



# Depakene/Depakote/ Depakote-ER (divalproex sodium)

Generic name: Valproic acid (Depakene),  
divalproex sodium (Depakote)

Available strengths: 250 mg capsule (Depakene);  
250 mg/5 mL syrup (Depakene Syrup);  
125 mg (sprinkle capsule), 125 mg, 250 mg,  
500 mg tablets (Depakote); 250 mg, 500 mg tablets  
(Depakote-ER)

Available in generic: Yes, except Depakote  
and Depakote-ER

Drug class: Anticonvulsant/mood stabilizer

## General Information

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**Depakene (valproic acid)** and **Depakote (divalproex sodium)** are better known as **anticonvulsants**—medications 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. In addition to its indication for epilepsy, Depakote has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of mania associated with bipolar disorder. The use of a medication for its approved indication is called *labeled use*. Physicians may also use other anticonvulsants that do not have an FDA-approved indication for treating bipolar disorder (e.g., Tegretol) when published clinical studies, case reports, or their own clinical experiences support the efficacy and safety of those treatments. This is known as an *unlabeled* (“off-label”) use of a medication. When Depakote and other anticonvulsants are used for treating mood disorders, they are called **mood stabilizers**.

Although Depakene and Depakote come in many dosage forms, valproic acid is the active medication. All the different preparations are converted in the body to valproic acid. Valproic acid is available in a gel capsule (Depakene), in syrup as sodium valproate (Depakene), in a sprinkle capsule as divalproex sodium (which may

be opened and sprinkled in food), in enteric-coated and extended-release tablets as divalproex sodium (Depakote and Depakote-ER), and in an injection form (Depacon). Depakote and Depakote-ER are enteric-coated tablets with equal parts of valproic acid and sodium valproate. Depakote and Depakote-ER are the most frequently used preparations, because the enteric-coated tablets are less irritating in the stomach, and the extended-release tablets can be dosed once a day.

Clinical studies have shown that Depakote and lithium are equally effective in treating acute mania and preventing relapse of bipolar disorder. Depakote is more effective in treating mixed episodes (characterized by both mania and depression coexisting in the same episode) and in rapid-cycling types of bipolar disorder (when the person experiences four or more manic or major depressive episodes in 1 year). Because Depakote is better tolerated and less toxic than lithium, it is currently the preferred medication for bipolar disorder.

Depakote and Depakote-ER are primarily referenced in this handout, but the discussion applies to the other derivatives of valproic acid as well. When referring to all the valproic acid formulations, the brand name Depakote is used for convenience in this handout.

## Dosing Information

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The usual starting dosage of Depakote is 250 mg twice a day, with the dosage increasing by 250 mg/day every 3–4 days until a therapeutic blood level is reached. Generally, the required dosage for treating acute mania is between 1,000 and 3,000 mg/day in divided doses. Depakote may be switched to once-a-day dosing with Depakote-ER.

## Common Side Effects

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The most common side effects from Depakote are sedation, tiredness, and gastrointestinal symptoms, including nausea, cramping, and diarrhea. Shifting all or most of the dosage close to bedtime may decrease daytime sedation. The enteric-coated tablets of Depakote and Depakote-ER are associated with fewer gastrointestinal side effects than with Depakene capsule or syrup.

Patients taking Depakote may experience tremor, impaired coordination, and clumsiness when walking (**ataxia**). Generally, these side effects are temporary and subside as tolerance to the medication develops. Some patients may experience hair loss (**alopecia**) while taking Depakote, which may be due to the medication's interference with zinc and selenium absorption. Taking a daily multivitamin with minerals containing zinc and selenium may stop and prevent hair loss. Depakote may induce significant weight gain. Patients taking Depakote should follow a sensible diet and exercise routinely to control their weight.

