

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020235/S011

**Trade Name: NEURONTIN CAPSULES 100 MG, 200 MG,
AND 400 MG**

Generic Name: GABAPENTIN

**Sponsor: PARKE-DAVIS PHARMACEUTICAL
RESEARCH, WARNER-LAMBERT COMPANY**

Approval Date: 09/29/98

Indication(s): TREATMENT OF EPILEPSY

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APPLICATION: 020235/S011

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020235/S011

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-235/S-011

Parke-Davis Pharmaceutical Research
Warner-Lambert Company
Attention: Janeth L. Turner, R.N., B.S.N.
Director, Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105

SEP 29 1998

Dear Ms. Turner:

Please refer to your supplemental new drug application dated September 13, 1996
received
September 16, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic
Act for Neurontin (gabapentin) Capsules, 100mg, 300mg, and 400mg.

We also acknowledge receipt of your amendment dated June 17, 1998.

Supplement 011 provides for revision of the **DOSAGE AND ADMINISTRATION** section of the package insert. Specifically, directions for use permit initiation of treatment with 900 mg/day by deletion of the requirement to titrate to 900 mg/day over a 3-day period.

The User Fee goal date for this application is December 18, 1998.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the attached draft labeling (package insert submitted June 17, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

¹Per agency policy as expressed in the "Interim Guidance: Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992."

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Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-235/S-011." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours, /

/S/

**APPEARS THIS WAY
ON ORIGINAL**

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020235/S011

FINAL PRINTED LABELING

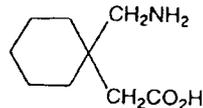
Neurontin®

(Gabapentin Capsules)

DESCRIPTION

Neurontin® (gabapentin capsules) is supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin. The inactive ingredients 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.

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



Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

CLINICAL PHARMACOLOGY

Mechanism of Action

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 interact with GABA receptors, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 μ M and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin 51 or 52, opiate mu, delta or kappa, voltage-sensitive calcium channel sites labeled with nifedipine or diltiazem, or at voltage-sensitive sodium channel sites with batrachotoxinin A 20-alpha-benzoate.

Several test systems ordinarily used to assess activity at the NMDA receptor have been examined. Results are contradictory. Accordingly, no general statement about the effects, if any, of gabapentin at the NMDA receptor can be made.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. The identity and function of this binding site 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. A 400-mg dose, for example, is about 25% less bioavailable than a 100-mg dose. Over the recommended dose range of 300 to 600 mg T.I.D., however, the differences in bioavailability are not large, and bioavailability is about 60 percent. Food has no effect on the rate and extent of absorption of gabapentin.

Distribution: Gabapentin circulates largely unbound (<3%) 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 2).

Special Populations: 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 patients with compromised renal function is necessary (see DOSAGE AND ADMINISTRATION).

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

Dosage adjustment in patients undergoing hemodialysis is necessary (see 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: No pharmacokinetic data are available in pediatric patients below the age of 18 years.

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

The effectiveness of Neurontin[®] as adjunctive therapy (added to other antiepileptic drugs) was established in three multicenter placebo-controlled, double-blind, parallel-group clinical trials in 705 adults with refractory partial seizures. 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. 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 T.I.D. 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 T.I.D. 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 T.I.D. (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 secondary generalized tonic-clonic seizures. Patients who experienced a secondary 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.

PARKE-DAVIS

Neurontin (Gabapentin Capsules)

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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 1).

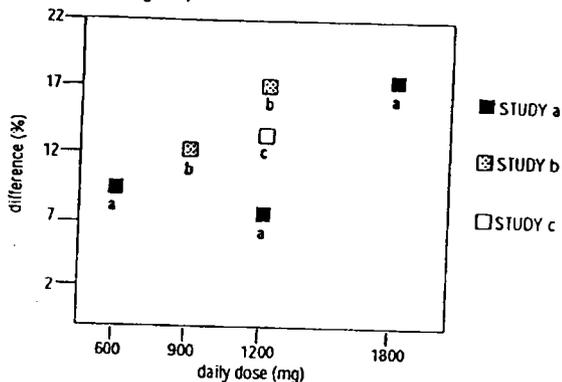


FIGURE 1. Responder Rate in Patients Receiving Neurontin® Expressed as a Difference from Placebo by Dose and Study

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.

INDICATIONS AND USAGE

Neurontin® (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.

CONTRAINDICATIONS

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

WARNINGS

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, 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 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 comprising 2085 patient-years of exposure, 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 Deaths

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.

