**TIAGABINE**

**Therapeutics**

**Brands**  • Gabitril  
*see index for additional brand names*

**Generic?**  Yes

**Class**  
• Anticonvulsant; selective GABA reuptake inhibitor (SGRI)

**Commonly Prescribed for**  
*Bold for FDA approved*

• Partial seizures (adjunctive; adults and children 12 years and older)
• Anxiety disorders
• Neuropathic pain/chronic pain

**How the Drug Works**  
• Selectively blocks reuptake of gamma-aminobutyric acid (GABA) by presynaptic and glial GABA transporters

**How Long Until It Works**  
• Should reduce seizures by 2 weeks
• Not clear that it works in anxiety disorders or chronic pain but some patients may respond, and if they do, therapeutic actions can be seen by 2 weeks

**If It Works**  
• The goal of treatment is complete remission of symptoms (e.g., seizures, anxiety)
• The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
• Treatment of chronic neuropathic pain most often reduces but does not eliminate symptoms and is not a cure since symptoms usually recur after medicine stopped
• Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists

**If It Doesn’t Work (for neuropathic pain or anxiety disorders)**  
• Many patients have only a partial response where some symptoms are improved but others persist

**Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory**

• May only be effective in a subset of patients with neuropathic pain or anxiety disorders, in some patients who fail to respond to other treatments, or it may not work at all
• Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
• Consider biofeedback or hypnosis for pain
• Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
• Switch to another agent with fewer side effects

**Best Augmenting Combos for Partial Response or Treatment Resistance**  
• Tiagabine is itself an augmenting agent for numerous other anticonvulsants in treating epilepsy

*For neuropathic pain, tiagabine can augment TCAs and SNRIs as well as gabapentin, other anticonvulsants, and even opiates if done by experts while carefully monitoring in difficult cases*

• For anxiety, tiagabine is a second-line treatment to augment SSRIs, SNRIs, or benzodiazepines

**Tests**  
• None for healthy individuals
• Tiagabine may bind to tissue that contains melanin, so for long-term treatment opthalmological checks may be considered

**Side Effects**

**How Drug Causes Side Effects**  
• CNS side effects may be due to excessive actions of GABA

**Notable Side Effects**  
* Sedation, dizziness, asthenia, nervousness, difficulty concentrating, speech/language problems, confusion, tremor
• Diarrhea, vomiting, nausea
• Ecchymosis, depression
How To Dose

- Adjunct to enzyme-inducing antiepileptic drugs: initial 4 mg once daily; after 1 week can increase dose by 4–8 mg/day each week; maximum dose generally 56 mg/day in 2–4 divided doses
- Dosing for chronic pain or anxiety disorders not well established, but start as low as 2 mg at night, increasing by 2 mg increments every few days as tolerated to 8–12 mg/day
- Exercise particular caution when prescribing in uninduced patients

Dosing Tips

- Usually administered as adjunctive medication to other anticonvulsants in the treatment of epilepsy
  ✽ Dosing recommendations are based on studies of adjunctive use with enzyme-inducing antiepileptic drugs, which lower plasma levels of tiagabine by half; thus, when tiagabine is used without enzyme-inducing antiepileptic drugs the dose may need to be significantly reduced and may require a much slower titration rate
  ✽ Also administered as adjunctive medication to benzodiazepines, SSRIs, and/or SNRIs in the treatment of anxiety disorders; and to SNRIs, gabapentin, other anticonvulsants, and even opiates in the treatment of chronic pain
  ✽ Dosing varies considerably among individual patients but is definitely at the lower end of the dosing spectrum for patients with chronic neuropathic pain or anxiety disorders (i.e., 2–12 mg either as a split dose or all at night)
  ✽ Patients with chronic neuropathic pain and anxiety disorders are far less tolerant of CNS side effects, so they require a much slower dosage titration as well as a lower maintenance dose
  ✽ Gastrointestinal absorption is markedly slowed by the concomitant intake of food, which also lessens the peak plasma concentrations
  ✽ Thus, for improved tolerability and consistent clinical actions, instruct patients to always take with food
  ✽ Side effects may increase with dose

