patients 3–12 years of age the incidence of these adverse events 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 events, 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.

Withdrawal Precipitated Seizure, Status Epilepticus

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

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving Neurontin[®] was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with Neurontin[®] across all 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[®].

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.) 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.

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 patients treated (2103 patient-years of exposure).

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.

PRECAUTIONS

Information for Patients

Patients should be instructed to take Neurontin[®] only as prescribed.

Patients should be advised that Neurontin[®] may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised 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.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Neurontin[®] or morphine should be reduced appropriately (see Drug Interactions).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin[®]. The value of monitoring gabapentin blood

concentrations has not been established. Neurontin[®] may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions

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 µg/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 µg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

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 TID) 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 TID; 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 TID; 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 TID; 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 (see PRECAUTIONS). 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 TID; 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[®]): Maalox reduced the bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration.

Effect of 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.

Drug/Laboratory Tests 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

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 (approximately 5 times the maximum recommended human dose on a mg/m² basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m² basis. The no-effect level was 500 mg/kg/day or approximately 1/2 of the human dose on a mg/m² basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m² basis. There was an increased incidence of hydronephrosis and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m² basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m² basis. Other than hydronephrosis and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m² basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300, and 1500 mg/kg/day, or less than approximately 1/4 to 8 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in 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.

Pediatric Use

Safety and effectiveness of Neurontin® (gabapentin) 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 PHARMACOLOGY, Clinical Studies).

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 events 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 CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections).

ADVERSE REACTIONS

Postherpetic Neuralgia

The most commonly observed adverse events 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 studies 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 event. The adverse events that most frequently led to withdrawal in Neurontin®-treated patients were dizziness, somnolence, and nausea.

Incidence in Controlled Clinical Trials

Table 2 lists treatment-emergent signs and symptoms 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. Adverse events were usually mild to moderate in intensity.

TABLE 2. Treatment-Emergent Adverse Event Incidence in Controlled Trials in Postherpetic Neuralgia (Events in at least 1% of Neurontin[®]-Treated Patients and Numerically More Frequent Than in the Placebo Group)

Body System/ Preferred Term	Neurontin [®] N=336 %	Placebo N=227 %
<u>Body as a Whole</u>		
Asthenia	5.7	4.8
Infection	5.1	3.5
Headache	3.3	3.1
Accidental injury	3.3	1.3
Abdominal pain	2.7	2.6
<u>Digestive System</u>		
Diarrhea	5.7	3.1
Dry mouth	4.8	1.3
Constipation	3.9	1.8
Nausea	3.9	3.1
Vomiting	3.3	1.8
Flatulence	2.1	1.8
<u>Metabolic and Nutritional Disorders</u>		
Peripheral edema	8.3	2.2
Weight gain	1.8	0.0
Hyperglycemia	1.2	0.4
<u>Nervous System</u>		
Dizziness	28.0	7.5
Somnolence	21.4	5.3
Ataxia	3.3	0.0
Thinking abnormal	2.7	0.0
Abnormal gait	1.5	0.0
Incoordination	1.5	0.0
Amnesia	1.2	0.9
Hypesthesia	1.2	0.9
<u>Respiratory System</u>		
Pharyngitis	1.2	0.4
<u>Skin and Appendages</u>		
Rash	1.2	0.9
<u>Special Senses</u>		
Amblyopia ^a	2.7	0.9
Conjunctivitis	1.2	0.0
Diplopia	1.2	0.0
Otitis media	1.2	0.0

^a Reported as blurred vision

Other events 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 events. 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 events by race.

Epilepsy

The most commonly observed adverse events 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 commonly observed adverse events 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, Neuropsychiatric Adverse Events).