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 Neurontin® 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

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 patients with epilepsy.

Phenytoin: In a single and multiple dose study of Neurontin® (400 mg T.I.D.) 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 T.I.D.; 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 T.I.D.; 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 T.I.D.; N = 12) are identical whether the drugs are administered alone or together.

Cimetidine: In the presence of cimetidine at 300 mg Q.I.D. (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 T.I.D.; 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.

Neurontin
0803G025DR



0803G025DR



0803G025DR

Neurontin (Gabapentin Capsules)

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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. Studies to attempt to define a mechanism by which this relatively rare tumor type is occurring are in progress. The relevance of this finding to carcinogenic risk in humans is unclear.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and two *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.

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 an 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 1/3 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 hydroureter 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 hydroureter, 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 1/3 to 8 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

It is not known if gabapentin is excreted in human milk and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, Neurontin[®] should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

No systematic studies in geriatric patients have been conducted. Adverse clinical events reported among 59 Neurontin[®] exposed patients over age 65 did not differ in kind from those reported for younger individuals. The small number of older individuals evaluated, however, limits the strength of any conclusions reached about the influence, if any, of age on the kind and incidence of adverse events or laboratory abnormality associated with the use of Neurontin[®].

Because Neurontin[®] is eliminated primarily by renal excretion, the dose of Neurontin[®] should be adjusted as noted in DOSAGE AND ADMINISTRATION (Table 2) for elderly patients with compromised renal function. Creatinine clearance is difficult to measure in outpatients and serum creatinine may be reduced in the elderly because of decreased muscle mass. Creatinine clearance (C_{cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

$$\text{for females } C_{cr} = (0.85)(140 - \text{age})(\text{wt}) / (72)(S_{cr})$$

$$\text{for males } C_{cr} = (140 - \text{age})(\text{wt}) / (72)(S_{cr})$$

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

ADVERSE REACTIONS

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

Approximately 7% of the 2074 individuals who received Neurontin[®] in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%).

Incidence in Controlled Clinical Trials

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients 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 non-drug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (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 ^b N = 378 %
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
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
Hematologic and Lymphatic Systems		
Leukopenia	1.1	0.5
Musculoskeletal System		
Myalgia	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
Respiratory System		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
Skin and Appendages		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
Urogenital System		
Impotence	1.5	1.1
Special Senses		
Diplopia	5.9	1.9
Amblyopia ^b	4.2	1.1
Laboratory Deviations		
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 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 (22/921) 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.

Neurontin (Gabapentin Capsules)

Other Adverse Events Observed During All Clinical Trials

Neurontin® has been administered to 2074 individuals during all clinical trials, 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 individuals 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 the previous table, 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, perleche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, hypoestrogen, 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.

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, jaundice, Stevens-Johnson syndrome.

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 recommended for add-on therapy in patients over 12 years of age. Evidence bearing on its safety and effectiveness in pediatric patients below the age of 12 is not available.

Neurontin® is given orally with or without food.

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. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300- or 400-mg capsules 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 T.I.D. schedule 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 adjustment in patients with compromised renal function or undergoing hemodialysis is recommended as follows:

TABLE 2. Neurontin® Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 T.I.D.
30—60	600	300 B.I.D.
15—30	300	300 Q.D.
<15	150	300 Q.O.D. ^a
Hemodialysis:	—	200-300 ^b

^a Every other day

^b Loading dose of 300 to 400 mg in patients who have never received Neurontin®, then 200 to 300 mg Neurontin® following each 4 hours of hemodialysis

HOW SUPPLIED

Neurontin® (gabapentin capsules) 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

Storage

Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only

Revised May 1998

Manufactured by:
Parke Davis Pharmaceuticals, Ltd.
Vega Baja, PR 00694

Distributed by:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020235/S011

MEDICAL REVIEW(S)

MEMORANDUM

DATE: July 30, 1997
FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120
TO: File, NDA 20-235
SUBJECT: Supervisory Review of Supplemental NDA _____

BACKGROUND

_____ This submission requested changes to the labeling for Neurontin, and contained data that the sponsor felt supported these changes. The requested changes were:

4) a change in the recommended initial dosing regimen to replace the current requirement in labeling of reaching 900 mg/day over 3 days to initial treatment with 900 mg/day.

The following data were submitted to support these changes:

33 PAGES REDACTED

**CONTAINED TRADE
SECRETS and/or
CONFIDENTIAL/
COMMERCIAL
INFORMATION**

New initial dosing regimen

Finally, the sponsor has requested that the labeling be changed to permit the initial dose to be 900 mg/day, to replace the current recommended initial dosing regimen of 300 mg/day on Day 1, 600 mg/day on Day 2, and 900 mg/day on Day 3.

