# Tegretol/Tegretol XR (carbamazepine) - Drug Summary

Novartis Pharmaceuticals Corporation





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Carbamazepine
(carbamazepine)

## BOXED WARNING

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) reported; increased risk w/ presence of HLA-B*1502 allele. Screen patients w/ ancestry in genetically at-risk populations for the presence of HLA-B*1502 prior to initiation of therapy. Avoid in patients testing positive for the allele unless benefits clearly outweigh risks. Aplastic anemia and agranulocytosis reported; obtain complete pretreatment hematological testing as a baseline and monitor closely if a patient exhibits low/decreased WBC or platelet counts during treatment. Consider discontinuation if evidence of significant bone marrow depression develops.

## COMMON BRAND NAMES

Tegretol, Tegretol-XR, Epitol, Carbamazepine

## THERAPEUTIC CLASS

Carboxamide

## DEA CLASS

RX

## ADULT DOSAGE & INDICATIONS

### Trigeminal Neuralgia

**Initial (Day 1):** 100mg bid (tab/tab, extended-release [ER]) or 1/2 tsp qid (200mg/day) (sus)
**Titrate:** May increase by up to 200mg/day using increments of 100mg q12h (tab/tab, ER) or 50mg (1/2 tsp) qid (sus) prn
**Maint:** 400-800mg/day. Attempt to reduce dose to minimum effective level or even to d/c therapy at least once every 3 months
**Max:** 1200mg/day

Beneficial results have also been reported in glossopharyngeal neuralgia

### Epilepsy

**Partial Seizures w/ Complex Symptomatology (Psychomotor, Temporal Lobe), Generalized Tonic-Clonic Seizures (Grand Mal), and Mixed Seizure Patterns of These, or Other Partial or Generalized Seizures:**

**Initial:** 200mg bid (tab/tab, ER) or 1 tsp qid (400mg/day) (sus)
**Titrate:** Increase at weekly intervals by adding up to 200mg/day bid (tab, ER) or tid or qid (all other formulations)
**Maint:** 800-1200mg/day
**Max:** 1200mg/day; doses up to 1600mg/day have been used in rare instances

**Combination Therapy:**
When added to existing anticonvulsant therapy, add gradually while other anticonvulsants are maintained or gradually decreased (except phenytoin, which may have to be increased)

### Conversions

**From Oral Carbamazepine Tabs to Carbamazepine Sus:**
Patients should be converted by administering the same number of mg/day in smaller, more frequent doses (eg, bid tabs to tid sus)

**From Carbamazepine Conventional Tabs to Carbamazepine ER Tabs:**
The same total daily mg dose of carbamazepine ER tabs should be administered

## PEDIATRIC DOSAGE & INDICATIONS

### Epilepsy

**Partial Seizures w/ Complex Symptomatology (Psychomotor, Temporal Lobe), Generalized Tonic-Clonic Seizures (Grand Mal), and Mixed Seizure Patterns of These, or Other Partial or Generalized Seizures:**

**<6 Years:**
**Initial:** 10-20mg/kg/day bid or tid (tab) or qid (sus)
**Titrate:** Increase weekly to tid or qid (tab/sus)
**Maint:** Optimal clinical response is achieved at daily doses <35mg/kg; no recommendation regarding safety at doses >35mg/kg/24 hrs

**6-12 Years:**
**Initial:** 100mg bid (tab/tab, ER) or 1/2 tsp qid (200mg/day) (sus)
**Titrate:** Increase at weekly intervals by adding up to 100mg/day bid (tab, ER) or tid or qid (all other formulations)
**Maint:** 400-800mg/day
**Max:** 1000mg/day

**>12 Years:**
**Initial:** 200mg bid (tab/tab, ER) or 1 tsp qid (400mg/day) (sus)
**Titrate:** Increase at weekly intervals by adding up to 200mg/day bid (tab, ER) or tid or qid (all other formulations)
**Maint:** 800-1200mg/day
**Max:**
**12-15 Years:** 1000mg/day
**>15 Years:** 1200mg/day

**Combination Therapy:**
When added to existing anticonvulsant therapy, add gradually while other anticonvulsants are maintained or gradually decreased (except phenytoin, which may have to be increased)

### Conversions

**From Oral Carbamazepine Tabs to Carbamazepine Sus:**
Patients should be converted by administering the same number of mg/day in smaller, more frequent doses (eg, bid tabs to tid sus)

**From Carbamazepine Conventional Tab to Carbamazepine ER Tabs:**
The same total daily mg dose of carbamazepine ER tabs should be administered

## ADMINISTRATION

Oral route

Take w/ meals.
Sus will produce higher peak levels than the same dose given as the tab; start patients given sus on lower doses and increase slowly to avoid unwanted side effects.

