TEXAS Health and Human Services

Medication Audit Criteria and Guidelines

Valproic Acid (Depakene®), Divalproex Sodium (Depakote®, Depakote ER®)

PEFC Approved: January 2021

Indications

- Bipolar disorder and other cyclic mood disorders
- Aggressive behavior secondary to a psychiatric disorder
- Disruptive, Impulse Control and Conduct Disorders
- Migraine Headache Prophylaxis; Chronic Headache disorders
- Clozapine induced seizure prophylaxis and treatment

Black Box Warning

- Hepatotoxicity, including fatalities, usually during the first 6 months of treatment. Children under the age of two years and patients with mitochondrial disorders are at higher risk. Monitor patients closely, and perform serum liver testing prior to therapy and at frequent intervals thereafter
- Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ
- Pancreatitis, including fatal hemorrhagic cases

Contraindications

- Hepatic disease or significant hepatic dysfunction
- Known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG)
- Suspected POLG-related disorder in children under two years of age
- Known hypersensitivity to the drug
- Urea cycle disorders
- Pregnant patients treated for prophylaxis of migraine headaches

Warnings and Precautions

- Hepatotoxicity; evaluate high risk populations and monitor serum liver tests

- Birth defects and decreased IQ following in utero exposure; only use to treat pregnant women with epilepsy or bipolar disorder if other medications are unacceptable; should not be administered to a woman of childbearing potential unless essential
- Pancreatitis; Should ordinarily discontinue
- Suicidal behavior or ideation; Antiepileptic drugs increase the risk of suicidal thoughts or behavior
- Bleeding and other hematopoietic disorders; monitor platelet counts and coagulation tests
- Hyperammonemia and hyperammonemic encephalopathy; measure ammonia level if unexplained lethargy and vomiting or changes in mental status, and also with concomitant topiramate use; consider discontinuation
- Hypothermia; Hypothermia has been reported during valproate therapy with or without associated hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reaction; discontinuation
- Somnolence in the elderly can occur. Dosage should be increased slowly and with regular monitoring for fluid and nutritional intake

Adverse Reactions

Side Effects Which Require Medical Attention

- Worsening confusion or disorientation
- Nausea, vomiting, diarrhea, abdominal discomfort or anorexia, pancreatitis
- Bruising or bleeding
- Clinically significant weight gain
- Tremors
- Signs/symptoms of infection (e.g., fever, sore throat, malaise, etc.)
- Ataxia, gait disturbances, dysarthria
- Sedation
- Alopecia
- Peripheral edema
- Rash
- Oligomenorrhea, signs/symptoms of hyperandrogenism
- Suicide ideation

Pregnancy and Breastfeeding

- See Black Box Warning, Contraindications, Warnings/Precautions.
- Review product-specific labeling. Consider risks/benefits in reviewing medication-specific labeling

Drug Interactions of Major Significance

See: Indiana Univ Drug Interaction Table
See: Lexicomp and Micromedex

Special Populations

Age-Specific Considerations

- Age younger than 10 years old due to high risk of hepatic toxicity
- Included in BEERS criteria
- Geriatric patients have increased amounts of free drug (use lower total plasma concentration or get free VPA plasma concentration)
- Women of child-bearing age (e.g., teratogenicity, polycystic ovarian syndrome)

Patient Monitoring Parameters

- CBC - with differential and platelet count - baseline then one (1) to two (2) weeks after each dosage increase, every 3 months for the first year of treatment, then annually and as clinically indicated
- Comprehensive Metabolic Panel (hepatic function, serum creatinine, BUN and electrolytes) – baseline, every 3 months for the first year of treatment, then annually and as clinically indicated.
- Pregnancy Test – baseline as appropriate, and as clinically indicated
- Valproic acid level –1-2 weeks after initiation, after each dosage change & as clinically indicated
- Weight – baseline, every 3 months for the first year of treatment, then annually and as clinically indicated
- Monitor for the emergence of suicidal ideation or behavior

Dosing

- See HHSC Psychiatric Drug Formulary for dosage guidelines.
- Exceptions to maximum dosage must be justified as per medication rule.
- Take with food to avoid stomach upset
- When changing to an ER formulation of divalproex sodium from non-ER formulation, the serum concentration would be expected to decrease by 8-20% and an increase of dose may be required
- Therapeutic ranges for the lab used should be listed on the report.