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 event. The adverse events 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 events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Incidence in Controlled Clinical Trials

Table 3 lists treatment-emergent signs and symptoms 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. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when Neurontin® was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 3. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials In Patients >12 years of age (Events in at least 1% of Neurontin® patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin® ^a N=543 %	Placebo ^a N=378 %
<u>Body As A Whole</u>		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
<u>Cardiovascular</u>		
Vasodilatation	1.1	0.3
<u>Digestive System</u>		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
<u>Hematologic and Lymphatic Systems</u>		
Leukopenia	1.1	0.5
<u>Musculoskeletal System</u>		
Myalgia	2.0	1.9
Fracture	1.1	0.8
<u>Nervous System</u>		
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	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
<u>Respiratory System</u>		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
<u>Skin and Appendages</u>		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
<u>Urogenital System</u>		
Impotence	1.5	1.1

TABLE 3. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials In Patients >12 years of age (Events in at least 1% of Neurontin[®] patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin ^{®a} N=543 %	Placebo ^a N=378 %
<u>Special Senses</u>		
Diplopia	5.9	1.9
Amblyopia ^b	4.2	1.1
<u>Laboratory Deviations</u>		
WBC Decreased	1.1	0.5

^a Plus background antiepileptic drug therapy

^b Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of Neurontin[®]-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with Neurontin[®]. The incidence of adverse events 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 events by race.

Table 4 lists treatment-emergent signs and symptoms 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 were numerically more common in the Neurontin[®] group. Adverse events were usually mild to moderate in intensity.

TABLE 4. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at least 2% of Neurontin[®] patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin ^{®a} N=119 %	Placebo ^a N=128 %
<u>Body As A Whole</u>		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
<u>Digestive System</u>		
Nausea and/or Vomiting	8.4	7.0

TABLE 4. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial (Events in at least 2% of Neurontin[®] patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin ^{®a} N=119 %	Placebo ^a N=128 %
<u>Nervous System</u>		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
<u>Respiratory System</u>		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8

^a Plus background antiepileptic drug therapy

Other events 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.

Other Adverse Events Observed During All Clinical Trials

Clinical Trials in Adults and Adolescents (Except Clinical Trials in Neuropathic Pain)

Neurontin[®] has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials (except clinical trials in patients with neuropathic pain), only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to Neurontin[®] who experienced an event of the type cited on at least one occasion while receiving Neurontin[®]. All reported events are included except those already listed in Table 3, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent:* asthenia, malaise, face edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent:* anorexia, flatulence, gingivitis; *Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare:* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, hypoenestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent:* arthralgia; *Infrequent:* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare:* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent:* pneumonia; *Infrequent:* epistaxis, dyspnea, apnea; *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent:* abnormal vision; *Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum,

hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare*: eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Clinical trials in Pediatric Patients With Epilepsy

Adverse events occurring during epilepsy clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

Body as a Whole: dehydration, infectious mononucleosis

Digestive System: hepatitis

Hemic and Lymphatic System: coagulation defect

Nervous System: aura disappeared, occipital neuralgia

Psychobiologic Function: sleepwalking

Respiratory System: pseudocroup, hoarseness

Clinical Trials in Adults With Neuropathic Pain of Various Etiologies

Safety information was obtained in 1173 patients during double-blind and open-label clinical trials including neuropathic pain conditions for which efficacy has not been demonstrated. Adverse events reported by investigators were grouped into standardized categories using modified COSTART IV terminology. Listed below are all reported events except those already listed in Table 2 and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Infrequent*: chest pain, cellulitis, malaise, neck pain, face edema, allergic reaction, abscess, chills, chills and fever, mucous membrane disorder; *Rare*: body odor, cyst, fever, hernia, abnormal BUN value, lump in neck, pelvic pain, sepsis, viral infection.

Cardiovascular System: *Infrequent*: hypertension, syncope, palpitation, migraine, hypotension, peripheral vascular disorder, cardiovascular disorder, cerebrovascular accident, congestive heart failure, myocardial infarction, vasodilatation; *Rare*: angina pectoris, heart failure, increased capillary fragility, phlebitis, thrombophlebitis, varicose vein.

