VALPROIC ACID

CONVULZOR

Rx

250 mg Extended-Release Tablet
(Equivalent to Divalproex Sodium)
ANTICONVULSANT/ANTIEPILEPTIC (Fatty Acid Derivative)

FORMULATION:
Each extended-release tablet contains:
Valproic Acid equivalent to Divalproex Sodium ..... 250 mg

PRODUCT DESCRIPTION:
Orange coloured, round, biconvex, plain on both sides and film-coated extended release tablets.

MECHANISM OF ACTION:
Valproic Acid dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

PHARMACODYNAMICS:
The relationship between plasma concentration and clinical response is not well-documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate may not provide a reliable index of the bioactive valproate species.
For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy
The therapeutic range in epilepsy is commonly considered to be 50 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Mania
In placebo-controlled clinical trials of acute mania, patients were dosed to clinical response with trough plasma concentrations between 85 and 125 mcg/mL

PHARMACOKINETICS:
Valproic acid and its salts are rapidly absorbed from the gastrointestinal tract; the rate, but not the extent, of absorption is delayed if given with or after food. Valproic acid is extensively metabolised in the liver, a large part by glucuronidation and the rest by a variety of complex pathways. It does not appear to enhance its own metabolism, but metabolism may be enhanced by other drugs which include hepatic microsomal enzymes. Valproic acid is extremely bound to plasma proteins. The extent of protein binding is concentration dependent and is stated to be about 90 to 95% at total concentrations of 50 micrograms/mL, falling to about 80 to 85% at 100 micrograms/mL. Reported half lives for valproic acid have ranged from about 5 to 20 hours; the shorter half-lives have generally been recorded in epileptic patients receiving multiple drug therapy. The target range of total plasma valproic acid is usually quoted as being 40 to 100 micrograms/mL (280 to 700 micromoles/litre) but routine monitoring of plasma concentrations are not generally considered to be of use as an aid to assessing control. Valproic acid crosses the placental barrier and small amounts are distributed into breastmilk.

INDICATIONS:
For the treatment of primary generalized seizures, has notable benefit in absence and myoclonic seizures, and is also used for partial seizures. It is also used to treat the acute manic phase of bipolar disorder and for the prophylaxis of migraine.

DOSAGE AND ADMINISTRATION:
Valproic Acid is an extended-release product intended for once-a-day oral administration. Valproic Acid tablets should be swallowed whole and should not be crushed or chewed, or as prescribed by the physician.
Mania: Initial dose is 25 mg/kg/day, increasing as rapidly as possible to achieve therapeutic response or desired plasma level. The maximum recommended dosage is 60 mg/kg/day.
Complex Partial Seizures: Start at 10 to 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/day to achieve optimal clinical response; if response is not satisfactory, check valproate plasma level; see full prescribing information for conversion to monotherapy . The maximum recommended dosage is 60 mg/kg/day.
Absence Seizures: Start at 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/day until seizure control or limiting side effects. The maximum recommended dosage is 60 mg/kg/day.
Migraine: The recommended starting dose is 500 mg/day for 1 week, thereafter increasing to 1000 mg/day.

CONTRAINDICATIONS:
- Valproic Acid should not be administered to patients with hepatic disease or significant hepatic dysfunction.
- Valproic Acid is contraindicated in patients with known hypersensitivity to the drug.
- Valproic Acid is contraindicated in patients with known urea cycle disorders

WARNINGS AND PRECAUTIONS:
Hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproate. 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. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, healthcare providers should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.
Caution should be observed when administering valproate products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When Valproic Acid 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. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.
The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

Pregnancy
Teratogenic Effects: Pregnancy Category D.

Fetal Risk Summary
All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about 15%), or other adverse outcomes regardless of drug exposure. Maternal valproate use during pregnancy for any indication increases the risk of congenital malformations, particularly neural tube defects, but also malformations involving other body systems (e.g., craniofacial defects, cardiovascular malformations). The risk of major structural abnormalities is greatest during the first trimester; however, other serious developmental effects can occur with valproate use throughout pregnancy. The rate of congenital malformations among babies born to epileptic mothers who used valproate during pregnancy has been shown to be about four times higher than the rate among babies born to epileptic mothers who used other anti-seizure monotherapies.
Several published epidemiological studies have indicated that children exposed to valproate in utero have lower cognitive test scores than children exposed to either another antiepileptic drug in utero or to non-antiepileptic drugs in utero.
In animal studies, offspring had structural malformations similar to those seen in humans and demonstrated behavioral deficits.