**Sus**
Do not administer simultaneously w/ other liquid medications or diluents.
Shake well before using.

**Tab, ER**
Swallow whole; do not chew or crush.

## HOW SUPPLIED

**Tab, Chewable:** 200mg*, (Tegretol) 100mg*; **Sus:** (Tegretol) 100mg/5mL [450mL]; **Tab:** (Tegretol, Epitol) 200mg*; **Tab, ER:** (Tegretol-XR) 100mg, 200mg, 400mg *scored

## CONTRAINDICATIONS

History of previous bone marrow depression, sensitivity to any of the tricyclic compounds (eg, amitriptyline, desipramine, imipramine, protriptyline, nortriptyline), coadministration w/ nefazodone. Concomitant use w/ an MAOI or w/in 14 days after discontinuing an MAOI.

## WARNINGS/PRECAUTIONS

D/C at 1st sign of rash; do not resume treatment and consider alternative therapy if signs/symptoms suggest SJS/TEN. Consider risks and benefits of therapy in patients known to be positive for HLA-A*3101. Patients w/ a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression. Drug reaction w/ eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity, reported; evaluate immediately if signs/symptoms (eg, fever, lymphadenopathy) are present and d/c if an alternative etiology cannot be established. Caution in patients w/ history of hypersensitivity reactions to anticonvulsants (eg, phenytoin, primidone, phenobarbital). Increased risk of suicidal thoughts or behavior reported. Has mild anticholinergic activity that may be associated w/ increased IOP; closely observe patients w/ increased IOP during therapy. Consider the possibility of activation of latent psychosis and, in elderly patients, of confusion or agitation. Avoid in patients w/ history of hepatic porphyria (eg, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda); acute attacks reported. Withdraw gradually to minimize potential of increased seizure frequency. Hyponatremia may occur and in many cases, appears to be caused by the syndrome of inappropriate antidiuretic hormone secretion; consider discontinuing therapy in patients w/ symptomatic hyponatremia. May cause fetal harm and symptoms representing neonatal withdrawal syndrome. Caution in patients w/ a mixed seizure disorder that includes atypical absence seizures; therapy associated w/ increased frequency of generalized convulsions in these patients. Caution in patients w/ history of cardiac conduction disturbance, cardiac/hepatic/renal damage, adverse hematologic or hypersensitivity reaction to other drugs, and interrupted courses of therapy w/ carbamazepine. Atrioventricular heart block (eg, 2nd- and 3rd-degree block) and hepatic effects (ranging from slight elevations in liver enzymes to rare cases of hepatic failure) reported. D/C if new or worsening clinical/lab evidence of liver dysfunction/hepatic damage, or active liver disease develops.

Interference w/ some pregnancy tests, decreased values of thyroid function tests, renal dysfunction, and eye changes reported. Higher prevalence of teratogenic effects w/ the use of anticonvulsants in combination therapy; if therapy is to be continued, monotherapy may be preferable for pregnant women. **Sus/Tab, Chewable 200mg:** Contains sorbitol; avoid w/ rare hereditary problems of fructose intolerance. **Tab, ER:** Coating is not absorbed and is excreted in the feces; may be noticeable in the stool.

## ADVERSE REACTIONS

Dizziness, drowsiness, unsteadiness, N/V.

