Medication Audit Criteria and Guidelines

Valproic Acid (Depakene® [DSC]), Divalproex Sodium (Depakote®, Depakote Sprinkles®, Depakote ER®)

PEFC Approved: February 2024

Indications

The PEFC acknowledges that there may be additional off-label indications that have supporting evidence for efficacy that are not listed below. If a medication is prescribed for an off-label indication, documentation in the patient chart is recommended.

Label:

- Mania
- Epilepsy
- Migraine headache prophylaxis

Off Label:

- Bipolar I and II maintenance
- Alcohol withdrawal syndrome, adjunct
- Bipolar depression
- Schizoaffective disorder, bipolar type
- Important Limitations—Because of the risk to the fetus (see Contraindications, Warnings and Precautions), should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other meds have failed to provide adequate symptom control or are otherwise unacceptable.

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, decreased IQ, and neurodevelopmental disorders
- Pancreatitis, including fatal hemorrhagic cases

Contraindications

- For use in prophylaxis of migraine headaches: women who are pregnant and those of childbearing potential who are not using effective contraception
- Hepatic disease or significant hepatic dysfunction
- Known hypersensitivity to the drug
- Known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG)
- Suspected POLG-related disorder in children under two years of age
- Urea cycle disorders

Warnings and Precautions

- Bleeding and other hematopoietic disorders: monitor platelet counts and coagulation tests
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reaction:usually presents with fever, rash, hymphadenopathy, and/or facial swelling in association with other organ system involvement
- Hepatotoxicity: evaluate high risk populations and monitor serum liver tests Immunologic: Stimulation of HIV and CMV virus replication may occur, but the clinical consequence is unknown
- Hyperammonemia: may be present despite normal LFTs. Measure ammonia level if unexplained lethargy and vomiting or changes in mental status.
- Hyperammonemia and encephalopathy associated with concomitant topiramate use
- Hypothermia: reported with or without associated hyperammonemia. Can also occur with concomitant topiramate
- Interaction with Carbapenem Antibiotics:valproate concentrations may be reduced, resulting in loss of seizure control. Monitor serum valproate concentrations
- Medication residue may rarely deposit in the stool
- Pancreatitis: should ordinarily discontinue
- Somnolence in the elderly can occur. Dosage should be increased slowly and with regular monitoring for fluid and nutritional intake
- Structural birth defects, decreased IQ, and neurodevelopmental disorders following in utero exposureSuicidal behavior or ideation: antiepileptic drugs increase the risk of suicidal thoughts or behavior
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- Urea cycle disorders: use is contraindicated as it may lead to hyperammonemic encephalopathy

- Use in Women of Childbearing Potential: only use to treat pregnant women with epilepsy or bipolar disorder if other medications fail to provide adequate symptom control or are otherwise unacceptable. Women should use effective contraception while using valproate.

Adverse Reactions

Not all-inclusive list, see: Lexicomp, Micromedex for more information.

Side effects with incidence >5% or greater than placebo:

- Cardiovascular:
  - Peripheral edema
- Dermatologic:
  - Alopecia
  - Rash
- Endocrine/Metabolic:
  - Anorexia
  - Increased appetite
  - Weight gain
  - Weight loss
- Gastrointestinal:
  - Abdominal pain
  - Constipation
  - Diarrhea
  - Dyspepsia
  - Nausea
- Hematologic:
  - Ecchymosis
  - Thrombocytopenia
- Musculoskeletal:
  - Back pain
- Neurologic:
  - Amnesia
  - Asthenia
  - Ataxia
  - Cognitive dysfunction
  - Dizziness
  - Headache
  - Parkinsonism
  - Somnolence
  - Tremor

- Ophthalmic:
  - Amblyopia/blurred vision
  - Diplopia
  - Nystagmus
- Otic:
  - Tinnitus
- Psychiatric:
  - Insomnia
  - Emotional lability
  - Nervousness
  - Thinking abnormal
- Respiratory:
  - Bronchitis
  - Rhinitis
  - Pharyngitis
- Other/Miscellaneous:
  - Accidental injury/falls
  - Fever
  - Flu syndrome
  - Infection

Serious adverse reactions:

- Endocrine/Metabolic:
  - Hyperammonemia
  - Hyponatremia
  - Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Gastrointestinal:
  - Pancreatitis
  - Vomiting
- Hematologic:
  - Neutropenia
  - Thrombocytopenia
- Hepatic Effects
  - Hepatotoxicity/hepatic failure
- Immunologic
  - Hypersensitivity reactions
- Neurologic
  - Hyperammonemic encephalopathy
- Psychiatric
  - Depression
  - Suicidal ideation

Drug Interactions of Major Significance

See: Contraindications

See: Indiana Univ Drug Interaction Table

See: Lexicomp, Micromedex for more information

Special Populations

- Pediatrics/Adolescents
  - See "Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health: Medication Tables (7th Version) 2023" for specific details.
- Geriatric
  - Included in BEERS criteria
  - Lower initial and maintenance doses (e.g., administration of 50-60% of usual dose) are recommended due to decreased elimination and increased incidences of somnolence.
  - Geriatric patients have increased amounts of free drug (use lower total plasma concentration or get free VPA plasma concentration)
- Renal impairment
  - Dosage adjustments are not necessary in patients with renal failure.
  - The unbound clearance of valproic acid is reduced by 27% in patients with CrCl < 10 mL/min.
  - Patients with renal failure have reduced protein binding leading to increased free levels of valproic acid. As a result, total concentrations may be misleading and free valproic acid concentration is preferred.
- Hepatic impairment
  - Liver disease impairs the capacity to eliminate valproate – use is contraindicated
- Hemodialysis
  - Hemodialysis reduces concentrations by about 20%
  - Dosage supplementation is not required in patients following hemodialysis
  - Protein binding is significantly reduced leading to increased free levels of valproic acid. As a result, total concentrations may be misleading and free valproic acid concentration is preferred.
- Pregnancy and Breastfeeding
  - See Black Box Warning
  - Review product-specific labeling. Consider risks/benefits in reviewing medication-specific labeling.

Patient Monitoring Parameters

Baseline Tests:

- Pregnancy test (females)
- CBC with differential
- CMP (evaluate hepatic function, serum creatinine, BUN, fasting glucose, and electrolytes)
- Weight
- Blood pressure
- Fasting lipids

Ongoing Tests:

- Pregnancy test (females) as clinically indicated
- CBC with differential - 1-2 weeks after initiation, 1-2 weeks after each dosage increase, every 3 months for the first year of treatment, then annually and as clinically indicated
- CMP (evaluate hepatic function, serum creatinine, fasting glucose, BUN and electrolytes) –every 3 months for the first year of treatment, then annually and as clinically indicated.
- Valproic acid level – 1-2 weeks after initiation, after each dosage change and as clinically indicated
- Weight –every 3 months for the first year of treatment, then annually and as clinically indicated
- Monitor for the emergence of suicidal ideation or behavior
- Blood pressure as clinically indicated
- Fasting lipids as clinically indicated

Dosing

- See HHSC Psychiatric Drug Formulary for dosage guidelines.
- If a medication is prescribed at dosages in excess of the Psychotropic Dosage Guidelines found in the HHS Psychiatric Drug Formulary, documentation in the patient chart is recommended.
- If a medication identified as reserve status in the HHS Psychiatric Drug Formulary, documentation of justification and adherence to the guidelines for use is recommended.
- 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.