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 α1-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 12 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) thiopeptide ring oxidation leading to the formation of 5-oxo-tiagabine; and 2) glucuronidation. The 5-oxo-tiagabine isolated does not demonstrate antiepileptic 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 65% of the remaining dose excreted in 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 of tiagabine increased by 56 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 Cmax 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) and 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 severe hepatic impairment 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.

Gender, Race and Cigarette Smoking: No specific pharmacokinetic studies were performed to investigate the effect of gender, race or 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 trials in 763 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 greater than or equal to a 50% reduction in CPS rate 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
**GABITRIL® (tiagabine hydrochloride) Tablets**

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=91)</th>
<th>GABITRIL 16 mg/day (N=51)</th>
<th>GABITRIL 32 mg/day (N=87)</th>
<th>GABITRIL 56 mg/day (N=56)</th>
<th>Combined 32 and 56 mg/day (N=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex Partial</td>
<td>Median Reduction</td>
<td>0.6</td>
<td>0.8</td>
<td>2.2*</td>
<td>2.9*</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
<td>9%</td>
<td>13%</td>
<td>25%</td>
<td>32%</td>
</tr>
<tr>
<td>All Partial</td>
<td>Median Reduction</td>
<td>0.2</td>
<td>1.2</td>
<td>2.7*</td>
<td>3.5*</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
<td>3%</td>
<td>12%</td>
<td>24%</td>
<td>36%</td>
</tr>
</tbody>
</table>

* p < 0.05
† Statistical significance was not assessed for median % reduction.
‡ N=72 and 75 for placebo and GABITRIL, respectively.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=107)</th>
<th>GABITRIL 16 mg BID (N=106)</th>
<th>GABITRIL 8 mg QID (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex Partial</td>
<td>Median Reduction</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
<td>4%</td>
<td>22%</td>
</tr>
<tr>
<td>All Partial</td>
<td>Median Reduction</td>
<td>0.5</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
<td>5%</td>
<td>19%</td>
</tr>
</tbody>
</table>

* 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 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 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=77)</th>
<th>GABITRIL 30 mg/day (N=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex Partial</td>
<td>Median Reduction</td>
<td>-0.1</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
<td>-1%</td>
</tr>
<tr>
<td>All Partial</td>
<td>Median Reduction</td>
<td>-0.5</td>
</tr>
<tr>
<td></td>
<td>Median % Reduction</td>
<td>-7%</td>
</tr>
</tbody>
</table>

* p < 0.05
† Statistical significance was not assessed for median % reduction.
‡ N=72 and 75 for placebo and GABITRIL, respectively.
Table 4: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events per 1000 Patients</th>
<th>Drug Patients with Events per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.8</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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.

Any consideration prescribing GABITRIL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Illness and its treatment may increase the risk for abnormal思想政治 events. However, suicidal thoughts and behavior are usually emergent events, and at any given point in time, a range of indications suggests that the risk applies to all AEDs prescribed as 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 symptoms and signs 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.

Withdrawal Seizures: As a rule, antiepileptic 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, 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 moderate in severity. 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 16% (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 single symptoms.

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, all 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...
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).

**Laboratory Tests**

**Therapeutic Monitoring of Plasma Concentrations of Tiagabine:** A therapeutic plasma concentration range for tiagabine 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 metabolism or 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 antiepileptic drugs (AEDs), whether or not an AED induces or does not induce metabolic enzymes is an important consideration. Carbamazepine, phenytoin, primidone, and phenobarbital are generally classified as enzyme inducers; valproate and gabapentin are not. GABITRIL is not intended to be a non-enzyme inducing AED (see PRECAUTIONS, General, Use in Non-Induced Patients).

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):**

**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. Phenoobarbital (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 carbamazepine caused 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:**

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**Phenytoin:** 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.

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CONTRAINDICATIONS
GABITRIL® (tiagabine hydrochloride) Tablets

In vitro data showed that tiagabine is 96% bound to human plasma protein and therefore has the potential to interact with other highly protein bound compounds. Such an interaction can potentially lead to higher free fractions of either tiagabine or the competing drug.

INTERAKTIONEN

GABITRIL mit Highly Protein Bound Drugs:

*COSTART* term substituted with a more clinically descriptive term.