In support of this change, they have submitted the results of Study 090, which compared the incidence of ADRs, with emphasis on the 4 most common ADRs seen in the earlier studies, with these 2 dosing regimens over the first week of dosing. I am persuaded that initiating treatment with 900 mg/day is likely not to result in significant difficulty, although the sponsor should be asked to submit detailed information about the 3 patients who received the proposed regimen and experienced syncope. (Interestingly, the sponsor points out that the current labeling does not reflect the actual dosing experience gained in the original controlled trials, most of which used a starting dose of 600 mg/day, a dose that did

not result in an unacceptable incidence of ADRs. I have been unable to locate in the file the reason for the slower titration described in labeling that was approved at that time [and which, of course, still persists], other than a statement made by the sponsor in the current submission that suggests it was done to be "conservative").

While the sponsor has not addressed the question of the effect of the new regimen on the ultimate effectiveness of the drug, I am comfortable concluding that no important effect would be expected. Further, I am willing to permit this new initial dosing to apply to both the adjunctive and mono-therapy setting, because the study was performed with Neurontin as adjunctive treatment.

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RECOMMENDATIONS

I recommend that the sponsor be informed that we find the application Approvable, but that the evidence supports Neurontin's use as monotherapy only in newly diagnosed patients. Further, the new initial dosing regimen is acceptable, but additional information needs to be submitted to support the sponsor's proposed statements about the use of higher doses. In addition, detailed information should be submitted about 3 patients in Study 090 who experienced syncope.

 /S/

Russell Katz, M.D.

Cc:
NDA 20-235
HFD-120
HFD-120/Katz/Leber/Ware
HFD-710/Sahlroot

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TABLE 4. Epilepsy History: Randomized Patients
(Page 2 of 2)

	Gabapentin (mg/day)			Carbamazepine N = 74	Any GBP N = 218	All Patients N = 292
	300 N = 72	900 N = 72	1800 N = 74			
Seizure Types Experienced Prior to Treatment^e, N (%) of Patients						
Simple Partial	17 (23.6)	21 (29.2)	27 (36.5)	32 (43.2)	65 (29.8)	97 (33.2)
Complex Partial	28 (38.9)	32 (44.4)	34 (45.9)	32 (43.2)	94 (43.1)	126 (43.2)
SGTC	32 (44.4)	38 (52.8)	41 (55.4)	37 (50.0)	111 (50.9)	148 (50.7)
GTC	22 (30.6)	14 (19.4)	11 (14.9)	17 (23.0)	47 (21.6)	64 (21.9)
Number of Seizures Of any Type Experienced Prior to Treatment^d						
N	72	71	71	72	214	286
Mean (SD)	8.7 (20.2)	7.1 (9.0)	5.7 (5.8)	6.2 (7.2)	7.2 (13.2)	6.9 (12.0)
Median	8.7	7.1	5.7	6.2	7.2	6.9
Range						
Prior AED/Benzodiazepine Therapy^c						
N (%) of Patients	12 (16.7)	15 (20.8)	18 (24.3)	11 (14.9)	45 (20.6)	56 (19.2)

^c In addition, 1 patient had myoclonic seizures; 1 patient had clonic seizures; 2 patients had tonic seizures; and 3 patients had unclassified seizures. Patients could have more than 1 type of seizure.

^d All patients had seizures prior to study entry; however, the precise number of seizures was not known for some patients.

^e Includes AEDs taken for seizure control at any time prior to the study, as well as benzodiazepines taken for indications other than seizures within 6 months of study entry.

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RR-REG 959-00033
 Gabapentin
 Capsules

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TABLE 7. Most Frequently^a Occurring Adverse Events: Study 945-88

