

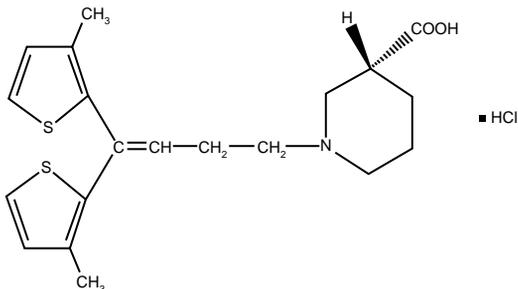
GABITRIL®

(tiagabine hydrochloride)

Tablets

DESCRIPTION

GABITRIL (tiagabine HCl) is an antiepilepsy drug available as 2 mg, 4 mg, 12 mg, 16 mg, and 20 mg tablets for oral administration. Its chemical name is (-)-(R)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]piperidine hydrochloride, its molecular formula is $C_{20}H_{25}NO_2S_2$ HCl, and its molecular weight is 412.0. Tiagabine HCl is a white to off-white, odorless, crystalline powder. It is insoluble in heptane, sparingly soluble in water, and soluble in aqueous base. The structural formula is:



Inactive Ingredients

GABITRIL tablets contain the following inactive ingredients: Ascorbic acid, colloidal silicon dioxide, crospovidone, hydrogenated vegetable oil wax, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, stearic acid, and titanium dioxide.

In addition, individual tablets contain:

2 mg tablets: FD&C Yellow No. 6.

4 mg tablets: D&C Yellow No. 10.

12 mg tablets: D&C Yellow No. 10 and FD&C Blue No. 1.

16 mg tablets: FD&C Blue No. 2.

20 mg tablets: D&C Red No. 30.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which tiagabine exerts its anti-seizure effect is unknown, although it is believed to be related to its ability, documented in *in vitro* experiments, to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. These experiments have shown that tiagabine binds to recognition sites associated with the GABA uptake carrier. It is thought that, by this action, tiagabine blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding on the surfaces of postsynaptic cells. Inhibition of GABA uptake has been shown for synaptosomes, neuronal cell cultures, and glial cell cultures. In rat-derived hippocampal slices, tiagabine has been shown to prolong GABA-mediated inhibitory post-synaptic potentials. Tiagabine increases the amount of GABA available in the extracellular space of the globus pallidus, ventral pallidum, and substantia nigra in rats at the ED_{50} and ED_{85}

doses for inhibition of pentylenetetrazol (PTZ)-induced tonic seizures. This suggests that tiagabine prevents the propagation of neural impulses that contribute to seizures by a GABA-ergic action.

Tiagabine has shown efficacy in several animal models of seizures. It is effective against the tonic phase of subcutaneous PTZ-induced seizures in mice and rats, seizures induced by the proconvulsant DMCM in mice, audiogenic seizures in genetically epilepsy-prone rats (GEPR), and amygdala-kindled seizures in rats. Tiagabine has little efficacy against maximal electroshock seizures in rats and is only partially effective against subcutaneous PTZ-induced clonic seizures in mice, picrotoxin-induced tonic seizures in the mouse, bicuculline-induced seizures in the rat, and photic seizures in photosensitive baboons. Tiagabine produces a biphasic dose-response curve against PTZ- and DMCM-induced convulsions, with attenuated effectiveness at higher doses.

Based on *in vitro* binding studies, tiagabine does not significantly inhibit the uptake of dopamine, norepinephrine, serotonin, glutamate, or choline and shows little or no binding to dopamine D1 and D2, muscarinic, serotonin 5HT_{1A}, 5HT₂, and 5HT₃, beta-1 and 2 adrenergic, alpha-1 and alpha-2 adrenergic, histamine H2 and H3, adenosine A₁ and A₂, opiate μ and K₁, NMDA glutamate, and GABA_A receptors at 100 μ M. It also lacks significant affinity for sodium or calcium channels. Tiagabine binds to histamine H1, serotonin 5HT_{1B}, benzodiazepine, and chloride channel receptors at concentrations 20 to 400 times those inhibiting the uptake of GABA.

PHARMACOKINETICS

Tiagabine is well absorbed, with food slowing absorption rate but not altering the extent of absorption. Although its elimination half-life is 7 to 9 hours in normal volunteers, it is only 4 to 7 hours in patients receiving hepatic enzyme-inducing drugs (carbamazepine, phenytoin, primidone, and phenobarbital). In clinical trials, most patients were induced.

Absorption and Distribution: Absorption of tiagabine is rapid, with peak plasma concentrations occurring at approximately 45 minutes following an oral dose in the fasting state. Tiagabine is nearly completely absorbed (>95%), with an absolute oral bioavailability of about 90%. A high fat meal decreases the rate (mean T_{max} was prolonged to 2.5 hours, and mean C_{max} was reduced by about 40%) but not the extent (AUC) of tiagabine absorption. In all clinical trials, tiagabine was given with meals.

The pharmacokinetics of tiagabine are linear over the single dose range of 2 to 24 mg. Following multiple dosing, steady state is achieved within 2 days.

Tiagabine is 96% bound to human plasma proteins, mainly to serum albumin and α 1-acid glycoprotein over the concentration range of 10 ng/mL to 10,000 ng/mL. While the relationship between tiagabine plasma concentrations and clinical response is not currently understood, trough plasma concentrations observed in controlled clinical trials at doses from 30 to 56 mg/day ranged from <1 ng/mL to 234 ng/mL.

Metabolism and Elimination: Although the metabolism of tiagabine has not been fully elucidated, *in vivo* and *in vitro* studies suggest that at least two metabolic pathways for

tiagabine have been identified in humans: 1) thiophene ring oxidation leading to the formation of 5-oxo-tiagabine; and 2) glucuronidation. The 5-oxo-tiagabine metabolite does not contribute to the pharmacologic activity of tiagabine.

Based on *in vitro* data, tiagabine is likely to be metabolized primarily by the 3A isoform subfamily of hepatic cytochrome P450 (CYP 3A), although contributions to the metabolism of tiagabine from CYP 1A2, CYP 2D6 or CYP 2C19 have not been excluded.