## DRUG INTERACTIONS

See Contraindications. Close monitoring of carbamazepine levels is indicated and dosage adjustment may be required when given w/ drugs that increase/decrease levels. CYP3A4 inhibitors (eg, azole antifungals, erythromycin, protease inhibitors) may increase levels. Coadministration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide levels; adjust dose and/or monitor levels of carbamazepine when used w/ loxapine, quetiapine, or valproic acid. CYP3A4 inducers (eg, cisplatin, doxorubicin, rifampin) may decrease levels. May decrease levels of CYP1A2, 2B6, 2C9/19, and 3A4 substrates; monitoring of concentrations or dosage adjustment of the concomitant agents may be necessary. When added to aripiprazole therapy, double aripiprazole dose and if carbamazepine is later withdrawn, reduce aripiprazole dose. When used w/ tacrolimus, monitoring of tacrolimus levels and appropriate dosage adjustments are recommended. Avoid w/ temsirolimus; consider dose adjustment of temsirolimus if coadministration is a must. Avoid w/ lapatinib; gradually titrate up dose of lapatinib if carbamazepine is started in a patient already taking lapatinib and reduce lapatinib dose when carbamazepine is discontinued. Monitor concentrations of valproate when carbamazepine is introduced or withdrawn in patients using valproic acid. May cause, or would be expected to cause, decreased levels of the following drugs, for which monitoring of concentrations or dosage adjustment may be necessary: acetaminophen, albendazole, alprazolam, aprepitant, buprenorphine, bupropion, citalopram, clonazepam, clozapine, corticosteroids (eg, prednisolone, dexamethasone), cyclosporine, dicumarol, dihydropyridine calcium channel blockers (eg, felodipine), doxycycline, ethosuximide, everolimus, haloperidol, imatinib, itraconazole, lamotrigine, levothyroxine, methadone, methsuximide, mianserin, midazolam, olanzapine, oxcarbazepine, paliperidone, phensuximide, phenytoin, praziquantel, protease inhibitors, risperidone, sertraline, sirolimus, tadalafil, theophylline, tiagabine, topiramate, tramadol, trazodone, TCAs (eg, imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone, zonisamide. May increase cyclophosphamide toxicity. May increase risk of neurotoxic side effects w/ lithium. Increased isoniazid-induced hepatotoxicity reported w/ isoniazid. Alterations of thyroid function reported w/ other anticonvulsant medications. May decrease levels of hormonal contraceptive products (eg, oral and levonorgestrel subdermal implant contraceptives) that may render contraceptives less effective; consider alternative or back-up method of contraception. Resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents (eg, pancuronium, vecuronium, rocuronium) reported w/ chronic carbamazepine administration; monitor closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher. Increased risk of developing hyponatremia w/ diuretics. **Sus:** Occurrence of stool precipitate reported w/ liquid chlorpromazine or thioridazine.

## PREGNANCY AND LACTATION

**Pregnancy:** Category D. Physicians are advised to recommend that pregnant patients enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.
**Lactation:** Not for use in nursing.

## MECHANISM OF ACTION

Carboxamide; has not been established. Appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Depresses thalamic potential and bulbar and polysynaptic reflexes.

## PHARMACOKINETICS

**Absorption:** $T_{max}$=1.5 hrs (sus), 4-5 hrs (tab), 3-12 hrs (tab, ER). **Distribution:** Plasma protein binding (76%); crosses the placenta; found in breast milk. **Metabolism:** Liver via CYP3A4; carbamazepine-10,11-epoxide (active metabolite). **Elimination:** Urine (72%; 3% unchanged), feces (28%); $T_{1/2}$=25-65 hrs (initial), 12-17 hrs (repeated doses).

## ASSESSMENT

Assess for hypersensitivity to the drug, known sensitivity to any of the tricyclic compounds, mixed seizure disorder, history of cardiac conduction disturbance, renal/hepatic impairment, any other conditions where treatment is contraindicated or cautioned, pregnancy/nursing status, and possible drug interactions. Perform detailed history and physical exam prior to treatment. Screen for HLA-B*1502 and HLA-A*3101 allele in suspected populations. Obtain baseline CBCs w/ platelets and reticulocytes and serum iron, LFTs, complete urinalysis, BUN determinations, and eye examination (including slit-lamp exam, funduscopy, and tonometry).

## MONITORING

Monitor for signs/symptoms of dermatologic reactions, DRESS, bone marrow depression, aplastic anemia, agranulocytosis, increase in seizure frequency, emergence or worsening of depression, suicidal thoughts/behavior, unusual changes in mood/behavior, latent psychosis, confusion or agitation in elderly patients, hepatic effects, and other adverse reactions. Periodically monitor WBC and platelet counts, LFTs, serum drug levels, complete urinalysis, BUN determinations, and eye examinations.

## PATIENT COUNSELING

Inform of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity, or hepatic reactions; advise to report to physician even if the signs and symptoms are mild or when occurring after extended use. Instruct to immediately contact physician if a skin reaction occurs. Inform about the increased risk of suicidal thoughts and behavior; advise to report behaviors of concern immediately and to be alert for the emergence/worsening of symptoms of depression, any unusual changes in mood or behavior, the emergence of suicidal thoughts, or behavior/thoughts about self-harm. Advise to report the use of any other prescription or nonprescription medications or herbal products. Instruct to exercise caution when taken w/ alcohol due to a possible additive sedative effect. Inform that drowsiness or dizziness may occur; caution against hazardous tasks. Encourage patients to enroll in the NAAED Pregnancy Registry.

## STORAGE

**Tab, Chewable:** 20-25°C (68-77°F). Protect from light/moisture. (Tegretol) **Tab, Chewable:** ≤30°C (86°F). Protect from light/moisture. **Sus:** ≤30°C (86°F). **Tab:** ≤30°C (86°F). Protect from moisture. **Tab, ER:** 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture. (Epitol) **Tab:** 20-25°C (68-77°F). Protect from moisture.

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