BODY SYSTEM/ Adverse Event	Gabapentin Dosage		Any Gabapentin N = 82
	300 mg/day N = 42	3600 mg/day N = 40	
BODY AS A WHOLE	9 (21.4)	9 (22.5)	18 (22.0)
Fatigue	3 (7.1)	4 (10.0)	7 (8.5)
Headache	3 (7.1)	3 (7.5)	6 (7.3)
DIGESTIVE SYSTEM	7 (16.7)	9 (22.5)	16 (19.5)
Anorexia	2 (4.8)	2 (5.0)	4 (4.9)
Diarrhea	1 (2.4)	2 (5.0)	3 (3.7)
Oral Cavity Laceration	2 (4.8)	0 (0.0)	2 (2.4)
Abdominal Pain	1 (2.4)	1 (2.5)	2 (2.4)
Constipation	1 (2.4)	1 (2.5)	2 (2.4)
Dental Abnormalities	0 (0.0)	2 (5.0)	2 (2.4)
Nausea &/or Vomiting	0 (0.0)	2 (5.0)	2 (2.4)
MUSCULOSKELETAL	1 (2.4)	5 (12.5)	6 (7.3)
Myalgia	1 (2.4)	3 (7.5)	4 (4.9)
Arthralgia	0 (0.0)	2 (5.0)	2 (2.4)
NERVOUS SYSTEM	11 (26.4)	22 (55.0)	33 (40.2)
Dizziness	4 (9.5)	7 (17.5)	11 (13.4)
Ataxia	2 (4.8)	8 (20.0)	10 (12.2)
Somnolence	3 (7.1)	6 (15.0)	9 (11.0)
Paresthesia	4 (9.5)	4 (10.0)	8 (9.8)
Nystagmus	2 (4.8)	5 (12.5)	7 (8.5)
Dysarthria	0 (0.0)	5 (12.5)	5 (6.1)
Tremor	1 (2.4)	3 (7.5)	4 (4.9)
Insomnia	3 (7.1)	0 (0.0)	3 (3.7)
PSYCHOBIOLOGIC	3 (7.1)	3 (7.5)	6 (7.3)
Psychosis	2 (4.8)	0 (0.0)	2 (2.4)
SKIN AND APPENDAGES	2 (4.8)	3 (7.5)	5 (6.1)
Rash	2 (4.8)	0 (0.0)	2 (2.4)
SPECIAL SENSES	5 (11.9)	2 (5.0)	7 (8.5)
Diplopia	0 (0.0)	2 (5.0)	2 (2.4)
Unusual Taste	2 (4.8)	0 (0.0)	2 (2.4)
Any Event	22 (52.4)	29 (72.5)	51 (62.2)

^a Adverse events experienced by ≥ 2 patients.

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TABLE 9. Adverse Events Occurring in ≥5% of Patients: Uncontrolled Studies 945-83 and 945-89
[Number (%) of Patients]

Adverse Event	Weighted Mean Gabapentin Dose (mg/day) ^a			Any Gabapentin N = 322
	≤2400 N = 48	>2400-3600 N = 163	>3600-4800 N = 111	
Dizziness	11 (22.9)	34 (20.9)	24 (21.6)	69 (21.4)
Somnolence	5 (10.4)	32 (19.6)	19 (17.1)	56 (17.4)
Weight Increase	3 (6.3)	29 (17.8)	23 (20.7)	55 (17.1)
Rhinitis	10 (20.8)	24 (14.7)	13 (11.7)	47 (14.6)
Headache	6 (12.5)	23 (14.1)	15 (13.5)	44 (13.7)
Fatigue	4 (8.3)	23 (14.1)	17 (15.3)	44 (13.7)
Upper Respiratory Infection	5 (10.4)	21 (12.9)	17 (15.3)	43 (13.4)
Ataxia	7 (14.6)	20 (12.3)	12 (10.8)	39 (12.1)
Myalgia	5 (10.4)	14 (8.6)	15 (13.5)	34 (10.6)
Skin Laceration	3 (6.3)	17 (10.4)	13 (11.7)	33 (10.2)
Viral Infection	2 (4.2)	17 (10.4)	14 (12.6)	33 (10.2)
Diarrhea	4 (8.3)	16 (9.8)	12 (10.8)	32 (9.9)
Nausea &/or Vomiting	7 (14.6)	16 (9.8)	8 (7.2)	31 (9.6)
Paresthesia	5 (10.4)	13 (8.0)	12 (10.8)	30 (9.3)
Insomnia	8 (16.7)	15 (9.2)	6 (5.4)	29 (9.0)
Tremor	4 (8.3)	10 (6.1)	13 (11.7)	27 (8.4)
Nervousness	6 (12.5)	15 (9.2)	5 (4.5)	26 (8.1)
Rash	3 (6.3)	15 (9.2)	7 (6.3)	25 (7.8)
Amblyopia	3 (6.3)	13 (8.0)	7 (6.3)	23 (7.1)
Back Pain	1 (2.1)	12 (7.4)	9 (8.1)	22 (6.8)
Nystagmus	2 (4.2)	11 (6.7)	7 (6.3)	20 (6.2)
Thinking Abnormal	2 (4.2)	9 (5.5)	8 (7.2)	19 (5.9)
Purpura	6 (12.5)	7 (4.3)	5 (4.5)	18 (5.6)
Abrasion	3 (6.3)	9 (5.5)	6 (5.4)	18 (5.6)
Amnesia	6 (12.5)	4 (2.5)	7 (6.3)	17 (5.3)
Pharyngitis	1 (2.1)	8 (4.9)	7 (6.3)	16 (5.0)

^a A weighted mean dose was calculated for each patient and all adverse events for that patient were ascribed to that dose whether or not the event occurred at that specific dose.