Approximately 2% of an oral dose of tiagabine is excreted unchanged, with 25% and 63% of the remaining dose excreted into the urine and feces, respectively, primarily as metabolites, at least 2 of which have not been identified. The mean systemic plasma clearance is 109 mL/min (CV = 23%) and the average elimination half-life for tiagabine in healthy subjects ranged from 7 to 9 hours. The elimination half-life decreased by 50 to 65% in hepatic enzyme-induced patients with epilepsy compared to uninduced patients with epilepsy.

A diurnal effect on the pharmacokinetics of tiagabine was observed. Mean steady-state C_{\min} values were 40% lower in the evening than in the morning. Tiagabine steady-state AUC values were also found to be 15% lower following the evening tiagabine dose compared to the AUC following the morning dose.

SPECIAL POPULATIONS

Renal Insufficiency: The pharmacokinetics of total and unbound tiagabine were similar in subjects with normal renal function (creatinine clearance >80 mL/min) and in subjects with mild (creatinine clearance 40 to 80 mL/min), moderate (creatinine clearance 20 to 39 mL/min), or severe (creatinine clearance 5 to 19 mL/min) renal impairment. The pharmacokinetics of total and unbound tiagabine were also unaffected in subjects with renal failure requiring hemodialysis.

Hepatic Insufficiency: In patients with moderate hepatic impairment (Child-Pugh Class B), clearance of unbound tiagabine was reduced by about 60%. Patients with impaired liver function may require reduced initial and maintenance doses of tiagabine and/or longer dosing intervals compared to patients with normal hepatic function (see **PRECAUTIONS**).

Geriatric: The pharmacokinetic profile of tiagabine was similar in healthy elderly and healthy young adults.

Pediatric: Tiagabine has not been investigated in adequate and well-controlled clinical trials in patients below the age of 12. The apparent clearance and volume of distribution of tiagabine per unit body surface area or per kg were fairly similar in 25 children (age: 3 to 10 years) and in adults taking enzyme-inducing antiepilepsy drugs ([AEDs] e.g., carbamazepine or phenytoin). In children who were taking a non-inducing AED (e.g., valproate), the clearance of tiagabine based upon body weight and body surface area was 2 and 1.5-fold higher, respectively, than in uninduced adults with epilepsy.

Gender, Race and Cigarette Smoking: No specific pharmacokinetic studies were conducted to investigate the effect of gender, race and cigarette smoking on the disposition of tiagabine. Retrospective pharmacokinetic analyses, however, suggest that there is no clinically important difference between

the clearance of tiagabine in males and females, when adjusted for body weight. Population pharmacokinetic analyses indicated that tiagabine clearance values were not significantly different in Caucasian (N=463), Black (N=23), or Hispanic (N=17) patients with epilepsy, and that tiagabine clearance values were not significantly affected by tobacco use.

Interactions with other Antiepilepsy Drugs: The clearance of tiagabine is affected by the co-administration of hepatic enzyme-inducing antiepilepsy drugs. Tiagabine is eliminated more rapidly in patients who have been taking hepatic enzyme-inducing drugs, e.g. carbamazepine, phenytoin, primidone and phenobarbital than in patients not receiving such treatment (see **PRECAUTIONS, Drug Interactions**).

Interactions with Other Drugs: See **PRECAUTIONS, Drug Interactions**.

CLINICAL STUDIES

The effectiveness of GABITRIL as adjunctive therapy (added to other antiepilepsy drugs) was examined in three multi-center, double-blind, placebo-controlled, parallel-group, clinical trials in 769 patients with refractory partial seizures who were taking at least one hepatic enzyme-inducing antiepilepsy drug (AED), and two placebo-controlled cross-over studies in 90 patients. In the parallel-group trials, patients had a history of at least six complex partial seizures (Study 1 and Study 2, U.S. studies), or six partial seizures of any type (Study 3, European study), occurring alone or in combination with any other seizure type within the 8-week period preceding the first study visit in spite of receiving one or more AEDs at therapeutic concentrations.

In the first two studies, the primary protocol-specified outcome measure was the median reduction from baseline in the 4-week complex partial seizure (CPS) rates during treatment. In the third study, the protocol-specified primary outcome measure was the proportion of patients achieving a 50% or greater reduction from baseline in the 4-week seizure rate of all partial seizures during treatment. The results given below include data for complex partial seizures and all partial seizures for the intent-to-treat population (all patients who received at least one dose of treatment and at least one seizure evaluation) in each study.

Study 1 was a double-blind, placebo-controlled, parallel-group trial comparing GABITRIL 16 mg/day, GABITRIL 32 mg/day, GABITRIL 56 mg/day, and placebo. Study drug was given as a four times a day regimen. After a prospective Baseline Phase of 12 weeks, patients were randomized to one of the four treatment groups described above. The 16-week Treatment Phase consisted of a 4-week Titration Period, followed by a 12-week Fixed-Dose Period, during which concomitant AED doses were held constant. The primary outcome was assessed for the combined 32 and 56 mg/day groups compared to placebo.

Study 2 was a double-blind, placebo-controlled, parallel-group trial consisting of an 8-week Baseline Phase and a 12-week Treatment Phase, the first 4 weeks of which constituted a Titration Period and the last 8 weeks a Fixed-Dose Period. This study compared GABITRIL 16 mg BID and 8 mg QID to placebo. The protocol-specified primary outcome measure was assessed separately for each group treated with GABITRIL.

The following tables display the results of the analyses of these two trials.

Table 1
Median Reduction and Median Percent Reduction from Baseline in 4-Week Seizure Rates in Study 1

		Placebo (N=91)	GABITRIL 16 mg/day (N=61)	GABITRIL 32 mg/day (N=87)	GABITRIL 56 mg/day (N=56)	Combined 32 + 56 mg/day (N=143)
Complex Partial	Median Reduction	0.6	0.8	2.2*	2.9*	2.6*
	Median % Reduction [†]	9%	13%	25%	32%	29%
All Partial	Median Reduction	0.2	1.2	2.7*	3.5*	2.9*
	Median % Reduction [†]	3%	12%	24%	36%	27%

* $p < 0.05$

[†] Statistical significance was not assessed for median % reduction.

