THERAPENTIN-60 - gabapentin, .gamma.-aminobutyric acid
Physician Therapeutics LLC

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.

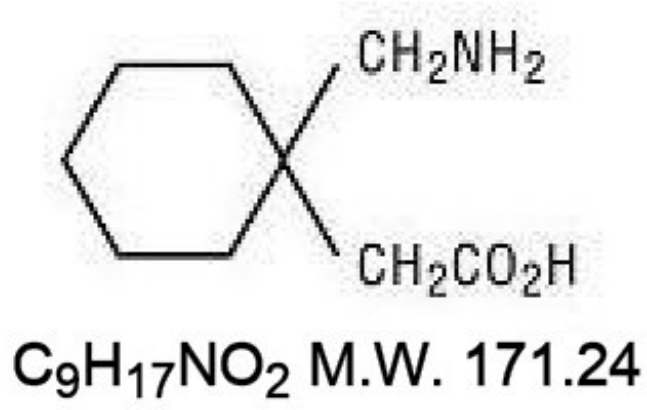
Therapentin-60

DESCRIPTION

Gabapentin Capsules, USP are supplied as imprinted hard gelatin capsules containing 100 mg, 300 mg and 400 mg of gabapentin, USP.

The inactive ingredients are mannitol, pre-gelatinized starch and talc. The 100 mg capsule shell contains titanium dioxide. The 300 mg capsule contains FDandC Red 40, DandC Yellow 10 and titanium dioxide. The 400 mg capsule shell contains FDandC Red 40, DandC Yellow 10 and titanium dioxide.

Gabapentin, USP is described as 1-(aminomethyl) cyclohexaneacetic acid with a molecular formula of C9H17NO2 and a molecular weight of 171.24. The structural formula of gabapentin is:



$C_9H_{17}NO_2$ M.W. 171.24

Gabapentin, USP is a white to off-white crystalline solid with a pKa1 of 3.7 and a pKa2 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 GABAA or GABAB 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 Cmax).

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 (Cmin) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see Special Populations: Patients With Renal Insufficiency, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

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

Special Populations:Adult Patients With Renal Insufficiency: Subjects (N=60) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine

clearance Greater than 60 mL/min) to 52 hours (creatinine clearance Less than 30 mL/min) and gabapentin renal clearance from about 90 mL/min (Greater than 60 mL/min group) to about 10 mL/min (Less than 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 (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. 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 Less than 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 Less than 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 Less than 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

Gabapentin 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 an11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain).A mean pain score during baseline of at least 4 was required for randomization (baseline mean pain score for Studies 1 and 2 combined was 6.4). Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication).

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

A significant reduction in weekly mean pain scores was seen by Week 1 in both studies, and significant differences were maintained to the end of treatment. Comparable treatment effects were observed in all

active treatment arms. Pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses. Figures 1 and 2 show these changes for Studies 1 and 2.