TIAGABINE (continued)
TIAGABINE

Overdose
- No fatalities have been reported; sedation, agitation, confusion, speech difficulty, hostility, depression, weakness, myoclonus, seizures, status epilepticus

Long-Term Use
- Safe

Habit Forming
- No

How to Stop
- Taper
- Epilepsy patients may seize upon withdrawal, especially if withdrawal is abrupt
- Discontinuation symptoms uncommon

Pharmacokinetics
- Primarily metabolized by CYP450 3A4
- Steady-state concentrations tend to be lower in the evening than in the morning
- Half-life approximately 7–9 hours
- Renally excreted

Drug Interactions
- Clearance of tiagabine may be reduced and thus plasma levels increased if taken with a non-enzyme-inducing antiepileptic drug (e.g., valproate, gabapentin, lamotrigine), so tiagabine dose may need to be reduced
- CYP450 3A4 inducers such as carbamazepine can lower the plasma levels of tiagabine
- CYP450 3A4 inhibitors such as nefazodone, fluvoxamine, and fluoxetine could theoretically increase the plasma levels of tiagabine
- Clearance of tiagabine is increased if taken with an enzyme-inducing antiepileptic drug (e.g., carbamazepine, phenobarbital, phenytoin, primidone) and thus plasma levels are reduced; however, no dose adjustments are necessary for treatment of epilepsy as the dosing recommendations for epilepsy are based on adjunctive treatment with an enzyme-inducing antiepileptic drug
- Despite common actions upon GABA, no pharmacodynamic or pharmacokinetic interactions have been shown when tiagabine is combined with the benzodiazepine triazolam or with alcohol

Other Warnings/Precautions
- Seizures have occurred in individuals without epilepsy who took tiagabine
- Risk of seizure may be dose-related; when tiagabine is used in the absence of enzyme-inducing antiepileptic drugs, which lower plasma levels of tiagabine, the dose may need to be reduced
- Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)
- Tiagabine may bind to melanin, raising the possibility of long-term ophthalmologic effects
- Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately

Do Not Use
- If there is a proven allergy to tiagabine

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Renal Impairment
- Although tiagabine is renally excreted, the pharmacokinetics of tiagabine in healthy patients and in those with impaired renal function are similar and no dose adjustment is recommended

Hepatic Impairment
- Clearance is decreased
- May require lower dose

Cardiac Impairment
- No dose adjustment recommended

Elderly
- Some patients may tolerate lower doses better

Children and Adolescents
- Safety and efficacy not established in children under age 12
- Maximum recommended dose generally 32 mg/day in 2–4 divided doses
Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- Antiepileptic Drug Pregnancy Registry: (888) 233–2334
- Taper drug if discontinuing
- Seizures, even mild seizures, may cause harm to the embryo/fetus
- Lack of definitive evidence of efficacy for chronic neuropathic pain or anxiety disorders suggests risk/benefit ratio is in favor of discontinuing tiagabine during pregnancy for those indications

Breast Feeding

- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- If drug is continued while breast feeding, infant should be monitored for possible adverse effects
- If infant shows signs of irritability or sedation, drug may need to be discontinued

Potential Advantages
- Treatment-resistant chronic neuropathic pain
- Treatment-resistant anxiety disorders

Potential Disadvantages
- May require 2–4 times a day dosing
- Needs to be taken with food

Primary Target Symptoms
- Incidence of seizures
- Pain
- Anxiety

Pearls
- Well studied in epilepsy
- Much use is off label
- Off-label use second-line and as an augmenting agent may be justified for treatment-resistant anxiety disorders and neuropathic pain and also for fibromyalgia
- Off-label use for bipolar disorder may not be justified
- One of the few agents that enhances slow-wave delta sleep, which may be helpful in chronic neuropathic pain syndromes
- Can be difficult to dose in patients who are not taking enzyme-inducing anticonvulsant drugs as the doses in uninduced patients have not been well studied, are generally much lower, and titration is much slower than in induced patients
- Can cause seizures even in patients without epilepsy, especially in patients taking other agents (antidepressants, antipsychotics, stimulants, narcotics) that are thought to lower the seizure threshold
Suggested Reading