Table 2
Median Reduction and Median Percent Reduction from Baseline in 4-Week Seizure Rates in Study 2

		Placebo (N=107)	GABITRIL 16 mg BID (N=106)	GABITRIL 8 mg QID (N=104)
Complex Partial	Median Reduction	0.3	1.6	1.3*
	Median % Reduction [†]	4%	22%	15%
All Partial	Median Reduction	0.5	1.6	1.3
	Median % Reduction [†]	5%	19%	13%

* $p < 0.027$, necessary for statistical significance due to multiple comparisons.

[†] Statistical significance was not assessed for median % reduction.

Figures 1 to 4 present the proportion of patients (X-axis) whose percent reduction from baseline in the all partial seizure rate was at least as great as that indicated on the Y axis in the three placebo-controlled adjunctive studies (Studies 1, 2, and 3). A positive value on the Y axis indicates an improvement from baseline (i.e., a decrease in seizure rate), while a negative value indicates a worsening from baseline (i.e., an increase in seizure rate). Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo.

Figure 1 indicates that the proportion of patients achieving any particular level of reduction in seizure rate was consistently higher for the combined GABITRIL 32 mg and 56 mg groups compared to the placebo group in Study 1. For example, Figure 1 indicates that approximately 24% of patients treated with GABITRIL experienced a 50% or greater reduction, compared to 4% in the placebo group.

Figure 1
Study 1

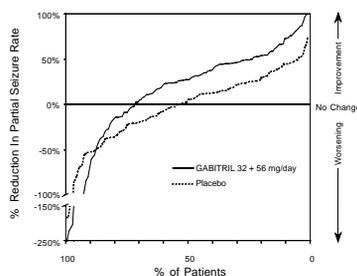


Figure 2 also displays the results for Study 1, which was a dose-response study, by treatment group, without combining

GABITRIL dosage groups. Figure 2 indicates a dose-response relationship across the three GABITRIL groups. The proportion of patients achieving any particular level of reduction in all partial seizure rates was consistently higher as the dose of GABITRIL was increased. For example, Figure 2 indicates that approximately 4% of patients in the placebo group experienced a 50% or greater reduction in all partial seizure rate, compared to approximately 10% of the GABITRIL 16 mg/day group, 21% of the GABITRIL 32 mg/day group, and 30% of the GABITRIL 56 mg/day group.

Figure 2
Study 1

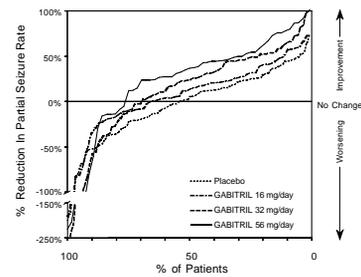
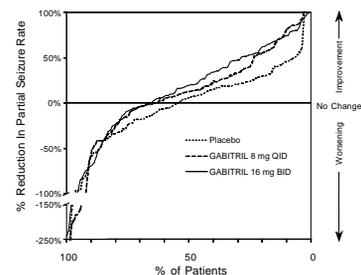


Figure 3 indicates that the proportion of patients achieving any particular level of reduction in partial seizure rate was consistently greater in patients taking GABITRIL than in those taking placebo in Study 2. (Study 2 compared placebo to GABITRIL 32 mg/day; one of the GABITRIL groups received 8 mg QID, while the other GABITRIL group received 16 mg BID). For example, Figure 3 indicates that approximately 7% of patients in the placebo group experienced a 50% or greater reduction in their partial seizure rate, compared to approximately 23% of patients in the GABITRIL 8 mg QID group and 28% of patients in the GABITRIL 16 mg BID group.

Figure 3
Study 2



Study 3 was a double-blind, placebo-controlled, parallel-group trial that compared GABITRIL 10 mg TID (N=77) with placebo (N=77). In this trial, patients were followed prospectively during a 12-week Baseline Phase and then randomized to receive study drug during an 18-week Treatment Phase. During the first 6 weeks of treatment (Titration Period), patients were titrated to 30 mg/day, after which they were maintained on this dose during the 12-week Fixed-Dose Period. The protocol-specified primary outcome measure (proportion of patients who achieved at least a 50% reduction from baseline in partial seizure rate) did not reach

statistical significance. However, analyses of the median reduction from baseline in 4-week partial seizure rate (the analyses presented above for Study 1 and Study 2) were performed and showed a statistically significant improvement compared to placebo in all partial and complex partial seizure rates (Table 3):

Table 3
Median Reduction and Median Percent Reduction from Baseline in 4-Week Seizure Rates in Study 3

		Placebo (N=77)	GABITRIL 30 mg/day (N=77)
Complex Partial ^{†‡}	Median Reduction	-0.1	1.3*
	Median % Reduction [†]	-1%	14%
All Partial	Median Reduction	-0.5	1.1*
	Median % Reduction [†]	-7%	11%

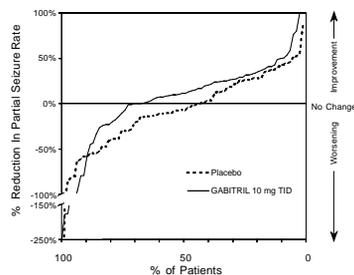
* $p < 0.05$

[†] Statistical significance was not assessed for median % reduction.

[‡] N=72 and 75 for placebo and GABITRIL, respectively.

Figure 4 indicates that the proportion of patients achieving any particular level of reduction in seizure activity was consistently higher in those taking GABITRIL than those taking placebo in Study 3. For example, Figure 4 indicates that approximately 5% of patients in the placebo group experienced a 50% or greater reduction in their partial seizure rate compared to approximately 10% of patients in the GABITRIL group.

Figure 4
Study 3



The two other placebo-controlled trials that examined the effectiveness of GABITRIL were small cross-over trials (N=46 and 44). Both trials included an open Screening Phase during which patients were titrated to an optimal dose and then treated with this dose for an additional 4 weeks. After this Open Phase, patients were randomized to one of two blinded treatment sequences (GABITRIL followed by placebo or placebo followed by GABITRIL). The Double-Blind Phase consisted of two Treatment Periods, each lasting 7 weeks (with a 3 week washout between periods). The outcome measures were median within patient differences between placebo and GABITRIL Treatment Periods in 4-week complex partial and all partial seizure rates. The reductions in seizure rates were statistically significant in both studies.