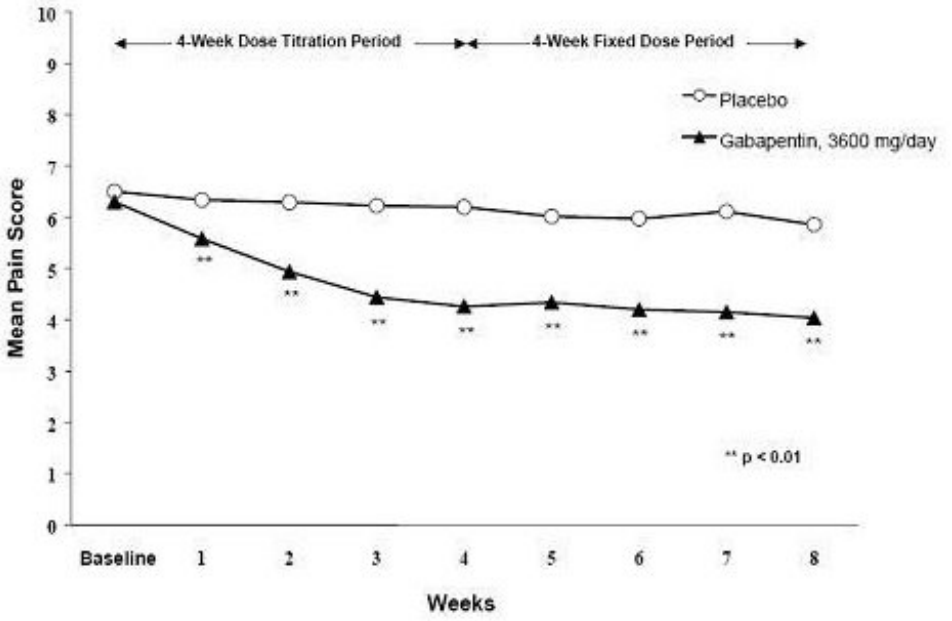


Figure 1. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 1

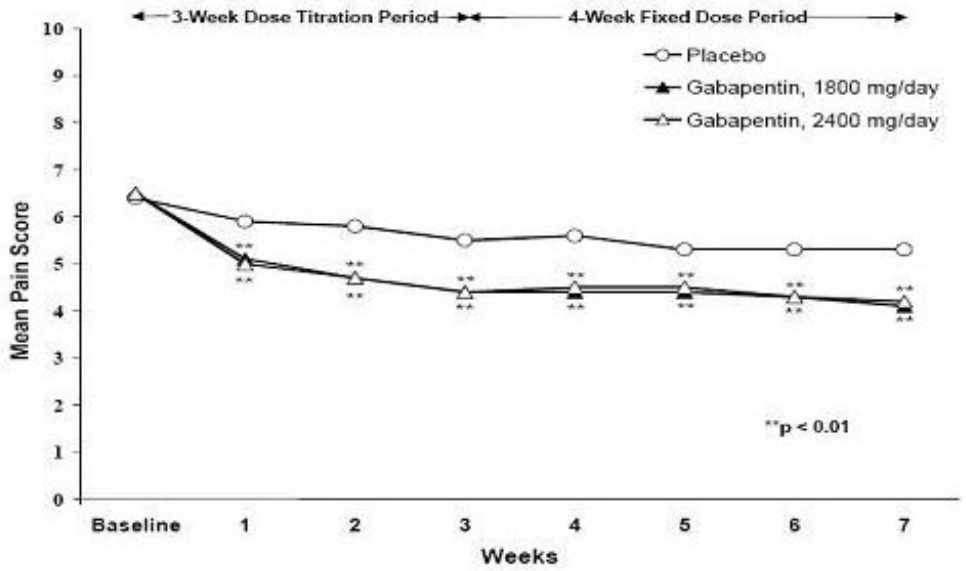


Figure 2. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 2

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

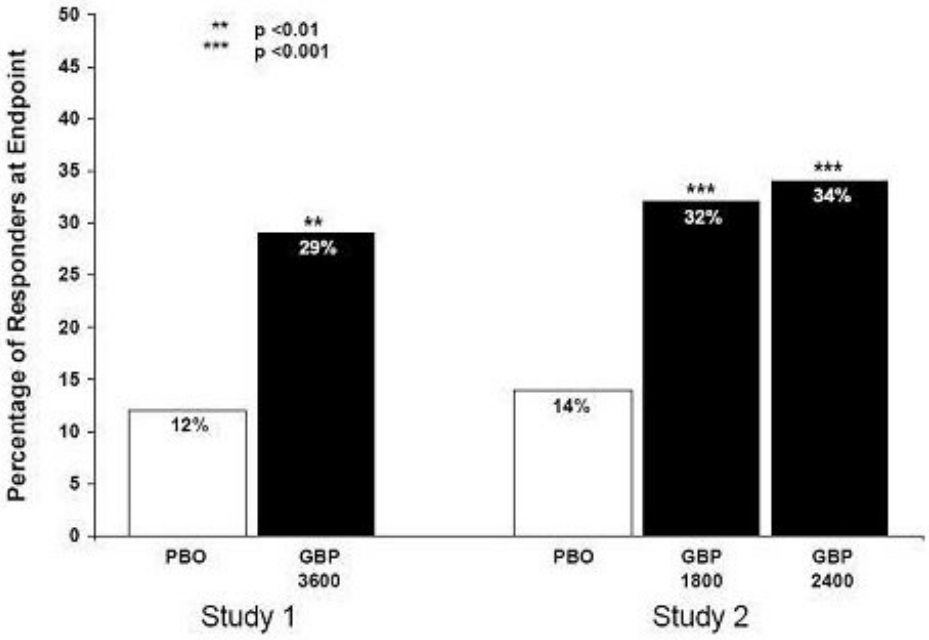


Figure 3. Proportion of Responders (patients with ≥50% reduction in pain score) at Endpoint: Controlled PHN Studies.

Epilepsy

The effectiveness of gabapentin 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, gabapentin 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 gabapentin 1200 mg/day divided TID with placebo. Responder rate was 23% (14/61) in the gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the gabapentin 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 gabapentin (N=101) with placebo (N=98). Additional smaller gabapentin 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 gabapentin 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 gabapentin 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 gabapentin 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 gabapentin 900 mg/day divided TID (N=111) and placebo (N=109). An additional gabapentin 1200 mg/day dosage group (N=52) provided dose-response data. A statistically significant difference in responder rate was seen in the gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the gabapentin 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day gabapentin (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of gabapentin 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 gabapentin 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, gabapentin; N=89, placebo) also showed a significant advantage for gabapentin over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of gabapentin 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).

