Depakote Tablets (divalproex sodium) - Drug Summary

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Depakote
(divalproex sodium)

BOXED WARNING

Fatal hepatic failure reported, usually during first 6 months of treatment. Serious/fatal hepatotoxicity may be preceded by nonspecific symptoms (eg, malaise, weakness, lethargy, facial edema, anorexia, vomiting) or a loss of seizure control in patients w/ epilepsy; monitor closely. Monitor LFTs prior to therapy and at frequent intervals thereafter, especially during first 6 months of treatment. Increased risk of developing fatal hepatotoxicity in children <2 yrs of age, especially if on multiple anticonvulsants, w/ congenital metabolic disorders, w/ severe seizure disorders accompanied by mental retardation, and w/ organic brain disease; use w/ extreme caution and as a sole agent. Increased risk of drug-induced acute liver failure and resultant death in patients w/ hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA polymerase gamma (POLG) gene (eg, Alpers-Huttenlocher syndrome). Contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and in children <2 yrs of age who are clinically suspected of having a mitochondrial disorder. In patients >2 yrs of age who are clinically suspected of having a hereditary mitochondrial disease, drug should only be used after other anticonvulsants have failed; closely monitor for the development of acute liver injury. May cause major congenital malformations, particularly neural tube defects (eg, spina bifida). May cause decreased IQ scores following in utero exposure. Should only be used to treat pregnant women w/ epilepsy or bipolar disorder if other medications have failed to control their symptoms or are otherwise unacceptable. Do not administer to a woman of childbearing potential unless the drug is essential to the management of her medical condition; use effective contraception. Life-threatening pancreatitis reported; d/c if pancreatitis is diagnosed and initiate alternative treatment. **Tab:** Contraindicated in pregnant women treated for migraine prophylaxis.

COMMON BRAND NAMES

Depakote Sprinkle, Depakote

THERAPEUTIC CLASS

Valproate compound

DEA CLASS

RX

ADULT DOSAGE & INDICATIONS

Epilepsy

Monotherapy and Adjunctive Therapy for Complex Partial Seizures and Simple and Complex Absence Seizures; Adjunctive Therapy w/ Multiple Seizure Types (eg, Absence Seizures):

Cap/Tab:
Complex Partial Seizures:
Initial: 10-15mg/kg/day
Titrate: Increase by 5-10mg/kg/week
Usual Therapeutic Range: 50-100mcg/mL
No recommendation regarding safety at doses >60mg/kg/day

Simple and Complex Absence Seizures:
Initial: 15mg/kg/day
Titrate: Increase weekly by 5-10mg/kg/day
Max: 60mg/kg/day

If daily dose >250mg/day, give in divided doses

Mania

Associated w/ Bipolar Disorder:
Tab:
Initial: 750mg/day in divided doses
Titrate: Increase dose as rapidly as possible to achieve lowest therapeutic dose
Max: 60mg/kg/day

Migraine

Prophylaxis:
Tab:
Initial: 250mg bid
Max: 1000mg/day

PEDIATRIC DOSAGE & INDICATIONS

Epilepsy

Monotherapy and Adjunctive Therapy for Complex Partial Seizures and Simple and Complex Absence Seizures; Adjunctive Therapy w/ Multiple Seizure Types (eg, Absence Seizures):

Cap/Tab:
Simple and Complex Absence Seizure:
Initial: 15mg/kg/day
Titrate: Increase weekly by 5-10mg/kg/day
Max: 60mg/kg/day

Complex Partial Seizures:
≥10 Years:
Initial: 10-15mg/kg/day
Titrate: Increase by 5-10mg/kg/week
Usual Therapeutic Range: 50-100mcg/mL
No recommendation regarding safety at doses >60mg/kg/day

If daily dose >250mg/day, give in divided doses

DOSING CONSIDERATIONS

Concomitant Medications
Complex Partial Seizures:
Conversion to Monotherapy: Reduce concomitant antiepilepsy drug dosage by approx 25% every 2 weeks; reduction may be started at initiation of divalproex therapy, or delayed by 1-2 weeks if seizures are likely to occur w/ a reduction