INDICATIONS AND USAGE

GABITRIL (tiagabine hydrochloride) is indicated as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures.

CONTRAINDICATIONS

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

WARNINGS

Withdrawal Seizures: As a rule, antiepilepsy drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency. In a placebo-controlled, double-blind, dose-response study (Study 1 described in **CLINICAL STUDIES**) designed, in part, to investigate the capacity of GABITRIL to induce withdrawal seizures, study drug was tapered over a 4-week period after 16 weeks of treatment. Patients' seizure frequency during this 4-week withdrawal period was compared to their baseline seizure frequency (before study drug). For each partial seizure type, for all partial seizure types combined, and for secondarily generalized tonic-clonic seizures, more patients experienced increases in their seizure frequencies during the withdrawal period in the three GABITRIL groups than in the placebo group. The increase in seizure frequency was not affected by dose. GABITRIL should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Cognitive/Neuropsychiatric Adverse Events: Adverse events most often associated with the use of GABITRIL were related to the central nervous system. The most significant of these can be classified into 2 general categories: 1) impaired concentration, speech or language problems, and confusion (effects on thought processes); and 2) somnolence and fatigue (effects on level of consciousness). The majority of these events were mild to moderate. In controlled clinical trials, these events led to discontinuation of treatment with GABITRIL in 6% (31 of 494) of patients compared to 2% (5 of 275) of the placebo-treated patients. A total of 1.6% (8 of 494) of the GABITRIL treated patients in the controlled trials were hospitalized secondary to the occurrence of these events compared to 0% of the placebo treated patients. Some of these events were dose related and usually began during initial titration.

Patients with a history of spike and wave discharges on EEG have been reported to have exacerbations of their EEG abnormalities associated with these cognitive/neuropsychiatric events. This raises the possibility that these clinical events may, in some cases, be a manifestation of underlying seizure activity (see **PRECAUTIONS, EEG**). In the documented cases of spike and wave discharges on EEG with cognitive/neuropsychiatric events, patients usually continued tiagabine, but required dosage adjustment.

Additionally, there have been postmarketing reports of patients who have experienced cognitive/neuropsychiatric symptoms, some accompanied by EEG abnormalities such as generalized spike and wave activity, that have been reported as nonconvulsant status epilepticus. Some reports describe recovery following reduction of dose or discontinuation of GABITRIL.

Status Epilepticus: In the three double-blind, placebo-controlled, parallel-group studies (Studies 1, 2, and 3), the incidence of any type of status epilepticus (simple, complex, or generalized tonic-clonic) in patients receiving GABITRIL was 0.8% (4 of 494 patients) versus 0.7% (2 of 275 patients) receiving placebo. Among the patients treated with GABITRIL across

all epilepsy studies (controlled and uncontrolled), 5% had some form of status epilepticus. Of the 5%, 57% of patients experienced complex partial status epilepticus. A critical risk factor for status epilepticus was the presence of a previous history; 33% of patients with a history of status epilepticus had recurrence during GABITRIL treatment. Because adequate information about the incidence of status epilepticus in a similar population of patients with epilepsy who have not received treatment with GABITRIL is not available, it is impossible to state whether or not treatment with GABITRIL is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with GABITRIL.

Sudden Unexpected Death In Epilepsy (SUDEP): There have been as many as 10 cases of sudden unexpected deaths during the clinical development of tiagabine among 2531 patients with epilepsy (3831 patient-years of exposure).

This represents an estimated incidence of 0.0026 deaths per patient-year. This rate is within the range of estimates for the incidence of sudden and unexpected deaths in patients with epilepsy not receiving GABITRIL (ranging from 0.0005 for the general population with epilepsy, 0.003 to 0.004 for clinical trial populations similar to that in the clinical development program for GABITRIL, to 0.005 for patients with refractory epilepsy). The estimated SUDEP rates in patients receiving GABITRIL are also similar to those observed in patients receiving other antiepilepsy drugs, chemically unrelated to GABITRIL, that underwent clinical testing in similar populations at about the same time. This evidence suggests that the SUDEP rates reflect population rates, not a drug effect.

PRECAUTIONS

General

Use in Non-Induced Patients: Virtually all experience with GABITRIL has been obtained in patients receiving at least one concomitant enzyme-inducing antiepilepsy drug (AED). Use in non-induced patients (e.g., patients receiving valproate monotherapy) may require lower doses or a slower dose titration of GABITRIL for clinical response. Patients taking a combination of inducing and non-inducing drugs (e.g., carbamazepine and valproate) should be considered to be induced.

Generalized Weakness: Moderately severe to incapacitating generalized weakness has been reported following administration of GABITRIL in 28 of 2531 (approximately 1%) patients with epilepsy. The weakness resolved in all cases after a reduction in dose or discontinuation of GABITRIL.

Binding in the Eye and Other Melanin-Containing Tissues: When dogs received a single dose of radiolabeled tiagabine, there was evidence of residual binding in the retina and uvea after 3 weeks (the latest time point measured). Although not directly measured, melanin binding is suggested. The ability of available tests to detect potentially adverse consequences, if any, of the binding of tiagabine to melanin-containing tissue is unknown and there was no systematic monitoring for relevant ophthalmological changes during the clinical development of GABITRIL. However, long term (up to one year) toxicological studies of tiagabine in dogs showed no treatment-related ophthalmoscopic

changes and macro- and microscopic examinations of the eye were unremarkable. Accordingly, although there are no specific recommendations for periodic ophthalmologic monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Use in Hepatically-Impaired Patients: Because the clearance of tiagabine is reduced in patients with liver disease, dosage reduction may be necessary in these patients.

Serious Rash: Four patients treated with tiagabine during the product's premarketing clinical testing developed what were considered to be serious rashes. In two patients, the rash was described as maculopapular; in one it was described as vesiculobullous; and in the 4th case, a diagnosis of Stevens Johnson Syndrome was made. In none of the 4 cases is it certain that tiagabine was the primary, or even a contributory, cause of the rash. Nevertheless, drug associated rash can, if extensive and serious, cause irreversible morbidity, even death.