Digestive System: *Infrequent*: gastroenteritis, increased appetite, gastrointestinal disorder, oral moniliasis, gastritis, tongue disorder, thirst, tooth disorder, abnormal stools, anorexia, liver function tests abnormal, periodontal abscess; *Rare*: cholecystitis, cholelithiasis, duodenal ulcer, fecal incontinence, gamma glutamyl transpeptidase increased, gingivitis, intestinal obstruction, intestinal ulcer, melena, mouth ulceration, rectal disorder, rectal hemorrhage, stomatitis.

Endocrine System: *Infrequent*: diabetes mellitus.

Hemic and Lymphatic System: *Infrequent:* ecchymosis, anemia; *Rare:* lymphadenopathy, lymphoma-like reaction, prothrombin decreased.

Metabolic and Nutritional: *Infrequent:* edema, gout, hypoglycemia, weight loss; *Rare:* alkaline phosphatase increased, diabetic ketoacidosis, lactic dehydrogenase increased.

Musculoskeletal: *Infrequent:* arthritis, arthralgia, myalgia, arthrosis, leg cramps, myasthenia; *Rare:* shin bone pain, joint disorder, tendon disorder.

Nervous System: *Frequent:* confusion, depression; *Infrequent:* vertigo, nervousness, paresthesia, insomnia, neuropathy, libido decreased, anxiety, depersonalization, reflexes decreased, speech disorder, abnormal dreams, dysarthria, emotional lability, nystagmus, stupor, circumoral paresthesia, euphoria, hyperesthesia, hypokinesia; *Rare:* agitation, hypertonia, libido increased, movement disorder, myoclonus, vestibular disorder.

Respiratory System: *Infrequent:* cough increased, bronchitis, rhinitis, sinusitis, pneumonia, asthma, lung disorder, epistaxis; *Rare:* hemoptysis, voice alteration.

Skin and Appendages: *Infrequent:* pruritus, skin ulcer, dry skin, herpes zoster, skin disorder, fungal dermatitis, furunculosis, herpes simplex, psoriasis, sweating, urticaria, vesiculobullous rash; *Rare:* acne, hair disorder, maculopapular rash, nail disorder, skin carcinoma, skin discoloration, skin hypertrophy.

Special Senses: *Infrequent:* abnormal vision, ear pain, eye disorder, taste perversion, deafness; *Rare:* conjunctival hyperemia, diabetic retinopathy, eye pain, fundi with microhemorrhage, retinal vein thrombosis, taste loss.

Urogenital System: *Infrequent:* urinary tract infection, dysuria, impotence, urinary incontinence, vaginal moniliasis, breast pain, menstrual disorder, polyuria, urinary retention; *Rare:* cystitis, ejaculation abnormal, swollen penis, gynecomastia, nocturia, pyelonephritis, swollen scrotum, urinary frequency, urinary urgency, urine abnormality.

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of Neurontin[®], the following adverse experiences have been reported in patients receiving marketed Neurontin[®]. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder such as dyskinesia, Stevens-Johnson syndrome.

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

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Neurontin[®] has not been evaluated in human studies.

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.

DOSAGE AND ADMINISTRATION

Neurontin[®] is given orally with or without food.

If Neurontin[®] dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week.

Postherpetic Neuralgia

In adults with postherpetic neuralgia, Neurontin[®] therapy may be initiated as a single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID). The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800 mg (divided TID). 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. Additional benefit of using doses greater than 1800 mg/day was not demonstrated.

Epilepsy

Neurontin[®] is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

Patients >12 years of age: The effective dose of Neurontin[®] is 900 to 1800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules, or 600 or 800 mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 or 400 mg capsules, or 600 or 800 mg tablets three times a day up to 1800 mg/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. The maximum time between doses in the TID schedule should not exceed 12 hours.

Pediatric Patients Age 3–12 years: The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of Neurontin[®] in patients 5 years of age and older is 25–35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day) (see CLINICAL PHARMACOLOGY, Pediatrics.) 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.

It is not necessary to monitor gabapentin plasma concentrations to optimize Neurontin[®] therapy. Further, because there are no significant pharmacokinetic interactions among Neurontin[®] and

other commonly used antiepileptic drugs, the addition of Neurontin® does not alter the plasma levels of these drugs appreciably.