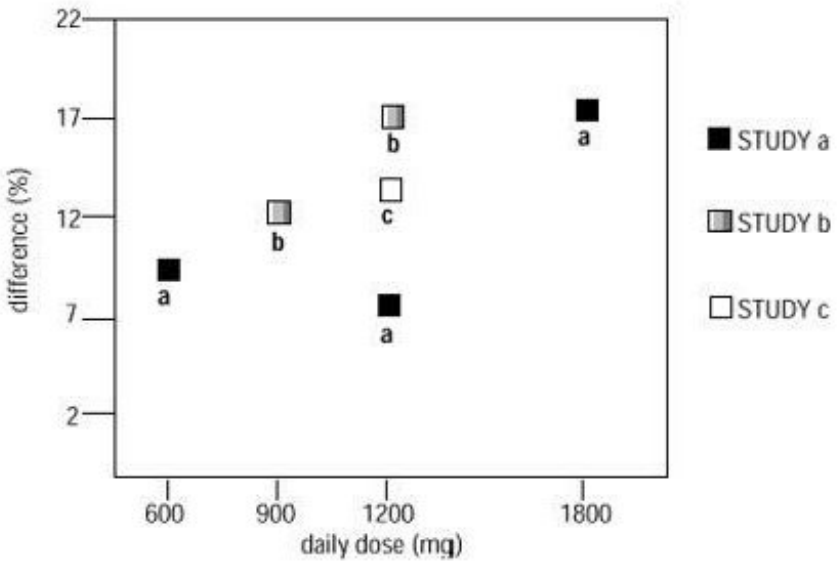


Figure 4.Responder Rate in Patients Receiving gabapentin Expressed as a Difference from Placebo by Dose and Study: Adjunctive Therapy Studies in Patients Greater than or equal to 12 Years of Age with Partial Seizures

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 gabapentin. 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 gabapentin (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 gabapentin group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for gabapentin (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day gabapentin (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

Gabapentin is indicated for the management of postherpetic neuralgia in adults.

Epilepsy

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. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 – 12 years.

CONTRAINDICATIONS

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

WARNINGS

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including gabapentin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients With events per 1000 patients	Relative Risk: Incidence of Events in Drug Patients /Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing gabapentin or any other AED must balance the risk of suicidal thoughts

or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

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 Greater than 12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients Greater than 12 years of age treated with gabapentin 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 gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

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 Greater than 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 gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, 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 gabapentin 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 gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin 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 gabapentin cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for patients

Patients should be instructed to take gabapentin only as prescribed.

Patients, their caregivers, and families should be counseled that AEDs, including gabapentin, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Patients should be advised that gabapentin 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 gabapentin 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 gabapentin or morphine should be reduced appropriately (see Drug Interactions).

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS, Pregnancy section).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established. Gabapentin 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 Cmax 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 gabapentin 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 gabapentin (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 gabapentin (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) Cmax and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; Cmax and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. 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 gabapentin 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 gabapentin 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 Cmax 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 ½ 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 hydroureter 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 hydroureter 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 ¼ 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.

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

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, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use

Safety and effectiveness of 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 gabapentin 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 gabapentin 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

Postherptic Neuralgia

The most commonly observed adverse events associated with the use of gabapentin 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 gabapentin 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 gabapentin-treated patients were dizziness, somnolence, and nausea.

Incidence in Controlled Clinical Trials

Table 3 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin treated patients with postherpetic neuralgia participating in placebo-controlled trials and that were numerically more frequent in the gabapentin group than in the placebo group. Adverse events were usually mild to moderate in intensity.

TABLE 3. Treatment-Emergent Adverse Event Incidence in Controlled Trials in Postherpetic Neuralgia (Events in at least 1% of gabapentin -Treated Patients and Numerically More Frequent Than in the Placebo Group)

Body System/	Gabapentin	Placebo
Preferred Term	N=336	N=227
	%	%
Body as a Whole		
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
Digestive System		
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
Metabolic and Nutritional Disorders		
Peripheral edema	8.3	2.2
Weight gain	1.8	0.0
Hyperglycemia	1.2	0.4
Nervous System		
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
Respiratory System		
Pharyngitis	1.2	0.4
Skin and Appendages		
Rash	1.2	0.9
Special Senses		
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 gabapentin in combination with other antiepileptic drugs in patients Greater than 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 gabapentin 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 Greater than 12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients Greater than 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 hyperkinesias (1.1%).

Incidence in Controlled Clinical Trials

Table 4 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin treated patients Greater than 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin 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 gabapentin 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 4. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials In Patients Greater than 12 years of age (Events in at least 1% of Gabapentin patients and numerically more frequent than in the placebo group)

Body System/	Gabapentin[a]	Placebo[a]
Adverse Event	N=543	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 Greater than 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 gabapentin - 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 gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin 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 5 lists treatment-emergent signs and symptoms that occurred in at least 2% of gabapentin ¬treated patients age 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. Adverse events were usually mild to moderate in intensity.

