**Important Update to the Prescribing Information for DEPAKOTE® (divalproex sodium) delayed-release tablets, for oral use, DEPAKOTE ER (divalproex sodium) extended-release tablets, for oral use, and DEPAKOTE Sprinkle Capsules (divalproex sodium delayed release capsules), for oral use.**

**On May 1, 2025, the Prescribing Information for DEPAKOTE (divalproex sodium) delayed-release tablets, for oral use, DEPAKOTE ER (divalproex sodium) extended-release tablets, for oral use, and DEPAKOTE Sprinkle Capsules (divalproex sodium delayed release capsules), for oral use was updated.**

**The following describes the major changes to the DEPAKOTE Prescribing Information and Patient Counseling section. Please refer to the full Prescribing Information to review all the changes:**

- **5.13 Serious Dermatologic Reactions**

  - Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and erythema multiforme (EM) have been reported with valproate treatment. Valproate should be discontinued at the first sign of a rash, unless the rash is clearly not drug related. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.12)]*. If signs or symptoms suggest TEN/SJS/AGEP/EM, use of this drug should not be resumed, and alternative therapy should be considered.

- **5.14 Angioedema**

  - Angioedema has been reported in patients treated with valproate in the postmarketing setting. Valproate should be discontinued immediately if symptoms of angioedema such as facial, perioral, or upper airway swelling occur. Valproate should be discontinued permanently if a clear alternative etiology for the reaction cannot be established *[see Contraindications (4)]*.

**INDICATIONS**

**Mania**

DEPAKOTE® ER (divalproex sodium), extended-release tablets for oral use, is a valproate and is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

DEPAKOTE® (divalproex sodium), delayed-release tablets for oral use, is a valproate and is indicated for the treatment of the manic episodes associated with bipolar disorder.

**References: 1.** DEPAKOTE [package insert]. North Chicago, IL: AbbVie Inc.
**2.** DEPAKOTE ER [package insert]. North Chicago, IL: AbbVie Inc.
**3.** DEPAKOTE Sprinkle Capsules [package insert]. North Chicago, IL: AbbVie Inc.

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A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility. A mixed episode is characterized by the criteria for a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The efficacy of DEPAKOTE ER is based in part on studies of DEPAKOTE in this indication, and was confirmed in a 3-week trial with patients meeting DSM-IV-TR criteria for bipolar I disorder, manic or mixed type, who were hospitalized for acute mania.

The efficacy of DEPAKOTE was established in 3-week trials with patients meeting DSM-III-R criteria for bipolar disorder who were hospitalized for acute mania.

The effectiveness of valproate for long-term use in mania, i.e., more than 3 weeks, has not been demonstrated in controlled clinical trials. Therefore, healthcare providers who elect to use DEPAKOTE or DEPAKOTE ER for extended periods should continually reevaluate the long-term risk-benefits of the drug for the individual patient.

### Epilepsy

DEPAKOTE ER is indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. DEPAKOTE ER is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that include absence seizures.

DEPAKOTE is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. DEPAKOTE is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

DEPAKOTE® Sprinkle Capsules (divalproex sodium), delayed release capsules for oral use, is indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. DEPAKOTE Sprinkle Capsules is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

### Migraine

DEPAKOTE and DEPAKOTE ER are indicated for prophylaxis of migraine headaches. There is no evidence that DEPAKOTE ER or DEPAKOTE is useful in the acute treatment of migraine headaches.

**References: 1.** DEPAKOTE [package insert]. North Chicago, IL: AbbVie Inc.
**2.** DEPAKOTE ER [package insert]. North Chicago, IL: AbbVie Inc.
**3.** DEPAKOTE Sprinkle Capsules [package insert]. North Chicago, IL: AbbVie Inc.

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**Important Limitations**

Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, neural tube defects, and other major congenital malformations, which may occur very early in pregnancy, valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.

For prophylaxis of migraine headaches, valproate is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception.

## IMPORTANT SAFETY INFORMATION[1-3]

**WARNING: LIFE-THREATENING ADVERSE REACTIONS**

**Hepatotoxicity**

***General Population:*** **Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.**

**Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When DEPAKOTE (divalproex sodium) delayed-release tablets, for oral use, DEPAKOTE ER (divalproex sodium) extended-release tablets, for oral use, or DEPAKOTE Sprinkle Capsules (divalproex sodium delayed release capsules), for oral use, is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.**

***Patients With Mitochondrial Disease*: There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g., Alpers Huttenlocher syndrome). DEPAKOTE, DEPAKOTE ER, and DEPAKOTE Sprinkle Capsules are contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and in children under two years of age who are clinically suspected of having a mitochondrial disorder. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, DEPAKOTE, DEPAKOTE ER, or DEPAKOTE Sprinkle Capsules should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with DEPAKOTE, DEPAKOTE ER, or DEPAKOTE Sprinkle Capsules for the development of acute liver injury, with regular clinical**

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**assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice.**

**Fetal Risk**

**Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores and neurodevelopmental disorders following *in utero* exposure.**

**Valproate is therefore contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception [see Contraindications (4)]. Valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.**

**Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. In such situations, effective contraception should be used [see Warnings and Precautions (5.2, 5.3, 5.4)].**

**A Medication Guide describing the risks of valproate is available for patients [see Patient Counseling Information (17)].**

**Pancreatitis**

**Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.**

**Valproate is contraindicated in patients:**

- with hepatic disease or dysfunction. Immediately discontinue drug if significant hepatic dysfunction is suspected or apparent. Progression of dysfunction has occurred in spite of discontinuation of valproate.
- known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers Huttenlocher syndrome) and in children under two years of age who are suspected of having a POLG-related disorder.
- being treated for prophylaxis of migraine headaches who are pregnant or in women of childbearing potential who are not using effective contraception.
- with known hypersensitivity to divalproex sodium, sodium valproate, or valproic acid.
- with known urea cycle disorders.

- Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate. Symptoms of unexplained hyperammonemic encephalopathy during valproate therapy require prompt treatment (including discontinuation of valproate).

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- Valproate can cause decreased IQ, neurodevelopmental disorders, neural tube defects, and other major congenital malformations (e.g., craniofacial defects, hypospadias, and cardiovascular and limb malformations). In epileptic mothers, the rate of congenital malformations with *in utero* exposure is about four times higher compared to the rate with *in utero* exposure to other anti-seizure monotherapies. Lower cognitive test scores, including decreased IQ scores, were associated with *in utero* valproate exposure compared with *in utero* exposure to either another or no antiepileptic drug (AED). Unless other medications have failed to provide adequate symptom control or are otherwise unacceptable, women of childbearing potential should not receive valproate.
- Valproate can increase the risk of suicidal thoughts or behavior. Patients treated with any AED should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior. Counsel patients and families to be alert for and to immediately report depression, any unusual changes in mood or behavior, or suicidal thoughts, behavior, or acts of self-harm.
- Valproate is associated with dose-related thrombocytopenia. Decreases in other cell lines and myelodysplasia have also been associated with valproate. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥110 µg/mL in females and ≥135 µg/mL in males or at 50 mg/kg/d. Check complete blood counts and coagulation times before starting therapy or surgery, at periodic intervals, and during pregnancy. Reduce dose or discontinue if hemorrhage, bruising, or hemostasis/coagulation disorder occur.
- Hyperammonemia has been associated with valproate; it may be present despite normal liver function tests and should be considered if hypothermia occurs. Asymptomatic elevations of ammonia are more common and require close monitoring. Discontinue valproate if ammonia increases.
- Concomitant administration of topiramate and valproate has been associated with hyperammonemia (with or without encephalopathy) in patients who have tolerated either drug alone.
- Hypothermia has been associated with valproate therapy both in conjunction with, and in the absence of, hyperammonemia. It can occur after starting topiramate treatment or after increasing the daily dose of topiramate. Consider stopping valproate if hypothermia develops.
- Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS)/multi-organ hypersensitivity reactions have been reported in patients taking valproate and may be fatal or life-threatening. Patients typically present with fever, rash, and lymphadenopathy associated with other organ system involvement, e.g., hematologic abnormalities. Early symptoms may not include rash. Regardless, immediately evaluate and discontinue therapy for any signs of hypersensitivity.
- Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and erythema multiforme (EM), have been reported with valproate treatment. Valproate should be discontinued at the first sign of a rash, unless the rash is clearly not drug related. If signs or symptoms suggest TEN/SJS/AGEP/EM, use of this drug should not be resumed, and alternative therapy should be considered.

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- Angioedema has been reported in patients treated with valproate. Valproate should be discontinued immediately and patient should be evaluated if symptoms of angioedema, such as facial, perioral, or upper airway swelling, occur.
- Aspirin, carbapenem antibiotics (such as ertapenem, imipenem, and meropenem), estrogen-containing hormonal contraceptives, and methotrexate may reduce serum valproate concentrations to subtherapeutic levels, resulting in loss of seizure control.
- Valproate may interact with drugs capable of enzyme induction; check valproate and concomitant drug levels periodically in the early course of therapy.
- In a clinical trial, somnolence was associated with valproate in some elderly dementia patients along with reduced nutritional intake; weight loss; and a trend to have a lower baseline albumin concentration, higher BUN, and lower valproate clearance. Discontinuation occurred in some patients.
- Cannabidiol and valproate in combined administration have been associated with an increased risk of ALT and/or AST elevation. This has been manageable by dose reduction or, in more severe cases, by discontinuation of one or both drugs. Liver function, including serum transaminase and total bilirubin levels, should be monitored during concomitant treatment.
- Rare reports of medication residue in the stool have occurred, some in patients with anatomic (ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times or in the context of diarrhea. If medication residue occurs, monitor plasma valproate levels and patient's clinical condition; alternative treatment may be considered.

## ADVERSE EVENTS[1-3]

**DEPAKOTE ER:** Most common adverse reactions (reported ≥15%) are abdominal pain, alopecia, asthenia, diarrhea, diplopia, dizziness, dyspepsia, headache, infection, insomnia, nausea, somnolence, thrombocytopenia, tremor, and vomiting.

**DEPAKOTE and DEPAKOTE Sprinkle Capsules:** Most common adverse reactions (reported ≥15%) are abdominal pain, alopecia, asthenia, diarrhea, diplopia, dizziness, headache, infection, insomnia, nausea, somnolence, thrombocytopenia, tremor, and vomiting.

**Please see the full Prescribing Information, including Boxed Warnings, for:**

**DEPAKOTE** https://www.rxabbvie.com/pdf/depakote.pdf, **including Medication Guide** https://www.rxabbvie.com/pdf/depakote_medguide.pdf

**DEPAKOTE ER** https://www.rxabbvie.com/pdf/dep3.pdf, **including Medication Guide** https://www.rxabbvie.com/pdf/dep3_medguide.pdf

**DEPAKOTE Sprinkle Capsules** https://www.rxabbvie.com/pdf/dep2.pdf, **including Medication Guide** https://www.rxabbvie.com/pdf/dep2_medguide.pdf

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