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3.4.2.3. Adverse Events by Intensity

Most adverse events (96%) were mild to moderate in intensity. Fifty-three patients had a total of 68 severe adverse events. Adverse events considered severe in 2 or

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APPLICATION NUMBER: 020235/S011

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Gabapentin
Capsules

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**ITEM 13.
PATENT AND MARKET EXCLUSIVITY INFORMATION
AND CERTIFICATION FOR GENERIC DRUG
ENFORCEMENT ACT OF 1992**

PATENT INFORMATION

- (1) NDA Number: 20-235 Supplement
- (2) Applicant: Parke-Davis Pharmaceutical Research Division
Warner-Lambert Company
P.O. Box 1047
Ann Arbor, MI 48106
- (3) Active Ingredient: 1-(aminomethyl)-1-cyclohexaneacetic acid
- (4) Medical Use: This supplement expands the approved indication in epilepsy to include monotherapy, and a maximum daily dosage of 4800 mg/day. It deletes the recommendation to initiate therapy with a titration over 3 days.
- (5) Strength: 100, 300, 400 mg capsules
- (6) Dosage Form: Capsules for oral administration
- (7) Trade Name: Neurontin[®]
- (8) Generic Name: Gabapentin
- (9) Patent Statement: US Patent Number 4, 087,544 which issued May 2, 1978, and which expires January 16, 2000, claims a method of treating certain forms of epilepsy, as well as faintness attacks, hypokinesia and cranial traumas, by enteral or parenteral administration of 1-(aminomethyl)-1-cyclohexaneacetic acid.
- US Patent Number 4,894,476 which issued January 16, 1990, and which expires May 2, 2008, claims a crystal form of 1-(aminomethyl)-1-cyclohexaneacetic acid.
- US Patent Number 5,084,479 which issued January 28, 1992, and which expires on January 2, 2010, claims a method for treating neurodegenerative diseases with 1-(aminomethyl)-1-cyclohexaneacetic acid.
- Each of US 4,087,544, US 4,894,476, and US 5,084,479 is assigned to Warner-Lambert Company.

PATENT INFORMATION

Neurontin® (Gabapentin) NDA #20-235 Supplement

August 12, 1996

Page 2

(9) Patent Statement:
(Continued)

The undersigned declares that Patent Numbers 4,087,544, 4,894,476 and 5,084,479, cover a crystal form and the use of Neurontin® (gabapentin) (1-(aminomethyl)-1-cyclohexaneacetic acid). Neurontin® is approved under section 505 of the Federal Food, Drug and Cosmetic Act.

August 12, 1996

Date



Elizabeth M. Anderson
Patent Agent
Registration No. 31,585

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Exclusivity Summary for NDA 20-235/S-011

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 20-235 SUPPL # S-011

Trade Name: Neurontin Capsules Generic Name: gabapentin

Applicant Name: Parke-Davis

HFD#: HFD-120

Approval Date If Known: 9/29/96

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES/___/NO/_X_/

b) Is it an effectiveness supplement? YES/_X_/NO/___

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES/_X_/NO/___

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity? YES/_X_/NO/___

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
The applicant requested 3 years of exclusivity on 9/23/96.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 4.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such) YES/___/NO/_X_/

If yes, NDA # Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 4.

Exclusivity Summary for NDA 20-235/S-011

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 4 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 4. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?

(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) **If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a).** If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 4.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those

Exclusivity Summary for NDA 20-235/S-011

conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 4:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. YES / / NO / /

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? YES / / NO / /

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: **Study 945-090**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): **Study 945-090**

Exclusivity Summary for NDA 20-235/S-011

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

Signature: / S / Date: 9/18/98

Title: Project Manager

Signature of Office/Division Director

Signature: / S / Date: 10/13/98

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

DA # 20-235

Supplement # S-011 Circle one: SE1, SE2, SE3, SE4, SE5, SE6

rFD-120 Trade (generic) name/dosage form: Neurontin® (gabapentin) Capsules 100mg, 300mg, 400mg

Action: AP AE NA Applicant Parke-Davis Therapeutic Class _____

Indication(s) previously approved: As adjunctive therapy in treatment of partial seizures with and without generalization in adults with epilepsy.