TABLE 5. 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 gabapentin patients and numerically more frequent than in the placebo group)

Body System/	Gabapentin[a]	Placebo[a]
Adverse Event	N=119	N=128
	%	%
Body As A Whole		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
Digestive System		
Nausea and/or Vomiting	8.4	7.0
Nervous System		
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

Respiratory System		
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)

Gabapentin has been administered to 4717 patients Greater than 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 4717 patients Greater than 12 years of age exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in Table 4, 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, 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, suicide attempt, 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.

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 3 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, suicide attempt; 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 gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. 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, 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 gabapentin 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 gabapentin 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

Gabapentin Capsules, USP are given orally with or without food.

If gabapentin dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week (a longer period may be needed at the discretion of the prescriber).

Postherpetic Neuralgia

In adults with postherpetic neuralgia, gabapentin 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

Gabapentin 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 Greater than 12 years of age: The effective dose of gabapentin 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 gabapentin 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.) Gabapentin 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 gabapentin therapy. Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma levels of these drugs appreciably.

If gabapentin 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 (CCr) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females $CCr = (0.85)(140 - age)(weight)/[(72)(SCr)]$

for males $CCr = (140 - age)(weight)/[(72)(SCr)]$

where age is in years, weight is in kilograms and SCr is serum creatinine in mg/dL.

Dosage adjustment in patients Greater than or equal to 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 6. Gabapentin Dosage Based on Renal Function

Renal Function	Total Daily					
Creatinine Clearance	Dose Range			Dose Regimen		
(mL/min)	(mg/day)			(mg)		
Greater than or equal to 60	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
Greater than 30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
Greater than 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 Less than 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 gabapentin in patients Less than 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

Gabapentin Capsules, USP are supplied as follows:

100 mg : Hard Gelatin Capsules size "3" with White Opaque Cap and White Opaque Body imprinted with 100 mg and IG321, filled
with White to Off-white powder; supplied in bottles of 100's count (NDC 31722-221-01) and 500's count (NDC 31722-221-05).

300 mg : Hard Gelatin Capsules size "1" with Yellow Opaque Cap and Yellow Opaque Body imprinted with 300 mg and IG322, filled
with White to Off-white powder; supplied in bottles of 100's count (NDC 31722-222-01) and 500's count (NDC 31722-222-05).

400 mg : Hard Gelatin Capsules size "0" with Orange Opaque Cap and Orange Opaque Body imprinted with 400 mg and IG323, filled
with White to Off-white powder; supplied in bottles of 100's count (NDC 31722-223-01) and 500's count (NDC 31722-223-05).

Rx only

Manufactured by:
InvaGen Pharmaceuticals, Inc.
Hauppauge, NY 11788

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

Rev: 01/10
Barcode
323-01-2010

Store at 20°-25°C (68°-7JOF). [See USP controlled room temperature.]

Camber Pharmaceuticals Inc. NDC 31722-222-01 Gabapentin Capsules, USP 300 mg Rx only 100 Capsules Each capsule contains 300 mg of gabapentin, USP. DOSAGE AND USE: See package insert for full prescribing information Store at 20°-25°C (68°-7JOF). [See USP controlled room temperature]. Manufactured for: Camber Pharmaceuticals, Inc. Piscataway, NJ 08854 Manufactured by: Invagen InvaGen Pharmaceuticals, Inc. Hauppauge, NY 11788 Rev:01/10 N3 31722-222-01 3 LOT: EXP:

Theramine (U.S. patent pending) capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids and polyphenol ingredients in specific proportions, for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. (PD) (IC). Must be administered under physician supervision.

Medical Foods
Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician’s care for the dietary management of diseases in patients with particular, unique or distinctive medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology, and that are used only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the Medical Food. Theramine has been developed, manufactured, and labeled in accordance with both the statutory definition of a Medical Food and FDA’s regulatory labeling guidelines. Theramine must be used while the patient is under the ongoing care of a physician.

PAIN DISORDERS (PD) INFLAMMATORY CONDITIONS (IC)
PD and IC as a Metabolic Deficiency Disease

A critical component of the definition of a Medical Food is that the product must address the distinct nutritional requirements of a particular disease or condition. FDA scientists have proposed a physiologic definition of distinctive nutritional requirements as follows: “the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences, recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions and drug therapies. Thus, the distinctive nutritional needs associated with a disease reflects the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism and excretion.” It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with a pain disorder responds to a tryptophan formulation by decreasing perceived pain, then a deficiency of tryptophan is assumed to exist. Patients with pain disorders and inflammatory conditions are known to have increased nutritional requirements for tryptophan, choline, arginine, GABA, flavonoids, and certain antioxidants. These nutritional requirements are such that they cannot be achieved by the modification of the normal diet alone, or by supplementing the diet.