Clinical Considerations
- Neural tube defects are the congenital malformation most strongly associated with maternal valproate use. The risk of spina bifida following in utero valproate exposure is generally estimated as 1-2%, compared to an estimated general population risk for spina bifida of about 0.06 to 0.07% (6 to 7 in 10,000 births).
- To prevent major seizures, women with epilepsy should not discontinue Valproic Acid abruptly, as this can precipitate status epilepticus with resulting maternal and fetal hypoxia and threat to life. Even minor seizures may pose some hazard to the developing embryo or fetus. However, discontinuation of the drug may be considered prior to and during pregnancy in individual cases if the seizure disorder severity and frequency do not pose a serious threat to the patient.
- Available prenatal diagnostic testing to detect neural tube and other defects should be offered to pregnant women using valproate.
- Evidence suggests that folic acid supplementation prior to conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population. It is not known whether the risk of neural tube defects in the offspring of women receiving valproate is reduced by folic acid supplementation. Dietary folic acid supplementation both prior to conception and during pregnancy should be routinely recommended for patients using valproate.
- Patients taking valproate may develop clotting abnormalities. A patient who had low fibrinogen when taking multiple anticonvulsants including valproate gave birth to an infant with afibrinogenemia who subsequently died of hemorrhage. If valproate is used in pregnancy, the clotting parameters should be monitored carefully.
- Patients taking valproate may develop hepatic failure. Fatal cases of hepatic failure in infants exposed to valproate in utero have also been reported following maternal use of valproate during pregnancy.

OVERDOSE AND TREATMENT:
Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2, 120 mcg/mL. In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

ADVERSE DRUG REACTIONS:
The most frequently reported adverse effects associated with valproate therapy are gastrointestinal disturbances, particularly at the start of therapy; enteric-coated formulations, taking doses with meals and starting with low doses may minimize symptoms. There may be increased appetite and weight gain in common. Less common adverse effects include oedema, headache, reversible prolongation of bleeding time, and thrombocytopenia. Leucopenia and bone marrow depression have been reported. Neurological adverse effects including ataxia, tremor, sedation, lethargy and confusion have been reported. Very rare cases of extrapyramidal symptoms or reversible dementia associated with cerebral atrophy have been reported. Increased alertness may occur, which is generally considered beneficial, but occasionally rashes and rarely hirsutism, acne, toxic epidermal necrolysis and Stevens-Johnson syndrome or erythema multiforme. Transient hair loss sometimes with regrowth of curly hair, has occurred. Irregular periods, amenorrhea and gynaecomastia have been reported rarely.
Liver dysfunction including hepatic failure has occasionally been reported, usually in the first few months of treatment, and requires valproate withdrawal; there have been fatalities. Elevation of liver enzyme values is common but normally transient and dose-related. Hyperammonemia has occurred, even in the absence of overt hepatic failure, and is sometimes associated with neurological symptoms; Hyperglycemia has been also reported. Pancreatitis has also been reported rarely, and fatalities have occurred; plasma amylase should be measured if there is acute abdominal pain, although the value of serum amylase as diagnostic tool has been questioned. In few patients there have been reports of reversible defects in renal tubular function (Fanconi's syndrome).
Congenital malformations have been reported in infants born to women who had received antiepileptics including valproate during pregnancy. Inflammatory reactions and pain have been reported at the injection site after intravenous doses.

DRUG INTERACTIONS:
Antibacterials: Raised valproate blood concentrations and symptoms consistent with valproate toxicity have been reported in a patient also given erythromycin.
Antidepressant: May antagonize the antiepileptic activity of valproate by lowering the convulsive threshold.
Gastrointestinal: Use with an antacid (aluminum and magnesium hydroxides) significantly increased the bioavailability of a valproic acid preparation in healthy subjects. Use of highly protein bound drugs with valproate may increase free valproate plasma concentrations.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

Keep all medicines out of reach of children.

AVAILABILITY:
Alu/Alu Blister Pack x 10's (Box of 10's).

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Manufactured by:
AKUMS DRUGS & PHARMACEUTICALS LTD.
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