Elderly
Reduce initial dose and titrate slowly; consider dose reductions or discontinuation in patients w/ decreased food/fluid intake or excessive somnolence

Adverse Reactions
Thrombocytopenia: Probability appears to increase significantly at total valproate concentrations of ≥110mcg/mL (females) or ≥135mcg/mL (males)

Discontinuation
Do not abruptly d/c

Other Important Considerations
In epileptic patients previously receiving valproic acid, initiate at the same daily dose and frequency; once the patient is stabilized, the frequency of divalproex may be adjusted to bid-tid

ADMINISTRATION

Oral route

Give w/ food or slowly titrate from initial dose in patients w/ GI irritation.

Cap
May be swallowed whole or the contents may be sprinkled on small amount of soft food.

To Administer w/ Food:
1. Hold the cap so that the end marked "THIS END UP" is straight up and the arrow on the cap is up.
2. To open the cap, gently twist it apart to separate the top from the bottom. It may be helpful to hold the cap over the food to which you will add the sprinkles. If you spill any of the cap contents, start over w/ a new cap and a new portion of food.
3. Place all the sprinkles onto a small amount (about a tsp) of soft food such as applesauce or pudding.
4. Make sure that all of the sprinkle/food mixture is swallowed right away. Do not chew the sprinkle/food mixture.
5. Drinking water right after taking the sprinkle/food mixture will help make sure all sprinkles are swallowed.
6. Throw away any unused sprinkle/food mixture; do not store any for future use.

Tab
Swallow whole; do not crush or chew.

HOW SUPPLIED

Cap, Delayed-Release: (Sprinkle) 125mg; **Tab, Delayed-Release:** 125mg, 250mg, 500mg

CONTRAINDICATIONS

Hepatic disease, significant hepatic dysfunction, known urea cycle disorders (UCDs). Mitochondrial disorders caused by mutations in mitochondrial DNA POLG (eg, Alpers-Huttenlocher syndrome) and children <2 yrs of age who are suspected of having a POLG-related disorder. **Tab:** Prophylaxis of migraine headaches in pregnant women.

WARNINGS/PRECAUTIONS

Caution w/ prior history of hepatic disease. D/C immediately if significant hepatic dysfunction (suspected or apparent) occurs. Hyperammonemic encephalopathy reported in patients w/ UCDs; d/c and initiate treatment if symptoms develop. Increased risk of suicidal thoughts or behavior reported. Dose-related thrombocytopenia and decreases in other cell lines and myelodysplasia reported; reduce dose or d/c if hemorrhage, bruising, or a disorder of hemostasis/coagulation occurs. Hyperammonemia reported and may be present despite normal LFTs. Measure ammonia levels if unexplained lethargy, vomiting, or mental status changes occur; hyperammonemic encephalopathy should be considered. Hypothermia w/ and in absence of hyperammonemia reported; consider discontinuation. 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 and do not resume if an alternative etiology cannot be established. Altered thyroid function tests and urine ketone tests reported. May stimulate replication of HIV and CMV. Medication residue in stool reported; check valproate levels and monitor clinical condition, and consider alternative treatment if clinically indicated.

ADVERSE REACTIONS

Diarrhea, N/V, somnolence, dizziness, dyspepsia, thrombocytopenia, asthenia, abdominal pain, tremor, headache, anorexia, diplopia, blurred vision, flu syndrome, infection.