Patients with pain disorders and inflammatory conditions frequently exhibit reduced plasma levels of tryptophan and GABA, and have been shown to respond to oral administration of GABA, arginine, tryptophan, or a 5-hydroxytryptophan formulation. Research has shown that tryptophan, arginine or GABA reduced diets result in a fall of circulating tryptophan, arginine, and/or GABA. Patients with pain disorders frequently exhibit activation of the degradation pathways that increases the turnover rate of GABA, arginine and/or tryptophan leading to a reduced level of production of serotonin, GABA or nitric oxide for a given precursor blood level. Research has also shown that a genetic predisposition to accelerated degradation can lead to increased precursor requirements in certain patients with pain disorders and inflammatory conditions.

Choline is required to fully potentiate acetylcholine synthesis by brain neurons. A deficiency of choline leads to reduced acetylcholine production by the neurons. Provision of tryptophan, arginine, GABA, choline and flavonoids with antioxidants, in specific proportions can restore the production of beneficial serotonin, nitric oxide, and acetylcholine, thereby reducing the perception of pain and reducing inflammation. L-Histidine is known to produce brain histamine that stimulates production of ACTH, producing cortisol to reduce inflammation.

PRODUCT DESCRIPTION

Primary Ingredients

Theramine consists of a proprietary formulation of Gamma Aminobutyric Acid, Choline Bitartrate, Whey Protein Hydrolysate, L-Arginine, L-Histidine, L-Glutamine, Theobromine, Griffonia See, Grape Seed, L-Serine, and Cinnamon in specific proportions. These ingredients fall into the classification of Generally Recognized as Safe (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been determined by the FDA to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186.

Amino Acids

Amino Acids are the building blocks of protein and are GRAS listed as they have been safely ingested by humans for thousands of years. The formulations of the amino acids in Theramine are equivalent to

those found in the usual human diet. Patients with pain disorders may require an increased amount of certain amino acids that cannot be obtained from normal diet alone. Tryptophan, for example, is an obligatory amino acid. The body cannot make tryptophan and must obtain tryptophan from the diet. Tryptophan is needed to produce serotonin. Serotonin is required to reduce pain. Patients with pain disorders and inflammatory conditions have altered serotonin metabolism.

Flavonoids

Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The specially formulated flavonoids found in Theramine cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response.

Other Ingredients

Theramine contains the following “inactive” or other ingredients, as fillers, excipients, and colorings: Gelatin, Silicon Dioxide, Tricalcium Phosphate, Vegetable Magnesium stearate, Cellulose, FDandC Blue#1, FDandC Red #3, Titanium Dioxide.

Physical Description

Theramine is a yellow to light brown powder. Theramine contains Gamma Aminobutyric Acid, Choline Bitartrate, Whey Protein Hydrolysate, L-Arginine, L-Histidine HCL, L-Glutamine, Theobromine, Griffonia Seed, Grape Seed, L-Serine, and Cinnamon. Each capsule consists of a proprietary blend of these ingredients in an amount of 366mg or 732mg per two (2) capsule dose.

CLINICAL PHARMACOLOGY

Mechanism of Action

Theramine acts by restoring and maintaining the balance of the neurotransmitters GABA, nitric oxide, serotonin, and acetylcholine that are associated with pain disorders and inflammatory conditions. Theramine stimulates the production ACTH to reduce inflammation.

Metabolism

The amino acids in Theramine are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in Theramine. Circulating tryptophan, arginine and choline blood levels determine the production of serotonin, nitric oxide, and acetylcholine.

Excretion

Theramine is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes.

INDICATIONS FOR USE

Theramine is intended for the clinical dietary management of the metabolic processes of pain disorders and inflammatory conditions.

CLINICAL EXPERIENCE

Administration of Theramine has demonstrated significant reduction in symptoms of pain and inflammation in patients with acute and chronic pain when used
for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. Administration of Theramine results in
the induction and maintenance of pain relief in patients with pain disorders and inflammatory conditions.

PRECAUTIONS AND CONTRAINDICATIONS

Theramine is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of Theramine.

ADVERSE REACTIONS
Ingestion of L-Tryptophan, L-Arginine, or Choline at high doses of up to 15 grams daily is generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps, and diarrhea. Theramine contains less than 1 gram per dose of amino acids however, some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each Theramine capsule does not exceed 300 mg.

DRUG INTERACTIONS
Theramine does not directly influence the pharmacokinetics of prescription drugs. Clinical experience has shown that administration of Theramine may allow for lowering the dose of co-administered drugs under physician supervision.