Information for Patients: Patients should be instructed to take GABITRIL only as prescribed.

Patients should be advised that GABITRIL may cause dizziness, somnolence, and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive nor to operate other complex machinery until they have gained sufficient experience on GABITRIL to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive depressive effects, caution should also be used when patients are taking other CNS depressants in combination with GABITRIL.

Because teratogenic effects were seen in the offspring of rats exposed to maternally toxic doses of tiagabine and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Because of the possibility that tiagabine may be excreted in breast milk, patients should be advised to notify those providing care to themselves and their children if they intend to breast-feed or are breast-feeding an infant.

Laboratory Tests

Therapeutic Monitoring of Plasma Concentrations of Tiagabine: A therapeutic range for tiagabine plasma concentrations has not been established. In controlled trials, trough plasma concentrations observed among patients randomized to doses of tiagabine that were statistically significantly more effective than placebo ranged from <1 ng/mL to 234 ng/mL (median, 10th and 90th percentiles are 23.7 ng/mL, 5.4 ng/mL, and 69.8 ng/mL, respectively). Because of the potential for pharmacokinetic interactions between GABITRIL and drugs that induce or inhibit hepatic metabolizing enzymes, it may be useful to obtain plasma levels of tiagabine before and after changes are made in the therapeutic regimen.

Clinical Chemistry and Hematology: During the development of GABITRIL, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his/her care.

EEG: Patients with a history of spike and wave discharges on EEG have been reported to have exacerbations of their EEG abnormalities associated with cognitive/neuropsychiatric events. This raises the possibility that these clinical events may, in some cases, be a manifestation of underlying seizure activity (see **WARNINGS, Cognitive/Neuropsychiatric Adverse Events**). In the documented cases of spike and wave discharges on EEG with cognitive/neuropsychiatric events, patients usually continued tiagabine, but required dosage adjustment.

Drug Interactions

In evaluating the potential for interactions among co-administered antiepilepsy drugs (AEDs), whether or not an AED induces or does not induce metabolic enzymes is an important consideration. Phenytoin, phenobarbital and carbamazepine are generally classified as enzyme inducers; valproate and gabapentin are not. GABITRIL is considered to be a non-enzyme inducing AED.

The drug interaction data described in this section were obtained from studies involving either healthy subjects or patients with epilepsy.

Effects of GABITRIL on other Antiepilepsy Drugs (AEDs):

Phenytoin: Tiagabine had no effect on the steady-state plasma concentrations of phenytoin in patients with epilepsy.

Carbamazepine: Tiagabine had no effect on the steady-state plasma concentrations of carbamazepine or its epoxide metabolite in patients with epilepsy.

Valproate: Tiagabine causes a slight decrease (about 10%) in steady-state valproate concentrations.

Phenobarbital or Primidone: No formal pharmacokinetic studies have been performed examining the addition of tiagabine to regimens containing phenobarbital or primidone. The addition of tiagabine in a limited number of patients in three well-controlled studies caused no systematic changes in phenobarbital or primidone concentrations when compared to placebo.

Effects of other Antiepilepsy Drugs (AEDs) on GABITRIL:

Carbamazepine: Population pharmacokinetic analyses indicate that tiagabine clearance is 60% greater in patients taking carbamazepine with or without other enzyme-inducing AEDs.

Phenytoin: Population pharmacokinetic analyses indicate that tiagabine clearance is 60% greater in patients taking phenytoin with or without other enzyme-inducing AEDs.

Phenobarbital (Primidone): Population pharmacokinetic analyses indicate that tiagabine clearance is 60% greater in patients taking phenobarbital (primidone) with or without other enzyme-inducing AEDs.

Valproate: The addition of tiagabine to patients taking valproate chronically had no effect on tiagabine pharmacokinetics, but valproate significantly decreased tiagabine binding *in vitro* from 96.3 to 94.8%, which resulted in an increase of approximately 40% in the free tiagabine concentration. The clinical relevance of this *in vitro* finding is unknown.

Interaction of GABITRIL with Other Drugs:

Cimetidine: Co-administration of cimetidine (800 mg/day) to

patients taking tiagabine chronically had no effect on tiagabine pharmacokinetics.

Theophylline: A single 10 mg dose of tiagabine did not affect the pharmacokinetics of theophylline at steady state.

Warfarin: No significant differences were observed in the steady-state pharmacokinetics of R-warfarin or S-warfarin with the addition of tiagabine given as a single dose. Prothrombin times were not affected by tiagabine.

Digoxin: Concomitant administration of tiagabine did not affect the steady-state pharmacokinetics of digoxin or the mean daily trough serum level of digoxin.

Ethanol or Triazolam: No significant differences were observed in the pharmacokinetics of triazolam (0.125 mg) and tiagabine (10 mg) when given together as a single dose. The pharmacokinetics of ethanol were not affected by multiple-dose administration of tiagabine. Tiagabine has shown no clinically important potentiation of the pharmacodynamic effects of triazolam or alcohol. Because of the possible additive effects of drugs that may depress the nervous system, ethanol or triazolam should be used cautiously in combination with tiagabine.

Oral Contraceptives: Multiple dose administration of tiagabine (8 mg/day monotherapy) did not alter the pharmacokinetics of oral contraceptives in healthy women of child-bearing age.

Antipyrine: Antipyrine pharmacokinetics were not significantly different before and after tiagabine multiple-dose regimens. This indicates that tiagabine does not cause induction or inhibition of the hepatic microsomal enzyme systems responsible for the metabolism of antipyrine.

Carcinogenesis: In rats, a study of the potential carcinogenicity associated with tiagabine HCl administration showed that 200 mg/kg/day (plasma exposure [AUC] 36 to 100 times that at the maximum recommended human dosage [MRHD] of 56 mg/day) for 2 years resulted in small, but statistically significant increases in the incidences of hepatocellular adenomas in females and Leydig cell tumors of the testis in males. The significance of these findings relative to the use of GABITRIL in humans is unknown. The no effect dosage for induction of tumors in this study was 100 mg/kg/day (17 to 50 times the exposure at the MRHD). No statistically significant increases in tumor formation were noted in mice at dosages up to 250 mg/kg/day (20 times the MRHD on a mg/m² basis).

