OXCARBAZEPINE

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

**Generic?** Yes

**Class**  
• Anticonvulsant, voltage-sensitive sodium channel antagonist

**Commonly Prescribed for**  
*(bold for FDA approved)*  
• Partial seizures in adults with epilepsy (monotherapy or adjunctive)  
• Partial seizures in children ages 4–16 with epilepsy (monotherapy or adjunctive)  
• Bipolar disorder

**How the Drug Works**  
✽ Acts as a use-dependent blocker of voltage-sensitive sodium channels  
✽ Interacts with the open channel conformation of voltage-sensitive sodium channels  
✽ Interacts at a specific site of the alpha pore-forming subunit of voltage-sensitive sodium channels  
• Inhibits release of glutamate

**How Long Until It Works**  
• For acute mania, effects should occur within a few weeks  
• May take several weeks to months to optimize an effect on mood stabilization  
• Should reduce seizures by 2 weeks

**If It Works**  
• The goal of treatment is complete remission of symptoms (e.g., seizures, mania)  
• Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists  
• Continue treatment indefinitely to avoid recurrence of mania and seizures

**If It Doesn’t Work (for bipolar disorder)**  
✽ Many patients have only a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of mood  
• Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory  
• Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent  
• Consider adding psychotherapy  
• For bipolar disorder, consider the presence of noncompliance and counsel patient  
• Switch to another mood stabilizer with fewer side effects  
• Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

**Best Augmenting Combos for Partial Response or Treatment Resistance**  
• Oxcarbazepine is itself a second-line augmenting agent for numerous other anticonvulsants, lithium, and atypical antipsychotics in treating bipolar disorder, although its use in bipolar disorder is not yet well studied  
• Oxcarbazepine may be a second- or third-line augmenting agent for antipsychotics in treating schizophrenia, although its use in schizophrenia is also not yet well studied

**Tests**  
• Consider monitoring sodium levels because of possibility of hyponatremia, especially during the first 3 months

**SIDE EFFECTS**

**How Drug Causes Side Effects**  
• CNS side effects theoretically due to excessive actions at voltage-sensitive sodium channels

**Notable Side Effects**  
✽ Sedation (dose-dependent), dizziness (dose-dependent), headache, ataxia (dose-dependent), nystagmus, abnormal gait, confusion, nervousness, fatigue  
✽ Nausea (dose-dependent), vomiting, abdominal pain, dyspepsia  
• Diplopia (dose-dependent), vertigo, abnormal vision  
✽ Rash
Life-Threatening or Dangerous Side Effects
- Hyponatremia
- Rare activation of suicidal ideation and behavior (suicidality)

Weight Gain
- Occurs in significant minority
- Some patients experience increased appetite

Sedation
- Occurs in significant minority
- Dose-related
- Less than carbamazepine
- More when combined with other anticonvulsants
- Can wear off with time, but may not wear off at high doses

Dosing Tips
- Doses of oxcarbazepine need to be about one-third higher than those of carbamazepine for similar results
- Usually administered as adjunctive medication to other anticonvulsants, lithium, or atypical antipsychotics for bipolar disorder
- Side effects may increase with dose
- Although increased efficacy for seizures is seen at 2,400 mg/day compared to 1,200 mg/day, CNS side effects may be intolerable at the higher dose
- Liquid formulation can be administered mixed in a glass of water or directly from the oral dosing syringe supplied
- Slow dose titration may delay onset of therapeutic action but enhance tolerability to sedating side effects
- Should titrate slowly in the presence of other sedating agents, such as other anticonvulsants, in order to best tolerate additive sedative side effects

Overdose
- No fatalities reported

Habit Forming
- No

How to Stop
- Taper
- Epilepsy patients may seize upon withdrawal, especially if withdrawal is abrupt
- Rapid discontinuation may increase the risk of relapse in bipolar disorder
- Discontinuation symptoms uncommon