Pediatric labeling of approved indication(s) is adequate _____ inadequate X

Indication in this application: Change in initial dosing regimen; directions for use permit initiation of treatment with 900 mg/day by deletion of the requirement to titrate to 900 mg/day over a 3-day period.

(For supplements, answer the following questions in relation to the proposed indication.)

- 1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.
- 2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing.
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
 - c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.
- 4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/
Signature of Preparer and Title (PM, CSO, MD, other)

9/18/98
Date

cc:Orig NDA

7-120/Div File

Action Package

J-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last 3/96

Gabapentin
Capsules

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ITEM 13.
CERTIFICATION FOR GENERIC DRUG ENFORCEMENT ACT OF 1992

Warner-Lambert Company certifies that it is not debarred, and to the best of its knowledge Warner-Lambert Company did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

**APPEARS THIS WAY
ON ORIGINAL**

COPY

MEMORANDUM

DATE: September 23, 1998
FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120
TO: File, NDA 20-235/S-011
SUBJECT: Supervisory Review of Sponsor's Response to Not Approvable Letter for Neurontin

As noted above, we have already determined that the proposal in what is now S-011 to permit initiation of treatment with 900 mg/day is acceptable

In that review, I noted that 3 patients experienced syncope, and I requested that additional data on these 3 patients be submitted

The sponsor has submitted additional data on these 3 patients, including case report forms. In one patient, the syncope occurred after a head injury, 8 days after discontinuation of treatment. In the

other 2, the event, though poorly described, occurred 3-7 days after patients would have achieved 900 mg/day under the current regimen.

The sponsor's proposed changes to the Dosage and Administration section of labeling are acceptable.

RECOMMENDATIONS

I recommend that the attached Approval letter be issued.

APPEARS THIS WAY
ON ORIGINAL

/S/

Russell Katz, M.D.

cc:
NDA 20-235/S-011
HFD-120
HFD-120/Katz/Leber/Ware

APPEARS THIS WAY
ON ORIGINAL

Review Notes

I. LABELING COMPARISON

The FPL from S-001 (0803G021), which was the last approved labeling for NDA 20-235, was manually compared line-by-line to the new draft labeling (0803G025DR) from S-011.

II. LABELING CHANGES

When FPL (0803G021) was compared to draft labeling (0803G025DR), the following changes were noted and are listed below by section:

Section	Note #	Approved Labeling from S-001 (0803G021)	Draft Labeling from S-011 (0803G025DR)
CLINICAL PHARMACOLOGY	#1		
PRECAUTIONS, Pediatric Use	#2		
ADVERSE EVENTS	#3		
DOSAGE & ADMINISTRATION	#4		
DOSAGE & ADMINISTRATION	#5		
HOW SUPPLIED	#6		

III. COMMENTS:

1. The cover letter for the 6/17/98 amendment, which contains the new draft labeling (0803G025DR), indicates that it provides revised labeling to reflect only the deletion of the recommendation to initiate 900mg/day dosing by titrating over a 3-day period. _____ In the August 26, 1997 approvable letter, the Agency indicated that this deletion was potentially approvable.
2. The changes identified as Notes #1, #2, and #4 are consistent with language described in the pediatric labeling regulations under 21 CFR 201.57(f)(9).
3. The change identified as Note #3 was submitted on 3/2/98 in an amendment to SLR-007 (as a Special Supplement-Changes Being Effected). The text of this new subsection was discussed and agreed upon by Dr. Katz, Neurology Team Leader, on 2/11/98.
4. The change identified as Note #6 is consistent with language described in Section 126 of FDAMA - Elimination of Certain Labeling Requirements.
5. No other changes were noted in the draft labeling (0803G025DR).

IV. CONCLUSIONS:

1. The changes identified as Notes #1, #2, #3, #4, and #6 are minor and are acceptable.
2. The clinical reviewer should determine if it is acceptable for the sponsor to delete the dosing titration recommendation. However, in the August 26, 1997 approvable letter, the Agency indicated that this deletion was potentially approvable.

APPEARS THIS WAY
ON ORIGINAL

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Page(s) Redacted

DRAFTING LABELING