Mutagenesis: Tiagabine produced an increase in structural chromosome aberration frequency in human lymphocytes *in vitro* in the absence of metabolic activation. No increase in chromosomal aberration frequencies was demonstrated in this assay in the presence of metabolic activation. No evidence of genetic toxicity was found in the *in vitro* bacterial gene mutation assays, the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells, the *in vivo* mouse micronucleus test, or an unscheduled DNA synthesis assay.

Impairment of Fertility: Studies of male and female rats administered dosages of tiagabine HCl prior to and during

mating, gestation, and lactation have shown no impairment of fertility at doses up to 100 mg/kg/day. This dose represents approximately 16 times the maximum recommended human dose (MRHD) of 56 mg/day, based on body surface area (mg/m²). Lowered maternal weight gain and decreased viability and growth in the rat pups were found at 100 mg/kg, but not at 20 mg/kg/day (3 times the MRHD on a mg/m² basis).

Pregnancy: Pregnancy Category C: Tiagabine has been shown to have adverse effects on embryo-fetal development, including teratogenic effects, when administered to pregnant rats and rabbits at doses greater than the human therapeutic dose.

An increased incidence of malformed fetuses (various craniofacial, appendicular, and visceral defects) and decreased fetal weights were observed following oral administration of 100 mg/kg/day to pregnant rats during the period of organogenesis. This dose is approximately 16 times the maximum recommended human dose (MRHD) of 56 mg/day, based on body surface area (mg/m²). Maternal toxicity (transient weight loss/reduced maternal weight gain during gestation) was associated with this dose, but there is no evidence to suggest that the teratogenic effects were secondary to the maternal effects. No adverse maternal or embryo-fetal effects were seen at a dose of 20 mg/kg/day (3 times the MRHD on a mg/m² basis).

Decreased maternal weight gain, increased resorption of embryos and increased incidences of fetal variations, but not malformations, were observed when pregnant rabbits were given 25 mg/kg/day (8 times the MRHD on a mg/m² basis) during organogenesis. The no effect level for maternal and embryo-fetal toxicity in rabbits was 5 mg/kg/day (equivalent to the MRHD on a mg/m² basis).

When female rats were given tiagabine 100 mg/kg/day during late gestation and throughout parturition and lactation, decreased maternal weight gain during gestation, an increase in stillbirths, and decreased postnatal offspring viability and growth were found. There are no adequate and well-controlled studies in pregnant women. Tiagabine should be used during pregnancy only if clearly needed.

Use in Nursing Mothers: Studies in rats have shown that tiagabine HCl and/or its metabolites are excreted in the milk of that species. Levels of excretion of tiagabine and/or its metabolites in human milk have not been determined and effects on the nursing infant are unknown. GABITRIL 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 have not been established. The pharmacokinetics of tiagabine were evaluated in pediatric patients age 3 to 10 years (see **CLINICAL PHARMACOLOGY** - Pediatric).

Geriatric Use: Because few patients over the age of 65 (approximately 20) were exposed to GABITRIL during its clinical evaluation, no specific statements about the safety or effectiveness of GABITRIL in this age group could be made.

ADVERSE REACTIONS

The most commonly observed adverse events in placebo-controlled, parallel-group, add-on epilepsy trials associated

with the use of GABITRIL in combination with other antiepilepsy drugs not seen at an equivalent frequency among placebo-treated patients were dizziness/light-headedness, asthenia/lack of energy, somnolence, nausea, nervousness/irritability, tremor, abdominal pain, and thinking abnormal/difficulty with concentration or attention.

Approximately 21% of the 2531 patients who received GABITRIL in clinical trials of epilepsy discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were dizziness (1.7%), somnolence (1.6%), depression (1.3%), confusion (1.1%), and asthenia (1.1%).

In Studies 1 and 2 (U.S. studies), the double-blind, placebo-controlled, parallel-group, add-on studies, the proportion of patients who discontinued treatment because of adverse events was 11% for the group treated with GABITRIL and 6% for the placebo group. The most common adverse events considered the primary reason for discontinuation were confusion (1.2%), somnolence (1.0%), and ataxia (1.0%).

Adverse Event Incidence in Controlled Clinical Trials:

Table 4 lists treatment-emergent signs and symptoms that occurred in at least 1% of patients treated with GABITRIL for epilepsy participating in parallel-group, placebo-controlled trials and were numerically more common in the GABITRIL group. In these studies, either GABITRIL or placebo was added to the patient's current antiepilepsy drug therapy. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when GABITRIL was added to concurrent antiepilepsy drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice when 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 4
Treatment-Emergent Adverse Event¹ Incidence in Parallel-Group, Placebo-Controlled, Add-On Trials (events in at least 1% of patients treated with GABITRIL and numerically more frequent than in the placebo group)

Body System/ COSTART	GABITRIL N=494 %	Placebo N=275 %
Body as a Whole		
Abdominal Pain	7	3
Pain (unspecified)	5	3
Cardiovascular		
Vasodilation	2	1
Digestive		
Nausea	11	9
Diarrhea	7	3
Vomiting	7	4
Increased Appetite	2	0
Mouth Ulceration	1	0
Musculoskeletal		
Myasthenia	1	0
Nervous System		

Dizziness	27	15
Asthenia	20	14
Somnolence	18	15
Nervousness	10	3
Tremor	9	3
Difficulty With Concentration/Attention*	6	2
Insomnia	6	4
Ataxia	5	3
Confusion	5	3
Speech Disorder	4	2
Difficulty With Memory*	4	3
Paresthesia	4	2
Depression	3	1
Emotional Lability	3	2
Abnormal Gait	3	2
Hostility	2	1
Nystagmus	2	1
Language Problems*	2	0
Agitation	1	0
Respiratory System		
Pharyngitis	7	4
Cough Increased	4	3
Skin and Appendages		
Rash	5	4
Pruritus	2	0

¹ Patients in these add-on studies were receiving one to three concomitant enzyme-inducing antiepilepsy drugs in addition to GABITRIL or placebo. Patients may have reported multiple adverse experiences; thus, patients may be included in more than one category.