If Neurontin® is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage in Renal Impairment

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

$$\begin{aligned} &\text{for females } C_{Cr} = (0.85)(140 - \text{age})(\text{weight}) / [(72)(S_{Cr})] \\ &\text{for males } C_{Cr} = (140 - \text{age})(\text{weight}) / [(72)(S_{Cr})] \end{aligned}$$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.

Dosage adjustment in patients ≥ 12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows (see dosing recommendations above for effective doses in each indication).

TABLE 5. Neurontin® Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥ 60	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
>30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
>15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 QD
15 ^a	100-300	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

^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.

The use of Neurontin® in patients < 12 years of age with compromised renal function has not been studied.

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.

HOW SUPPLIED

Neurontin[®] (gabapentin) capsules, tablets and oral solution are supplied as follows:

100 mg capsules;

White hard gelatin capsules printed with “PD” on one side and “Neurontin[®]/100 mg” on the other; available in:

Bottles of 100: N 0071-0803-24

Unit dose 50's: N 0071-0803-40

300 mg capsules;

Yellow hard gelatin capsules printed with “PD” on one side and “Neurontin[®]/300 mg” on the other; available in:

Bottles of 100: N 0071-0805-24

Unit dose 50's: N 0071-0805-40

400 mg capsules;

Orange hard gelatin capsules printed with “PD” on one side and “Neurontin[®]/400 mg” on the other; available in:

Bottles of 100: N 0071-0806-24

Unit dose 50's: N 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: N 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: N 0071-0401-24

250 mg/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: N0071-2012-23

Storage (Capsules)

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

Storage (Tablets)

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

Storage (Oral Solution)

Store refrigerated, 2°-8°C (36°-46°F)

Rx only

Revised September 2003

Capsules and Tablets:

Manufactured by:

Pfizer Pharmaceuticals, Ltd.

Vega Baja, PR 00694

Oral Solution:

Manufactured for:

Pfizer Pharmaceuticals, Ltd.

Vega Baja, PR 00694

Distributed by: _____



Parke-Davis

Division of Pfizer Inc, NY, NY 10017

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75-5800-00-4

Attachment 2
Completed Suicide Reports

Control Number. 3551076

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date.
38	M			2000	08	8/15/2000	02/22/2000	08/02/2000

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PARKE DAVIS PHARMACEUTICALS	032-0945-M0000010	3551076-5	EX	3454425	F	1

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
NEURONTIN	PS	ORAL		ORAL		
CARBAMAZEPINE	SS					
(LOPRAZOLAM)	SS					
SERTRALIN (SERTRALINE)	C					
(PERICIAZIN (PERICIAZINE)	C					
(PROTHIPENDYL) (PROTHIPENDYL)	C					

Outcome

Outcome
DE

Source

Source
FGN
HP
SDY

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	
NON-ACCIDENTAL OVERDOSE	

Neurontin Indications:

Control Number 3661327

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date.
	M			2001	02	2/5/2001		01/22/2001

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status:	Seq
	PARKE DAVIS PHARMACEUTICALS	001-0945-M0100100	3661327-4	EX	3606736	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
NEURONTIN	PS					
UNSPECIFIED MEDICATIONS	SS					

Outcome

Outcome
DE

Source

Source
CSM
HP

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications:

Control Number 3915659

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
	M					5/13/2002	4/5/2002	5/1/2002

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	A208483	3915659-2	EX	3789050	F	1

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
ZOLOFT	PS				4/5/2002	4/9/2002
GABAPENTIN	SS					4/9/2002
OXYCONTIN	SS					

Outcome

Outcome
DE

Source

Source
CSM

Reactions Referenced

COSTART/MedDRA	Onset
ABDOMINAL PAIN NOS	
ABDOMINAL PAIN UPPER	
COMPLETED SUICIDE	
DRUG INEFFECTIVE	
GASTROINTESTINAL DISORDER N	
GUN SHOT WOUND	
MARKEDLY REDUCED DIETARY IN	
MEDICATION ERROR	