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).

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:

Adverse events were usually mild or moderate in intensity. GABITRIL or placebo was added to the patient’s current antiepilepsy drug therapy. 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 Events in Controlled Clinical Trials: Table 5 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.

To provide additional information regarding the effects of in utero exposure to GABITRIL, physicians are advised to recommend that pregnant patients taking GABITRIL enroll in the 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:

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, Special Populations, 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/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 (1.2%), confusion (1.1%), and ataxia (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%).
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 6 shows adverse events reported at a rate of ≥ 5% in at least one GABITRIL group and more frequent than in the placebo group. Among these events, depression, tremor, dyspepsia, gastroenteritis, nausea and vomiting, myalgia, diplopia, headache, anxiety, acne, sinusitis, and incoordination were more frequent than in the placebo group. Among these events, depression, tremor, dyspepsia, gastroenteritis, nausea and vomiting, myalgia, diplopia, headache, anxiety, acne, sinusitis, and incoordination.

Table 6: 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)

<table>
<thead>
<tr>
<th>Body System/ COSTART Term</th>
<th>GABITRIL 56 mg (N=57) %</th>
<th>GABITRIL 32 mg (N=68) %</th>
<th>Placebo (N=91) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>21</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Infection</td>
<td>19</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td>7</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3</td>
<td>7</td>
<td>4</td>
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<tr>
<td><strong>Digestive System</strong></td>
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<tr>
<td>Diarrhea</td>
<td>2</td>
<td>10</td>
<td>6</td>
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<tr>
<td><strong>Hemic and Lymphatic System</strong></td>
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<tr>
<td>Ecchymosis</td>
<td>0</td>
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<tr>
<td><strong>Musculoskeletal System</strong></td>
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<tr>
<td>Myalgia</td>
<td>5</td>
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<td>3</td>
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<tr>
<td><strong>Nervous System</strong></td>
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<tr>
<td>Dizziness</td>
<td>28</td>
<td>31</td>
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<tr>
<td>Asthenia</td>
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<td>18</td>
<td>15</td>
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<tr>
<td>Tremor</td>
<td>21</td>
<td>14</td>
<td>1</td>
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<tr>
<td>Somnolence</td>
<td>19</td>
<td>21</td>
<td>17</td>
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<tr>
<td>Nervousness</td>
<td>14</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Difficulty with Concentration/Attention*</td>
<td>14</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Ataxia</td>
<td>9</td>
<td>6</td>
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</tr>
<tr>
<td>Depression</td>
<td>7</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Insomnia</td>
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<tr>
<td>Abnormal Gait</td>
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<td>3</td>
<td>3</td>
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<tr>
<td>Hostility</td>
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<td>2</td>
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<tr>
<td><strong>Respiratory System</strong></td>
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<tr>
<td>Pharyngitis</td>
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<td>8</td>
<td>6</td>
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<td><strong>Special Senses</strong></td>
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<td>Amblyopia</td>
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<td>9</td>
<td>8</td>
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<tr>
<td><strong>Urogenital System</strong></td>
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<tr>
<td>Urinary Tract Infection</td>
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<td>2</td>
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</tbody>
</table>

† Patients in this study were receiving one to three concomitant enzyme-inducing 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 weight, age, 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 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 myalgia; infrequent: Absence, cellulitis, facial edema, halitosis, herpetic, 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, cholecytis, 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: Frequent: Goiter and hypothyroidism.


Metabolic and Nutritional: Frequent: Edema, peripheral edema, weight gain, and weight loss; infrequent: Dehydration, hypercholesterolemia, hyperglycemia, hypoglycemia, hypokalemia, and hyponatremia.


Nervous System: Frequent: Depersonalization, dysaphria, euphoria, hallucination, hyperkinesia, hypertension, hypokinesia, hypothesia, 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, dizziness, encephalopathy, entrapment, leg cramps, limbic increased, limb 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, hiccupps, 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 vescicular rash.

Special Senses: Frequent: Abnormal vision, ear pain, otitis media, and tinnitus.

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.