* COSTART term substituted with a more clinically descriptive term.

Other events reported by 1% or more of patients treated with GABITRIL but equally or more frequent in the placebo group were: accidental injury, chest pain, constipation, flu syndrome, rhinitis, anorexia, back pain, dry mouth, flatulence, ecchymosis, twitching, fever, amblyopia, conjunctivitis, urinary tract infection, urinary frequency, infection, dyspepsia, gastroenteritis, nausea and vomiting, myalgia, diplopia, headache, anxiety, acne, sinusitis, and incoordination.

Study 1 was a dose-response study including doses of 32 mg and 56 mg. Table 5 shows adverse events reported at a rate of $\geq 5\%$ in at least one GABITRIL group and more frequent than in the placebo group. Among these events, tremor, difficulty with concentration/attention, and perhaps asthenia exhibited a positive relationship to dose.

Table 5
Treatment-Emergent Adverse Event Incidence in Study 1[†]
(events in at least 5% of patients treated with GABITRIL 32 or 56 mg and numerically more frequent than in the placebo group)

Body System/ COSTART Term	GABITRIL	GABITRIL	Placebo (N=91) %
	56 mg (N=57) %	32 mg (N=88) %	
Body as a Whole			
Accidental Injury	21	15	20
Infection	19	10	12
Flu Syndrome	9	6	3
Pain	7	2	3
Abdominal Pain	5	7	4
Digestive System			
Diarrhea	2	10	6
Hemic and Lymphatic System			
Ecchymosis	0	6	1
Musculoskeletal System			
Myalgia	5	2	3
Nervous System			

Dizziness	28	31	12
Asthenia	23	18	15
Tremor	21	14	1
Somnolence	19	21	17
Nervousness	14	11	6
Difficulty With			
Concentration/Attention*	14	7	3
Ataxia	9	6	6
Depression	7	1	0
Insomnia	5	6	3
Abnormal Gait	5	5	3
Hostility	5	5	2
Respiratory System			
Pharyngitis	7	8	6
Special Senses			
Amblyopia	4	9	8
Urogenital System			
Urinary Tract Infection	5	0	2

[†] Patients in this study were receiving one to three concomitant enzyme-inducing antiepilepsy drugs in addition to GABITRIL or placebo. Patients may have reported multiple adverse experiences; thus, patients may be included in more than one category.

* COSTART term substituted with a more clinically descriptive term.

The effects of GABITRIL in relation to those of placebo on the incidence of adverse events and the types of adverse events reported were independent of age, weight, and gender. Because only 10% of patients were non-Caucasian in parallel-group, placebo-controlled trials, there is insufficient data to support a statement regarding the distribution of adverse experience reports by race.

Other Adverse Events Observed During All Clinical Trials: GABITRIL has been administered to 2531 patients during all phase 2/3 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 2531 patients exposed to GABITRIL who experienced events of the type cited on at least one occasion while receiving GABITRIL. All reported events are included except those already listed above, events seen only three times or fewer (unless potentially important), events very unlikely to be drug-related, and those too general to be informative. Events are included without regard to determination of a causal relationship to tiagabine.

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:* Allergic reaction, chest pain, chills, cyst, neck pain, and malaise. *Infrequent:* Abscess, cellulitis, facial edema, halitosis, hernia, neck rigidity, neoplasm, pelvic pain, photosensitivity reaction, sepsis, sudden death, and suicide attempt.

Cardiovascular System: *Frequent:* Hypertension, palpitation, syncope, and tachycardia. *Infrequent:* Angina pectoris, cerebral ischemia, electrocardiogram abnormal, hemorrhage, hypotension, myocardial infarct, pallor, peripheral vascular disorder, phlebitis, postural hypotension, and thrombophlebitis.

Digestive System: *Frequent:* Gingivitis and stomatitis. *Infrequent:* Abnormal stools, cholecystitis, cholelithiasis, dysphagia, eructation, esophagitis, fecal incontinence, gastritis, gastrointestinal hemorrhage, glossitis, gum hyperplasia, hepatomegaly, increased salivation, liver function tests abnormal, melena, periodontal abscess, rectal hemorrhage, thirst, tooth caries, and ulcerative stomatitis.

Endocrine System: *Infrequent:* Goiter and hypothyroidism.

Hemic and Lymphatic System: *Frequent:* Lymphadenopathy. *Infrequent:* Anemia, erythrocytes abnormal, leukopenia, petechia, and thrombocytopenia.

Metabolic and Nutritional: *Frequent:* Edema, peripheral edema, weight gain, and weight loss. *Infrequent:* Dehydration, hypercholesterolemia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, and hyponatremia.

Musculoskeletal System: *Frequent:* Arthralgia. *Infrequent:* Arthritis, arthrosis, bursitis, generalized spasm, and tendinous contracture.

Nervous System: *Frequent:* Depersonalization, dysarthria, euphoria, hallucination, hyperkinesia, hypertonia, hypesthesia, hypokinesia, hypotonia, migraine, myoclonus, paranoid reaction, personality disorder, reflexes decreased, stupor, twitching, and vertigo. *Infrequent:* Abnormal dreams, apathy, choreoathetosis, circumoral paresthesia, CNS neoplasm, coma, delusions, dry mouth, dystonia, encephalopathy, hemiplegia, leg cramps, libido increased, libido decreased, movement disorder, neuritis, neurosis, paralysis, peripheral neuritis, psychosis, reflexes increased, and urinary retention.

Respiratory System: *Frequent:* Bronchitis, dyspnea, epistaxis, and pneumonia. *Infrequent:* Apnea, asthma, hemoptysis, hiccups, hyperventilation, laryngitis, respiratory disorder, and voice alteration.

Skin and Appendages: *Frequent:* Alopecia, dry skin, and sweating. *Infrequent:* Contact dermatitis, eczema, exfoliative dermatitis, furunculosis, herpes simplex, herpes zoster, hirsutism, maculopapular rash, psoriasis, skin benign neoplasm, skin carcinoma, skin discolorations, skin nodules, skin ulcer, subcutaneous nodule, urticaria, and vesiculobullous rash.