OVERDOSE
There is a negligible risk of overdose with Theramine as the total amount of amino acids in a one month supply (90 capsules) is less than 30 grams. Overdose symptoms may include diarrhea, weakness, and nausea.

POST-MARKETING SURVEILLANCE
Post-marketing surveillance has shown no serious adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to Theramine flavonoid ingredients, including Cinnamon, Cocoa, and Grape Seed. These reactions were temporary, transient in nature and subsided within 24-hours.

DOSAGE AND ADMINISTRATION
Recommended Administration
For the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. Take two (2) capsules every four hours or as directed by physician. As with most amino acid formulations Theramine should be taken without food to increase the absorption of key ingredients.

How Supplied
Theramine is supplied in purple and white, size 0 capsules in bottles of 60 and 90 capsules.
Physician Supervision
Theramine is a Medical Food product available by prescription only and may be used per FDA law, and product labeling only while the patient is under ongoing physician supervision.

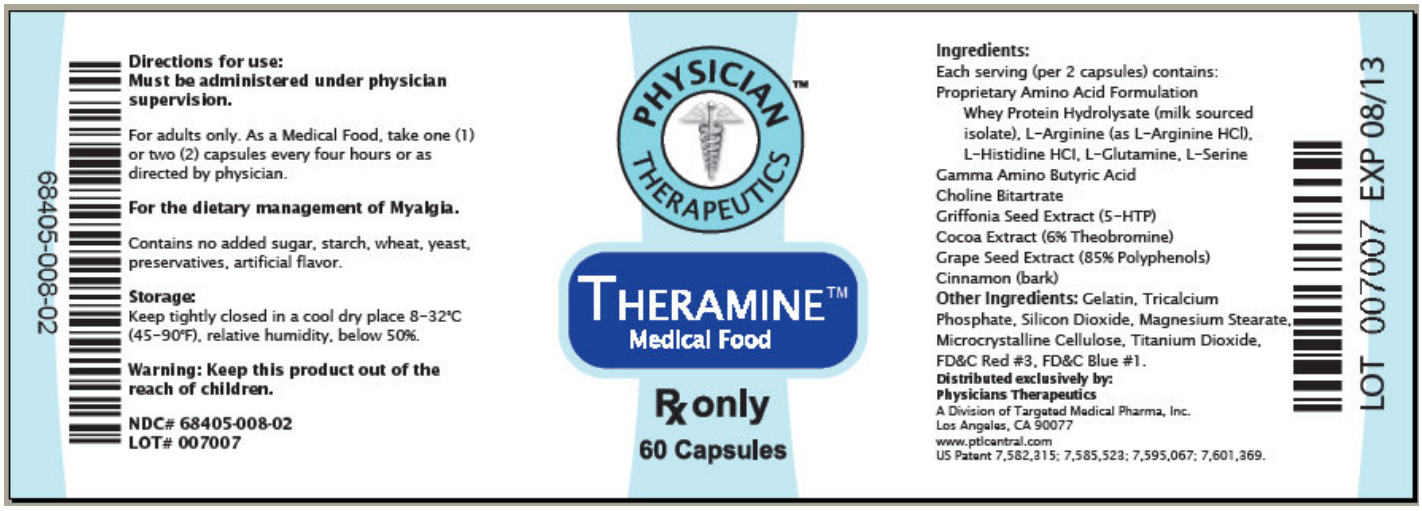
U.S. patent pending
Manufactured by Arizona Nutritional Supplements, Inc. Chandler AZ 85225
Distributed exclusively by Physician Therapeutics LLC, a wholly owned subsidiary of Targeted Medical Pharma Inc. Los Angeles, CA
www.ptlcentral.com NDC: 68405-008-02 NDC: 68405-008-03