Postmarketing Reports

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

Skin and subcutaneous tissue disorders: Bullous dermatitis

Eye disorders: vision blurred

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. Other accompanying GABITRIL overdose, alone or in combination with other drugs, have included: seizures including status epilepticus in patients with and without underlying seizure disorders, nonconvulsive status epilepticus, respiratory arrest, coma, loss of consciousness, ataxia, dizziness, confusion, somnolence, drowsiness, agitation, aggression, sedation, lethargy, myoclonus, spina bifida, dysphagia, tremors, disorientation, psychotic disorder, vomiting, hostility, and temporary paralyzis. Respiratory depression was seen in a number of patients, including children, in the context of seizures.
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 support 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

General:
The blood level of tiagabine obtained after a given dose depends on whether the patient also is receiving a drug that induces the metabolism of tiagabine. The presence of an inducer means that the attained blood level will be substantially reduced. Dosing should take the presence of concomitant medications into account. GABITRIL (tiagabine HCl) is recommended as adjunctive therapy for the treatment of partial seizures in patients 12 years and older. The following dosing recommendations apply to all patients taking GABITRIL:

- GABITRIL is given orally and should be taken with food.
- Do not use a loading dose of GABITRIL.
- Dose titration: Rapid escalation and/or large dose increments of GABITRIL should not be used.
- Missed dose(s): If the patient forgets to take the prescribed dose of GABITRIL at the scheduled time, the patient should not attempt to make up for the missed dose by increasing the next dose. If a patient has missed multiple doses, patient should refer back to his or her physician for possible re-titration as clinically indicated.
- Dosage adjustment of GABITRIL should be considered whenever a change in the patient’s enzyme-inducing status occurs as a result of the addition, discontinuation, or dose change of the enzyme-inducing agent.

Induced Adults and Adolescents 12 Years or Older: The following dosing recommendations apply to patients who are already taking enzyme-inducing antiepilepsy drugs (AEDs) (e.g., carbamazepine, phenytoin, primidone, and phenobarbital). Such patients are considered induced patients when administering GABITRIL. 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 and well-controlled clinical trials.

Non-Induced Adults and Adolescents 12 Years or Older: The following dosing recommendations apply to patients who are taking non-enzyme-inducing AEDs. Such patients are considered non-induced patients:

Following a given dose of GABITRIL, the estimated plasma concentration in the non-induced patients is more than twice that in patients receiving enzyme-inducing agents. Use in non-induced patients requires lower doses of GABITRIL. These patients may also require a slower titration of GABITRIL compared to that of induced patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, General, Use in Non-Induced Patients).

<table>
<thead>
<tr>
<th>Initiation and Titratin Schedule</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1: Initiate at 4 mg once daily</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>Week 2: Increase total daily dose by 4 mg</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>Week 3: Increase total daily dose by 4 mg</td>
<td>12 mg/day</td>
</tr>
<tr>
<td>Week 4: Increase total daily dose by 4 mg</td>
<td>16 mg/day</td>
</tr>
<tr>
<td>Week 5: Increase total daily dose by 4 to 8 mg</td>
<td>20 to 24 mg/day</td>
</tr>
<tr>
<td>Week 6: Increase total daily dose by 4 to 8 mg</td>
<td>24 to 32 mg/day</td>
</tr>
<tr>
<td>Usual Adult Maintenance Dose Induced Patients:</td>
<td>32 to 56 mg/day in two to four divided doses</td>
</tr>
</tbody>
</table>

Table 7: Typical Dosing Titration Regimen for Patients Already Taking Enzyme-Inducing AEDs

How Supplied: GABITRIL tablets are available in four dosage strengths.

- 2 mg orange-peach, round tablets, debossed with $\text{GAB}$ on one side and 402 on the opposite side, are available in bottles of 30 (NDC 63459-402-30).
- 4 mg yellow, round tablets, debossed with $\text{GAB}$ on one side and 404 on the opposite side, are available in bottles of 30 (NDC 63459-404-30).
- 12 mg green, ovaloid tablets, debossed with $\text{GAB}$ on one side and 412 on the opposite side, are available in bottles of 30 (NDC 63459-412-30).
- 16 mg blue, ovaloid tablets, debossed with $\text{GAB}$ on one side and 416 on the opposite side, are available in bottles of 30 (NDC 63459-416-30).