Special Senses: *Frequent:* Abnormal vision, ear pain, otitis media, and tinnitus. *Infrequent:* Blepharitis, blindness, deafness, eye pain, hyperacusis, keratoconjunctivitis, otitis externa, parosmia, photophobia, taste loss, taste perversion, and visual field defect.

Urogenital System: *Frequent:* Dysmenorrhea, dysuria, metrorrhagia, urinary incontinence, and vaginitis. *Infrequent:* Abortion, amenorrhea, breast enlargement, breast pain, cystitis, fibrocystic breast, hematuria, impotence, kidney failure, menorrhagia, nocturia, papanicolaou smear suspicious, polyuria, pyelonephritis, salpingitis, urethritis, urinary urgency, and vaginal hemorrhage.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of GABITRIL have not been evaluated in human studies.

OVERDOSAGE

Human Overdose Experience: Human experience of acute overdose with GABITRIL is limited. Eleven patients in clinical trials took single doses of GABITRIL up to 800 mg. All patients fully recovered, usually within one day. The most common symptoms reported after overdose included somnolence, impaired consciousness, agitation, confusion, speech difficulty, hostility, depression, weakness, and myoclonus. One patient who ingested a single dose of 400 mg experienced generalized tonic-clonic status epilepticus, which responded to intravenous phenobarbital.

Eleven individuals (including five children <7 years old) not in tiagabine clinical trials accidentally ingested tiagabine in single doses up to 20 mg. These individuals were asymptomatic in six cases. Symptoms exhibited in at least one of the other five individuals included ataxia, confusion, somnolence, impaired consciousness, impaired speech, agitation, lethargy, drowsiness, and myoclonus. One individual experienced a tonic-clonic seizure but was taking other agents which may be associated with seizures. All individuals recovered, usually within one day.

Management of Overdose: There is no specific antidote for overdose with GABITRIL. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of clinical status of the patient. Since tiagabine is mostly metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial. A Certified Poison Control Center should be consulted for up to date information on the management of overdose with GABITRIL.

DOSAGE AND ADMINISTRATION

GABITRIL (tiagabine HCl) is recommended as adjunctive therapy in patients 12 years and older. GABITRIL is given orally and should be taken with food.

Adequate and controlled clinical studies with GABITRIL were conducted in patients taking enzyme-inducing AEDs (e.g., phenytoin, carbamazepine, and barbiturates). Patients taking only non-enzyme-inducing AEDs (e.g., valproate, gabapentin, and lamotrigine) may require lower doses or a slower titration of GABITRIL for clinical response.

Adults and Adolescents 12 Years or Older: In adolescents 12 to 18 years old, GABITRIL should be initiated at 4 mg once daily. Modification of concomitant antiepilepsy drugs is not necessary, unless clinically indicated. The total daily dose of GABITRIL may be increased by 4 mg at the beginning of Week 2. Thereafter, the total daily dose may be increased by 4 to 8 mg at weekly intervals until clinical response is achieved or up to 32 mg/day. The total daily dose should be given in divided doses two to four times daily. Doses above 32 mg/day have been tolerated in a small number of adolescent patients for a relatively short duration.

In adults, GABITRIL should be initiated at 4 mg once daily. Modification of concomitant antiepilepsy drugs is not necessary,

unless clinically indicated. The total daily dose of GABITRIL may be increased by 4 to 8 mg at weekly intervals until clinical response is achieved or, up to 56 mg/day. The total daily dose should be given in divided doses two to four times daily. Doses above 56 mg/day have not been systematically evaluated in adequate well-controlled trials.

Experience is limited in patients taking total daily doses above 32 mg/day using twice daily dosing. A typical dosing titration regimen for patients taking enzyme-inducing AEDs is provided in Table 6.

Table 6
Typical Dosing Titration Regimen for Patients Taking Enzyme-Inducing AEDs

	Initiation and Titration Schedule	Total Daily Dose
Week 1	Initiate at 4 mg once daily	4 mg/day
Week 2	Increase total daily dose by 4 mg	8 mg/day (in two divided doses)
Week 3	Increase total daily dose by 4 mg	12 mg/day (in three divided doses)
Week 4	Increase total daily dose by 4 mg	16 mg/day (in two to four divided doses)
Week 5	Increase total daily dose by 4 to 8 mg	20 to 24 mg/day (in two to four divided doses)
Week 6	Increase total daily dose by 4 to 8 mg	24 to 32 mg/day (in two to four divided doses)
Usual Adult Maintenance Dose:	32 to 56 mg/day in two to four divided doses	

HOW SUPPLIED

GABITRIL tablets are available in five dosage strengths.

2 mg orange-peach, round tablets, debossed with  on one side and 402 on the opposite side, are available in bottles of 100 (NDC 63459-402-01).

4 mg yellow, round tablets, debossed with  on one side and 404 on the opposite side, are available in bottles of 100 (NDC 63459-404-01).

12 mg green, ovaloid tablets, debossed with  on one side and 412 on the opposite side, are available in bottles of 100 (NDC 63459-412-01).

16 mg blue, ovaloid tablets, debossed with  on one side and 416 on the opposite side, are available in bottles of 100 (NDC 63459-416-01).

20 mg pink, ovaloid tablets, debossed with  on one side and 420 on the opposite side, are available in bottles of 100 (NDC 63459-420-01).

Recommended Storage: Store tablets at controlled room temperature, between 20-25°C (68-77°F). See USP. Protect from light and moisture.

ANIMAL TOXICOLOGY

In repeat dose toxicology studies, dogs receiving daily oral doses of 5 mg/kg/day or greater experienced unexpected CNS effects throughout the study. These effects occurred acutely and included marked sedation and apparent visual impairment which was characterized by a lack of awareness of objects, failure to fix on and follow moving objects, and absence of a blink reaction. Plasma exposures (AUCs) at 5 mg/kg/day were equal to those in humans receiving the maximum recommended daily human dose of 56 mg/day. The effects were reversible upon cessation of treatment and were not associated with any observed structural abnormality. The implications of these findings for humans are unknown.

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