Usual Dosage Range
- 1,200–2,400 mg/day

Dosage Forms
- Tablet 150 mg, 300 mg, 600 mg
- Liquid 300 mg/5 mL

How to Dose
- Monotherapy for seizures or bipolar disorder: initial 600 mg/day in 2 doses; increase every 3 days by 300 mg/day; maximum dose generally 2,400 mg/day
- Adjunctive: initial 600 mg/day in 2 doses; each week can increase by 600 mg/day; recommended dose 1,200 mg/day; maximum dose generally 2,400 mg/day
- When converting from adjunctive to monotherapy in the treatment of epilepsy, titrate concomitant drug down over 3–6 weeks while titrating oxcarbazepine up over 2–4 weeks, with an initial daily oxcarbazepine dose of 600 mg divided in 2 doses
**Pharmacokinetics**
- Metabolized in the liver
- Renally excreted
- Inhibits CYP450 2C19
- **Oxcarbazepine is a prodrug for 10-hydroxy carbazepine**
- This main active metabolite is sometimes called the monohydroxy derivative or MHD, and is also known as licarbazepine
- **Half-life of parent drug is approximately 2 hours; half-life of MHD is approximately 9 hours; thus oxcarbazepine is essentially a prodrug rapidly converted to its MHD, licarbazepine**
- A mild inducer of CYP450 3A4
- Food does not affect absorption

**Do Not Use**
- If patient is taking an MAOI
- If there is a proven allergy to any tricyclic compound
- If there is a proven allergy to oxcarbazepine

**Drug Interactions**
- Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)
- Strong inducers of CYP450 cytochromes (e.g., carbamazepine, phenobarbital, phenytoin, and primidone) can decrease plasma levels of the active metabolite MHD
- Verapamil may decrease plasma levels of the active metabolite MHD
- Oxcarbazepine can decrease plasma levels of hormonal contraceptives and dihydropyridine calcium antagonists
- Oxcarbazepine at doses greater than 1,200 mg/day may increase plasma levels of phenytoin, possibly requiring dose reduction of phenytoin

**Other Warnings/Precautions**
- Because oxcarbazepine has a tricyclic chemical structure, it is not recommended to be taken with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI until 2 weeks after discontinuing oxcarbazepine
- Because oxcarbazepine can lower plasma levels of hormonal contraceptives, it may also reduce their effectiveness
- May exacerbate angle-closure glaucoma
- May need to restrict fluids and/or monitor sodium because of risk of hyponatremia
- Use cautiously in patients who have demonstrated hypersensitivity to carbamazepine

**SPECIAL POPULATIONS**

**Renal Impairment**
- Oxcarbazepine is renally excreted
- Elimination half-life of active metabolite MHD is increased
- Reduce initial dose by half; may need to use slower titration

**Hepatic Impairment**
- No dose adjustment recommended for mild to moderate hepatic impairment
- Use with caution in patients with severe impairment

**Cardiac Impairment**
- No dose adjustment recommended

**Elderly**
- Older patients may have reduced creatinine clearance and require reduced dosing
- Elderly patients may be more susceptible to adverse effects
- Some patients may tolerate lower doses better