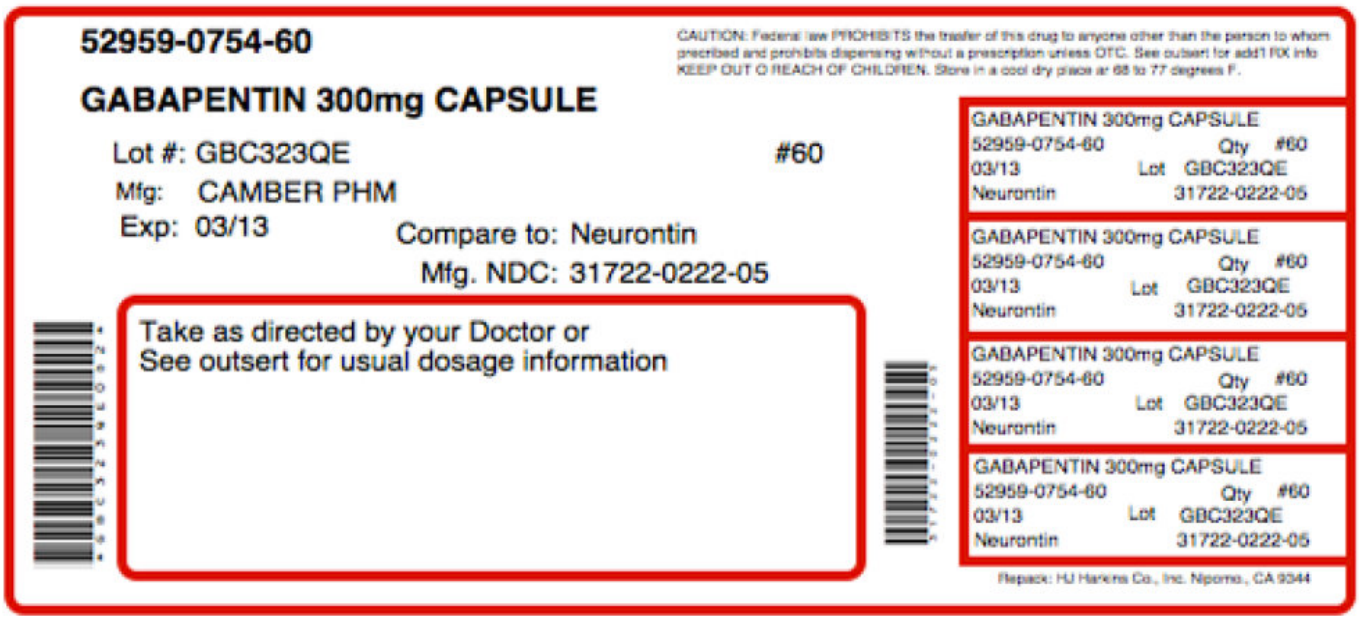
Storage
Store in a cool dry place 45-90o F (8-32o C) relative humidity below 50%. Theramine is supplied in a recyclable plastic bottle with a child-resistant cap.

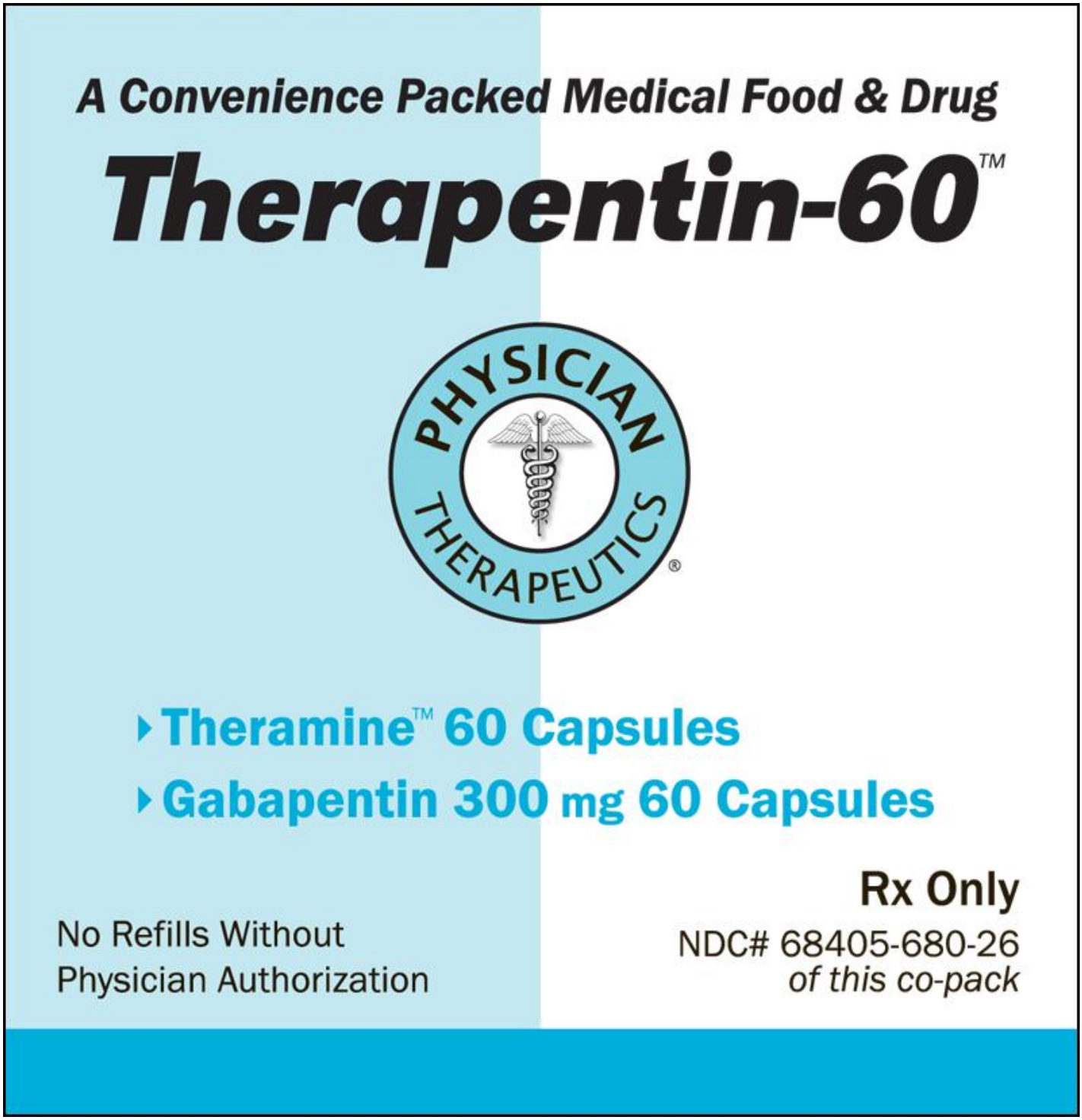
68405-008-02 Directions for use: Must be administered under physician supervision. For adults only. As a Medical Food, take one (1) or two (2) capsules every four hours or as directed by physician. For the dietary management of Myalgia. Contains no added sugar, starch, wheat, yeast, preservatives, artificial flavor. Storage: Keep tightly closed in a cool dry place 8-32°C (45-90°F), relative humidity, below 50%. Warning: Keep this product out of the reach of children. NDC# 68405-008-02 LOT# 007007 PHYSICIAN THERAPEUTICS THERAMINE Medical Food Rx only 60 Capsules Ingredients: Each serving (per 2 capsules) contains: Proprietary Amino Acid Formulation Whey Protein Hydrolysate (milk sourced isolate), L-Arginine (as L-Arginine HCl), L-Histidine HCI, L-Glutamine, L-Serine Gamma Amino Butyric Acid Choline Bitartrate Griffonia Seed Extract (5-HTP) Cocoa Extract (6% Theobromine) Grape Seed Extract (85% Polyphenols) Cinnamon (bark) Other Ingredients: Gelatin, Tricalcium Phosphate, Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, Titanium

