



Carbatrol/Tegretol/Tegretol-XR (carbamazepine)

Generic name: Carbamazepine

Available strengths: 100 mg (chewable), 200 mg tablets;

100 mg/5 mL oral suspension;

100 mg, 200 mg, 400 mg extended-release tablets

(Tegretol-XR); 200 mg, 300 mg extended-release capsules (Carbatrol)

Available in generic: Yes, except Carbatrol and Tegretol-XR

Drug class: Anticonvulsant/mood stabilizer

General Information

Carbamazepine is better known as an anticonvulsant—a medication for treating epilepsy. This may present some confusion for patients, as well as their families, when they are prescribed an anticonvulsant without a history of seizures. In the past decade, anticonvulsants have increasingly become the medications of choice for the treatment of bipolar disorder, particularly in acute mania. Carbamazepine was approved only for the treatment of epilepsy and neuralgic pain (trigeminal neuralgia) by the U.S. Food and Drug Administration; this is known as its *labeled use*. In clinical practice, physicians often prescribe medications for *unlabeled* (“off-label”) uses when published clinical studies, case reports, or their own clinical experiences support the efficacy and safety of these medications for these unapproved indications. When carbamazepine and other anticonvulsants are used for treating mood disorders, they are considered **mood stabilizers**.

Clinical studies have shown the effectiveness of carbamazepine for treating acute mania. Carbamazepine may also be effective in maintenance therapy to prevent relapse of mania. In treatment-resistant bipolar disorder, patients usually do better when carbamazepine is used in combination with another mood stabilizer, such as lithium. For some patients with rapid-cycling bipolar illness (those with four or more manic or depressive episodes a year), carbamazepine alone or in combination with another mood stabilizer may be more effective for stabilizing from frequent cycling.

It is not totally clear how some anticonvulsants are effective for seizures and bipolar disorder. The anticonvulsants, which have very complex effects on the central nervous system, may be effective by controlling “kindling” in the areas of the brain from which the psychiatric disorder emanates. Kindling is a phenomenon that occurs when repeated subthreshold stimulation is applied to certain regions of the brain and sensitizes them, setting

off a cascade of events leading to seizures or manic behavior. By decreasing electrical conduction or neurotransmitter activity in unstable brain cells, anticonvulsants are effective in controlling seizures and bipolar illness.

Dosing Information

The starting dosage of carbamazepine in treatment of bipolar disorder is 200 mg twice a day. The dosage is normally increased by 200 mg/day every 3–5 days. The therapeutic dosage depends on attaining a therapeutic blood level. Generally, the dosage range is 400–1,200 mg/day. Blood levels of carbamazepine should be monitored weekly for the first 4 weeks to ensure that adequate levels are achieved to produce the therapeutic response. Although therapeutic levels are attained with a given dosage, in about 2–4 weeks the levels may drop off significantly. This is due to carbamazepine's ability to speed up its own metabolism. The patient's dosage may need to be increased again to achieve the desired therapeutic level.

Carbamazepine is also available in extended-release capsule (Carbatrol) and tablet (Tegretol-XR) preparations, which require only once-a-day dosing. Carbamazepine also comes in a liquid preparation in a concentration of 100 mg/5 mL.

Common Side Effects

The most common side effects from carbamazepine are sedation, tiredness, nausea, and dizziness. At higher dosages, patients may experience jerky eye movements (**nystagmus**) or double vision (**diplopia**) and impaired coordination or clumsiness. Generally, these side effects are temporary and subside as tolerance to the medication develops.

Adverse Reactions and Precautions

Carbamazepine may cause drowsiness and impair alertness, especially at the start of therapy. Patients should use caution when driving or performing tasks that require alertness.

Agranulocytosis and **aplastic anemia** are very rare but serious—potentially fatal—adverse reactions from carbamazepine. Agranulocytosis presents with a sudden drop in the concentration of white blood cells (**leukopenia**). When a particular type of white blood cells (**granulocytes**), which are important for fighting infections, are severely decreased (**agranulocytosis**, or without granulocytes), the individual is susceptible to life-threatening infections. The risk of carbamazepine-induced agranulocytosis is very low. When detected early and with carbamazepine discontinued, patients recover completely. Early warning signs of infection, including sore throat, fever, and malaise, should be brought to the attention of the physician.

Another rare and potentially fatal adverse reaction is **aplastic anemia**, a condition in which the bone marrow stops producing blood cells, including platelets (important for clotting), white blood cells, and red blood cells. The risk of aplastic anemia from carbamazepine, however, is very rare. If it occurs, the individual may develop infections because of low white cells, anemia because of low red blood cells, and bleeding abnormalities because of low platelets. Some physicians may order a pretreatment complete blood count and repeat the test periodically, but many do not because carbamazepine-induced aplastic anemia is so rare. Instead, the physician will instruct the patient to report intractable infections, frequent bruising, frequent bleeding tendencies (e.g., bleeding of the gums from brushing teeth), and prolonged bleeding time.