DRUG INTERACTIONS

Drugs that affect the level of expression of hepatic enzymes (eg, phenytoin, carbamazepine, phenobarbital) may increase valproate clearance; monitor valproate and concomitant drug concentrations whenever enzyme-inducing drugs are introduced or withdrawn. Concomitant use w/ aspirin decreases protein binding and inhibits metabolism of valproate; use w/ caution. Carbapenem antibiotics may reduce serum concentrations to subtherapeutic levels, resulting in loss of seizure control. Concomitant use w/ felbamate increases valproate C_{max}; may require decrease in valproate dosage. Rifampin increases oral clearance; may require valproate dosage adjustment. Reduces the clearance of amitriptyline and nortriptyline; consider lowering the dose of amitriptyline/nortriptyline. May decrease levels of carbamazepine while increasing carbamazepine-10,11-epoxide serum levels. Inhibits metabolism of diazepam, ethosuximide, phenobarbital, and phenytoin; monitor drug serum concentrations and adjust dose appropriately. Monitor for neurological toxicity w/ concomitant barbiturate therapy. Breakthrough seizures reported w/ concomitant use w/ phenytoin. Use w/ clonazepam may induce absence status in patients w/ history of absence seizures. Increased $T_{1/2}$ of lamotrigine, and serious skin reactions reported; reduce lamotrigine dose. Monitor coagulation tests when coadministered w/ anticoagulants. May decrease zidovudine clearance in HIV-seropositive patients. Concomitant use w/ topiramate has been associated w/ hypothermia and hyperammonemia, w/ or w/o encephalopathy.

PREGNANCY AND LACTATION

Pregnancy: Category D (for epilepsy and for manic episodes w/ bipolar disorder) or X (for prophylaxis of migraine headaches). Physicians should encourage pregnant patients to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.
Lactation: Caution in nursing.

MECHANISM OF ACTION

Valproate compound; has not been established. Suggested that activity in epilepsy is related to increased brain concentrations of GABA.

PHARMACOKINETICS

Absorption: (Tab) T_{max}=4 hrs (fasted), 8 hrs (fed); (Cap) T_{max}=3.3 (fasted), 4.8 hrs (fed). **Distribution:** V_d=11L (total valproate), 92L (free valproate); found in breast milk, CSF. **Metabolism:** Liver; mitochondrial β-oxidation (major), glucuronidation. **Elimination:** Urine (30-50% glucuronide conjugate, <3% unchanged); $T_{1/2}$=9-16 hrs (250-1000mg dose).

ASSESSMENT

Assess for hepatic dysfunction, history of hepatic disease, pancreatitis, history of hypersensitivity to the drug, mitochondrial disorders caused by mutations in mitochondrial POLG, children <2 yrs of age who are suspected of having a POLG-related disorder, other conditions where treatment is contraindicated or cautioned, pregnancy/nursing status, and possible drug interactions. Assess LFTs, CBCs, and coagulation parameters. Evaluate for UCDs, especially in high-risk patients (eg, history of unexplained encephalopathy or coma).

MONITORING

Monitor for hypersensitivity reactions, pancreatitis, hepatotoxicity, hyperammonemia, hypothermia, DRESS, drug-induced acute liver failure, acute liver injury, emergence/worsening of depression, suicidality or unusual changes in behavior, medication residue in stool, and other adverse reactions. Monitor LFTs frequently, especially during first 6 months. Monitor fluid/nutritional intake, ammonia levels, CBCs, and coagulation parameters. Perform periodic plasma concentration determinations of valproate and concomitant drugs during the early course of therapy.

PATIENT COUNSELING

Instruct to take ud. Inform pregnant women and women of childbearing potential about the risk in pregnancy (eg, birth defects, decreased IQ); advise to use effective contraception while on therapy and counsel about alternative therapeutic options. Instruct to notify physician if pregnant/intending to become pregnant. Encourage patients to enroll in the NAAED Pregnancy Registry. Advise to notify physician if depression, suicidal thoughts/behavior, or thoughts about self-harm emerge; instruct to report behaviors of concern. Counsel about signs/symptoms of pancreatitis, hepatotoxicity, hyperammonemia, or hyperammonemic encephalopathy; advise to notify physician if any symptoms or adverse effects occur. Advise not to engage in hazardous activities (eg, driving/operating machinery) until the effects of the drug are known. Inform that a fever associated w/ other organ system involvement (eg, rash, lymphadenopathy) may be drug-related; instruct to report to physician. Instruct patients to notify their healthcare provider if they notice medication residue in the stool.

STORAGE

Cap: <25°C (77°F). **Tab:** <30°C (86°F).

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