Neurontin Indications:

Indication
PERIPHERAL NEUROPATHY NOS

Control Number 3915941

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
	M					5/13/2002	1/1/2001	5/1/2002

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq:
	PFIZER PHARMACEUTICALS	001-0945-M0200490	3915941-9	EX	3789052	F	1

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
NEURONTIN	PS					4/9/2002
SERTRALINE HCL	SS	75 MG, (DAILY)			4/5/2002	4/9/2002
OXYCODONE HCL	SS					

Outcome

Outcome
DE
OT

Source

Source
CSM

Reactions Referenced

COSTART/MedDRA	Onset
ABDOMINAL PAIN NOS	
COMPLETED SUICIDE	
EATING DISORDER NEC	
GASTROINTESTINAL DISORDER N	
GUN SHOT WOUND	
IDIOSYNCRATIC DRUG REACTION	

Neurontin Indications

Indication
PERIPHERAL NEUROPATHY NOS

Control Number 3977792

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
72	M					9/19/2002	8/1/2002	9/6/2002

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	2002057053	3977792-9	EX	3843112	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	1200 MG (400 MG, TID),		ORAL	3/1/2001	

Outcome

Outcome
DE
LT
OT

Source

Source
CR
FGN
HP

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications

Indication
PERIPHERAL NEUROPATHY NOS

Control Number 3992628

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
	M					10/11/2002	7/1/2002	10/1/2002

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	2002060656	3992628-8	EX	3853840	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
NEURONTIN	PS				1/1/2002	1/1/2002
ETHANOL	SS				1/1/2002	1/1/2002
UNSPECIFIED ANTIDEPRESSANTS	C					

Outcome

Outcome
DE

Source

Source
CR
FGN
HP

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications:

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	2002064869	4009078-0	EX	3864545	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
NEURONTIN	PS					

Outcome

Outcome
DE
OT

Source

Source
CSM

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications.

NEURONTIN

PS

Outcome

Outcome
DE

Source

Source
CSM

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications:

Indication
BIPOLAR DISORDER

Control Number 4055087

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
50				2003	2	2/10/2003		12/12/2002

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	2003003075	4055087-5	EX	3924377	1	

Drug Information SubForm

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	2003003076	4055102-9	EX	3903986	1	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		
AMOXAPINE	SS	ORAL		ORAL		
QUETIAPINE	SS	ORAL		ORAL		

Outcome

Outcome
DE

Source

Source
HP
LIT

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	
NON-ACCIDENTAL OVERDOSE	

Neurontin Indications

Control Number 4103106

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
21				2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq.
	WWS PFIZER PHARMACEUTICALS	2003016415	4103106-X	EX	3941439		

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		
HALOPERIDOL	SS	ORAL		ORAL		
BENZATROPINE MESILATE (BENZATROPINE	SS	ILL-DEFINED DISORDER				

Outcome

Outcome
DE

Source

Source
HP LIT

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications.

Indication
ILL-DEFINED DISORDER NOS

Control Number 4103108

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
11	F			2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	WWS PFIZER PHARMACEUTICALS	2003016399	4103108-3	EX	3941441	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	(ONCE), ORAL		ORAL		
NORTRIPTYLINE HCL	SS	6000 MG (ONCE), ORAL		ORAL		

Outcome

Outcome
DE
HO
OT

Source

Source
HP
LIT

Reactions Referenced

COSTART/MedDRA	Onset
ARRHYTHMIA NOS	
BLOOD PH INCREASED	
BLOOD POTASSIUM DECREASED	
BLOOD SODIUM INCREASED	
CARDIAC ARREST	
COMPLETED SUICIDE	
CONVULSIONS NOS	
DISSEMINATED INTRAVASCULAR C	
HYPOGLYCAEMIA NOS	
HYPOTENSION NOS	
INTESTINAL ISCHAEMIA	
INTESTINAL PERFORATION NOS	
LOSS OF CONSCIOUSNESS	
OLIGURIA	
SEPSIS NOS	
TACHYCARDIA NOS	