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

Medication Guide
GABITRIL® (gāb-i-tril)
(tiagabine hydrochloride)
Tablets

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

What is the most important information I should know about GABITRIL?
Do not stop taking GABITRIL without first talking to your healthcare provider.
Stopping GABITRIL suddenly can cause serious problems.
GABITRIL can cause serious side effects, including:
1. GABITRIL may cause seizures in people who do not have epilepsy. If you do not have a seizure disorder and you take GABITRIL, you may have a seizure or seizures that do not stop (status epilepticus).
2. Like other antiepileptic drugs, GABITRIL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood
Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?
Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
Keep all follow-up visits with your healthcare provider as scheduled.
Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop GABITRIL without first talking to a healthcare provider.
Stopping GABITRIL suddenly can cause serious problems. If you have epilepsy and stop a seizure medicine suddenly, you may have more frequent seizures or seizures that will not stop (status epilepticus).

What is GABITRIL?
GABITRIL is a prescription medicine used with other medicines to treat partial seizures in adults and children age 12 and older.

Who should not take GABITRIL?
Do not take GABITRIL if you are allergic to tiagabine hydrochloride or any of the other ingredients in GABITRIL. See the end of this Medication Guide for a complete list of ingredients in GABITRIL.

What should I tell my healthcare provider before taking GABITRIL?
Before taking GABITRIL, tell your healthcare provider if you:
   - have or have had depression, mood problems, or suicidal thoughts or behavior
   - have liver problems
   - have a history of seizures that do not stop (status epilepticus)
   - have any other medical conditions
   - are pregnant or plan to become pregnant. It is not known if GABITRIL can harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking GABITRIL. You and your healthcare provider will decide if you should take GABITRIL while you are pregnant.
   - If you become pregnant while taking GABITRIL, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAEED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicines during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
   - are breastfeeding or plan to breastfeed. It is not known if GABITRIL passes into breast milk or if it can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take GABITRIL.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Taking GABITRIL with certain other medicines can cause side effects or affect how well they work. Do not start or stop any other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine. Always tell your healthcare provider if there are any changes in any other medicines that you take.

How should I take GABITRIL?
Take GABITRIL exactly as your healthcare provider tells you.
Your healthcare provider may change your dose.
GABITRIL should be taken with food.
Do not stop taking GABITRIL without talking to your healthcare provider.
Stopping GABITRIL suddenly can increase your chances of having a seizure or cause seizures that will not stop.
If you miss a dose of GABITRIL, do not take 2 doses of GABITRIL at the same time. Contact your healthcare provider if you miss more than one dose.
If you take too much GABITRIL, call your healthcare provider or local Poison Control Center right away.

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

What are possible side effects of GABITRIL?
See “What is the most important information I should know about GABITRIL?”
GABITRIL may cause other serious side effects including:
   - seizures that can happen more often or become worse
   - trouble concentrating, problems with speech and language, feeling confused, feeling sleepy and tired, and problems thinking
   - weakness all over your body
   - eye and vision problems
   - serious rash
Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of GABITRIL include:
   - dizziness
   - lack of energy
   - drowsiness
   - nausea
   - nervousness
   - tremor
   - stomach pain
GABITRIL® (tiagabine hydrochloride) Tablets

- abnormal thinking
- difficulty with concentration or attention

These are not all the possible side effects of GABITRIL. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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

**How should I store GABITRIL?**
- Store GABITRIL between 68°F to 77°F (20°C to 25°C)
- Keep GABITRIL out of light
- Keep GABITRIL dry

**Keep GABITRIL and all medicines out of the reach of children.**

**General Information about GABITRIL**

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

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

For more information, call 1-888-483-8279.

**What are the ingredients in GABITRIL?**

**Active Ingredient:** tiagabine hydrochloride

**Inactive Ingredients:** ascorbic acid, colloidal silicon dioxide, crospovidone, hydrogenated vegetable oil wax, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, stearic acid and titanium dioxide.

In addition:
- the 2 mg tablets contain FD&C Yellow No. 6
- the 4 mg tablets contain D&C Yellow No. 10
- the 12 mg tablets contain D&C Yellow No. 10 and FD&C Blue No. 1
- the 16 mg tablets contain FD&C Blue No. 2

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

GABMG-003

May 2018

Rx only

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