**Children and Adolescents**
- Approved as adjunctive therapy or monotherapy for partial seizures in children 4 and older
- Ages 4–16 (adjunctive): initial 8–10 mg/kg per day or less than 600 mg/day in 2 doses; increase over 2 weeks to 900 mg/day (20–29 kg), 1,200 mg/day (29.1–39 kg), or 1,800 mg/day (>39 kg)
- When converting from adjunctive to monotherapy, titrate concomitant drug down over 3–6 weeks while titrating oxcarbazepine up by no more than 10 mg/kg per day each week, with an initial daily...
Oxcarbazepine dose of 8–10 mg/kg per day divided in 2 doses
- Monotherapy: initial 8–10 mg/kg per day in 2 doses; increase every 3 days by 5 mg/kg per day; recommended maintenance dose dependent on weight
  - 0–20 kg (600–900 mg/day);
  - 21–30 kg (900–1,200 mg/day);
  - 31–40 kg (900–1,500 mg/day);
  - 41–45 kg (1,200–1,500 mg/day);
  - 46–55 kg (1,200–1,800 mg/day);
  - 56–65 kg (1,200–2,100 mg/day);
  - over 65 kg (1,500–2,100 mg)
- Children below age 8 may have increased clearance compared to adults
- 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 (PLLRR 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
- Oxcarbazepine is structurally similar to carbamazepine, which is thought to be teratogenic in humans
- Use during first trimester may raise risk of neural tube defects (e.g., spina bifida) or other congenital anomalies
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- If drug is continued, perform tests to detect birth defects
- If drug is continued, start on folate 1 mg/day to reduce risk of neural tube defects
- Antiepileptic Drug Pregnancy Registry: (888) 233–2334
- Taper drug if discontinuing
- For bipolar patients, oxcarbazepine should generally be discontinued before anticipated pregnancies
- Seizures, even mild seizures, may cause harm to the embryo/fetus
- Recurrent bipolar illness during pregnancy can be quite disruptive
- For bipolar patients, given the risk of relapse in the postpartum period, some form of mood stabilizer treatment may need to be restarted immediately after delivery if patient is unmedicated during pregnancy
- Atypical antipsychotics may be preferable to lithium or anticonvulsants such as oxcarbazepine if treatment of bipolar disorder is required during pregnancy
- Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary
- 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
  - Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis
  - Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder
  - Atypical antipsychotics and anticonvulsants such as valproate may be safer than oxcarbazepine during the postpartum period when breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Treatment-resistant bipolar and psychotic disorders
- Those unable to tolerate carbamazepine but who respond to carbamazepine

Potential Disadvantages
- Patients at risk for hyponatremia

Primary Target Symptoms
- Incidence of seizures
- Severity of seizures
- Unstable mood, especially mania
**Pearls**

* Some evidence of effectiveness in treating acute mania; included in American Psychiatric Association’s bipolar treatment guidelines as an option for acute treatment and maintenance treatment of bipolar disorder

* Some evidence of effectiveness as adjunctive treatment in schizophrenia and schizoaffective disorders

* Oxcarbazepine is the 10-keto analog of carbamazepine, but not a metabolite of carbamazepine

* Less well investigated in bipolar disorder than carbamazepine

* Oxcarbazepine seems to have the same mechanism of therapeutic action as carbamazepine but with fewer side effects

* Specifically, risk of leukopenia, aplastic anemia, agranulocytosis, elevated liver enzymes, or Stevens-Johnson syndrome and serious rash associated with carbamazepine does not seem to be associated with oxcarbazepine

* Skin rash reactions to carbamazepine may resolve in 75% of patients with epilepsy when switched to oxcarbazepine; thus, 25% of patients who experience rash with carbamazepine may also experience it with oxcarbazepine

* Oxcarbazepine has much less prominent actions on CYP 450 enzyme systems than carbamazepine, and thus fewer drug-drug interactions

* Specifically, oxcarbazepine and its active metabolite, the monohydroxy derivative (MHD), cause less enzyme induction of CYP450 3A4 than the structurally related carbamazepine

* The active metabolite MHD, also called licarbazepine, is a racemic mixture of 80% S-MHD (active) and 20% R-MHD (inactive)

* A related compound, APTIOM, is a dibenz[b,f]azepine-5-carboxamide derivative of eslicarbazepine and is also extensively converted to eslicarbazepine

* APTIOM is now approved as an anticonvulsant, but adequate studies have not been conducted on its potential use as a mood stabilizer

* Most significant risk of oxcarbazepine may be clinically significant hyponatremia (sodium level <125 m mol/L), most likely occurring within the first 3 months of treatment, and occurring in 2–3% of patients

* Unknown if this risk is higher than for carbamazepine

* Since SSRIs can sometimes also reduce sodium due to SIADH (syndrome of inappropriate antidiuretic hormone production), patients treated with combinations of oxcarbazepine and SSRIs should be carefully monitored, especially in the early stages of treatment

* By analogy with carbamazepine, could theoretically be useful in chronic neuropathic pain

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**Suggested Reading**