Neurontin Indications

Indication
ILL-DEFINED DISORDER NOS

Control Number 4103109

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
36				2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status:	Seq
	WWS PFIZER PHARMACEUTICALS	2003016396	4103109-5	EX	3941427	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		
OXYCODONE (OXYCODONE)	SS	ORAL		ORAL		
PAROXETINE HCL	SS	ORAL		ORAL		

Outcome

Outcome
DE
OT

Source

Source
HP
LIT

Reactions Referenced

COSTART/MedDRA	Onset
CARDIO-RESPIRATORY ARREST	
COMPLETED SUICIDE	

Neurontin Indications:

Indication
ILL-DEFINED DISORDER NOS

Control Number 4103110

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
38				2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	WWS PFIZER PHARMACEUTICALS	2003016417	4103110-1	EX	3941429	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		
ZOLPIDEM TARTRATE	SS	ORAL		ORAL		

Outcome

Outcome
DE

Source

Source
HP
LIT

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications.

Indication
ILL-DEFINED DISORDER NOS

Control Number 4103119

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
19				2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number.	F/U Status.	Seq
	WWS PFIZER PHARMACEUTICALS	2003016395	4103119-8	EX	3941433	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		
VALPROIC ACID	SS	ORAL		ORAL		
OLANZAPINE	SS	ORAL		ORAL		
ALL OTHER THERAPEUTIC PRODUCTS	SS	ORAL		ORAL		

Outcome

Outcome
DE

Source

Source
HP
LIT

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	
DRUG LEVEL NOS INCREASED	

Neurontin Indications

Indication
ILL-DEFINED DISORDER NOS

Control Number 4103162

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
54				2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq.
	PFIZER PHARMACEUTICALS	2003016394	4103162-9	EX	3941490	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		

Outcome

Outcome
DE

Source

Source
HP LIT

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications

Indication
ILL-DEFINED DISORDER NOS

Control Number 4103187

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
54				2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	2003016397	4103187-3	EX	3941496	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		
AMITRIPTYLINE HYDROCHLORIDE	SS	ORAL		ORAL		
ZOLPIDEM TARTRATE	SS	ORAL		ORAL		
ALL OTHER THERAPEUTIC PRODUCTS	SS	ORAL		ORAL		

Outcome

Outcome
DE

Source

Source
HP LIT

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications

Indication
ILL-DEFINED DISORDER NOS

Control Number 4103190

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
52				2003	4	4/25/2003		4/14/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	PFIZER PHARMACEUTICALS	2003016387	4103190-3	EX	3941503	1	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
GABAPENTIN	PS	ORAL		ORAL		
GALENIC /PARACETAMOL/CODEINE/ (CODEI	SS	ORAL		ORAL		
FOSINOPRIL SODIUM	SS	ORAL		ORAL		
ALL OTHER THERAPEUTIC PRODUCTS	C	ORAL				

Outcome

Outcome
DE

Source

Source
HP
LIT

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications

Indication
ILL-DEFINED DISORDER NOS

Control Number 4105635

Patient Information

Age	Sex	Location	Date of Birth	Year of Receipt	Month of receipt	Date of receipt	Event Date	Manufacturer Date
	M			2003	4	4/30/2003	1/1/2003	4/17/2003

Report Information

Source Code	Manufacturer	Manufacturer Control Num	Image ID	Report Type	Case Number	F/U Status	Seq
	WWS PFIZER PHARMACEUTICALS	2003017239	4105635-1	EX	3943540	I	

Drug Information SubForm

Drug	Suspect Status	Dosage	Units	Administration	Start Date	Stop Date
NEURONTIN	PS	900 MG (300 , THREE TI		ORAL		
ALPRAZOLAM	C					
ATENOLOL	C					
ALLOPURINOL	C					
FUROSEMIDE	C					
MINOXIDIL	C					

Outcome

Outcome
DE

Source

Source
HP

Reactions Referenced

COSTART/MedDRA	Onset
COMPLETED SUICIDE	

Neurontin Indications

Indication
PAIN NOS