The risk of agranulocytosis may increase when carbamazepine is taken in combination with other medications that potentiate this risk. For example, carbamazepine should not be taken with Clozaril (clozapine), because the combination may increase the risk of agranulocytosis.

Occasionally, carbamazepine causes mild elevation in liver enzyme levels, but there is rarely liver damage. The liver enzyme elevation is usually transient, and levels eventually return to normal. However, closer monitoring of liver function is warranted when liver enzyme levels are elevated. Discontinuation of carbamazepine may be necessary if liver enzyme levels increase to three times normal.

Use in Pregnancy and Breastfeeding: Pregnancy Category D

Carbamazepine crosses the placenta and may cause harm to the fetus. Cases of newborns with head and facial abnormalities, developmental delays, and spinal cord defects (**spina bifida**) have been reported in women who took carbamazepine during pregnancy. The risk appears to be highest when carbamazepine is taken in the first trimester. The use of carbamazepine should therefore be avoided in pregnancy whenever possible, especially in the first trimester. However, when carbamazepine is stopped and reoccurrence of mania occurs, the physician may discuss the need to restart carbamazepine after the first trimester or seek an alternative medication or treatment.

Nursing mothers should not take carbamazepine, because it is excreted in breast milk and may be harmful to the baby when ingested. If stopping the medication is not an alternative, breastfeeding should not be started or should be discontinued.

Possible Drug Interactions

Carbamazepine can affect the liver enzymes that metabolize many different medications, including carbamazepine itself, thus lowering the medications' concentration and diminishing their effectiveness. Conversely, other medications can also hinder the metabolism of carbamazepine and increase its levels. The clinically significant drug interactions reported with carbamazepine are summarized in the table below.

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| Tagamet (cimetidine), Prozac (fluoxetine), Luvox (fluvoxamine), Depakote (divalproex), erythromycin, Biaxin (clarithromycin), Calan (verapamil), Cardizem (diltiazem), Nizoral (ketoconazole), Diflucan (fluconazole), Darvon (propoxyphene), and isoniazid (e.g., INH) | These medications, when combined with carbamazepine, can increase the blood levels of carbamazepine to toxic levels. Dosages of these medications may need to be lowered when the medications are used in combination with carbamazepine. |
| Oral contraceptives, Coumadin (warfarin), Dilantin (phenytoin), theophylline, Plendil (felodipine), benzodiazepines (e.g., Valium), Doryx (doxycycline), Haldol (haloperidol), phenothiazines (e.g., Mellaril), Wellbutrin (bupropion), and cyclosporine | When carbamazepine is combined with these medications, it can lower their blood levels and decrease their effectiveness. For example, decreased effectiveness of an oral contraceptive may possibly lead to an unintended pregnancy. |

Patients taking carbamazepine should not consume alcohol because the combination may increase sedation and drowsiness. Moreover, the sedative effects of alcohol may act as a depressant, obscuring the therapeutic effects of carbamazepine and complicating treatment.

Overdose

Carbamazepine overdose is extremely hazardous, and the severity of toxic symptoms depends on the amount ingested. In small children the lethal dose is much lower than for an adult. Early symptoms of carbamazepine toxicity include neuromuscular disturbances, such as jerky eye movements (**nystagmus**), muscle jerks (**myoclonus**), increased reflex reactions (**hyperreflexia**), and severe nausea and vomiting. Symptoms of higher overdose, including respiratory depression, convulsions, cardiac arrhythmia, shock, and coma, may result in death, especially in small children.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought as well, because the information on the prescription label can be helpful to the treating physician in determining the number of pills ingested.

Special Considerations

- If you miss a dose, take it as soon as possible, within 2–3 hours of the scheduled dosing. If it is close to your next scheduled dose, skip the missed dose and continue on your regular dosing schedule, but do not take double doses.
- Take carbamazepine immediately after meals or with food to decrease stomach upset.
- Contact your physician if you have persistent symptoms of infection, including fever, sore throat, or malaise, and unusual signs of bleeding or bruising.
- Carbamazepine may cause sedation and drowsiness, especially during initiation of therapy, and impair your alertness. Use caution when driving or performing tasks that require alertness.
- Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication.
- Keep your medication out of reach of children. Overdose in small children is very dangerous.

If you have any questions about your medication, consult your physician or pharmacist.

Notes