Dioxide, FDandC Red #3, FDandC Blue #1. Distributed exclusively by: Physicians Therapeutics A Division of Targeted Medical Pharma, Inc. Los Angeles, CA 90077 www.ptlcentral.com US Patent 7,582,315; 7,585,523; 7,595,067; 7,601,369. LOT 007007 EXP 08/13

A Convenience Packed Medical Food and Drug Therapentin-60 PHYSICIAN THERAPEUTICS > Theramine 60 Capsules > Gabapentin 300 mg 60 Capsules No Refills Without Physician Authorization Rx Only NDC# 68405-680-26 of this co-pack







THERAPENTIN-60

gabapentin, .gamma.-aminobutyric acid kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68405-680

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68405-680-26	1 in 1 KIT		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 BOTTLE	60
Part 2	1 BOTTLE	60

Part 1 of 2

GABAPENTIN

gabapentin capsule

Product Information	
Item Code (Source)	NDC:52959-754(NDC:31722-222)
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
GABAPENTIN (UNII: 6CW7F3G59X) (GABAPENTIN - UNII:6CW7F3G59X)	GABAPENTIN	300 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	yellow (Yellow Opaque Cap and Yellow Opaque Body)	**Score**	no score
Shape	CAPSULE	**Size**	21mm
Flavor		**Imprint Code**	IG322;300mg
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:52959-754-60	60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090705	05/17/2011	

Part 2 of 2

THERAMINE 60

.gamma.-aminobutyric acid capsule

Product Information

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
.GAMMA.-AMINOBUTYRIC ACID (UNII: 2ACZ6IPC6I) (.GAMMA.-AMINOBUTYRIC ACID - UNII:2ACZ6IPC6I)	.GAMMA.-AMINOBUTYRIC ACID	100 mg

Inactive Ingredients

Ingredient Name	Strength
GELATIN (UNII: 2G86QN327L)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TRICALCIUM PHOSPHATE (UNII: K4C08XP666)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POWDERED CELLULOSE (UNII: SMD1X3XO9M)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	purple (PURPLE, WHITE)	**Score**	no score
Shape	CAPSULE	**Size**	20mm
Flavor		**Imprint Code**	;
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

Medical Food		05/17/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		05/17/2011	

Labeler - Physician Therapeutics LLC (931940964)

Establishment

Name	Address	ID/FEI	Business Operations
Invagen Pharmaceuticals, Inc.		165104469	manufacture

Establishment

Name	Address	ID/FEI	Business Operations
Targeted Medical Pharma Inc.		126962740	manufacture

Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company, Inc.		147681894	repack

Revised: 8/2011 Physician Therapeutics LLC