## Adverse Reactions and Precautions

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

Due to reported cases of liver failure in patients taking Depakote, the FDA required manufacturers to issue a stern warning of potential liver toxicity in its labeling requirements. It appears that the risk is greatest in children younger than 2 years of age, and the risk declines significantly in adults. Because it is impossible to predict when liver toxicity will occur, liver function tests are recommended before treatment and every 6 months thereafter. Although liver toxicity is rare, patients should be aware of the potential risk and should be encouraged to report early symptoms of possible liver disease to their physician, including loss of appetite, tiredness, nausea, and yellowing of skin and eyes (**jaundice**).

Another potentially rare adverse reaction to Depakote is pancreatitis. Cases of life-threatening pancreatitis, which may occur shortly after starting therapy or after several years of use, have been reported in children and adults who were taking Depakote. Early warning symptoms of pancreatitis include severe abdominal pain, loss of appetite, nausea, and vomiting. The patient should seek immediate medical attention if these symptoms occur.

Depakote may cause a decrease in platelets (**thrombocytopenia**), which are routinely measured when the physician orders a complete blood count. If this condition occurs, generally, the decrease in platelets is mild and has little or no clinical consequence. In rare instances, Depakote may significantly lower platelets and result in clotting dysfunction and bleeding.

## Use in Pregnancy and Breastfeeding: Pregnancy Category D

Among women who took Depakote during the first trimester of pregnancy, a higher incidence of spinal cord defect (**spina bifida**) and abnormal brain development in their children has been found. Women should not receive Depakote if they are pregnant, or the medication should be discontinued if they plan to become pregnant. However, if the woman is prone to relapse, which may pose greater harm to the mother and unborn child if Depakote is discontinued, the physician may consider maintaining the medication with the patient's consent. The risk of birth defects from Depakote may be reduced if the mother takes 1 mg of folic acid, a B vitamin, daily during pregnancy. Use of Depakote should be restricted whenever possible to the second and third trimesters.

Nursing mothers should not take Depakote or other preparations, 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

Depakote can affect the liver enzymes that metabolize different medications and may reduce their metabolism, thus increasing their concentrations—and their adverse effects. Conversely, other medications can inhibit the metabolism of Depakote and increase its concentration in the blood. The clinically significant drug interactions reported with Depakote are summarized in the table below.

Tagamet (cimetidine), erythromycin, Prozac (fluoxetine), Luvox (fluvoxamine), phenothiazine antipsychotics (e.g., Thorazine and Mellaril), nonsteroidal anti-inflammatory medications (e.g., Motrin, aspirin)	When any of these medications are combined with Depakote, the medication may inhibit the metabolism of Depakote and increase Depakote levels.
Tegretol (carbamazepine), phenobarbital, Dilantin (phenytoin), Zarontin (ethosuximide), and rifampin	When any of these medications are combined with Depakote, Depakote levels may be decreased, leading to decreased effectiveness of Depakote.
Lamictal (lamotrigine)	Depakote may increase the blood levels of Lamictal, which can increase the risk of a potentially severe rash. When these two medications are used together, Lamictal dosages are increased very gradually.
Coumadin (warfarin)	The effects of Coumadin, an anticoagulant, may be increased when combined with Depakote, which may increase the risk of bleeding.

Patients taking Depakote 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 Depakote and complicating treatment.

## Overdose

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Overdose with Depakote may be fatal, depending on the amount ingested and the age and size of the person. In seniors, for example, the lethal dose is lower than that for a younger adult. Symptoms include somnolence, confusion, seizures, heart block, and coma. Depakote overdose may cause significant respiratory depression, which is often fatal if medical treatment is not immediate.

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

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- 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.
- Depakote-ER, the extended-release form, is intended for once-a-day dosing. Swallow the tablets whole and do not crush or chew them. If stomach upset occurs, take Depakote after meals or with food.
- Contact your physician if you have persistent abdominal symptoms, including pain, loss of appetite, nausea, vomiting, and jaundice.
- Depakote 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, because overdose in small children is very dangerous.

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

## Notes

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