

with this. Do not stop taking or your contraception until you have discussed this with your doctor. Your doctor will advise you further.
Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking.

Precautions while taking this medicine:

Valproic acid is an antidepressant, and therefore there is a concern that it can potentially worsen depression and increase suicidality. There is a need to appropriately monitor patients for clinical worsening, suicidality, and unusual changes in behavior. Patients must also be screened for bipolar disorder because treatment with an antidepressant alone can increase the likelihood of a mixed/ manic episode.

SPECIAL WARNINGS:

- Liver dysfunction
- Pancreatitis

Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting, or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anti-convulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

- Carbapenem agents

The concomitant use of valproate and carbapenem agents is not recommended.

- Patients with known or suspected mitochondrial disease.

CONTRAINDICATIONS:

This is contraindicated in the following situations:

- In pregnancy.
- In women of childbearing potential unless the conditions of the pregnancy prevention programs are fulfilled.
- Active liver disease.
- Personal or family history of severe hepatic dysfunction, drug related.
- Patients with known urea cycle disorders.
- Hypersensitivity or any other ingredient of the preparation.
- Porphyria.
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme 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.

STORAGE CONDITIONS AND OTHER INFORMATION:

- Dosage as directed by the physician.
- To be dispensed in the prescription of a registered medical practitioner only.
- Store below 30°C in a dry place, protect from light.
- Keep out of the reach of children.

ہدایات:

- **خودک ڈاکڑ کی ہدایت کے مطابق استعمال کریں۔**
- **دوا کو ۳۰°C کی پستی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔**
- **صرف ریٹریڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔**
- **بچوں کی پہنچ سے دور رکھیں۔**

Manufactured by:

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Art no: 591/1

DIVALPRO®

Tablets and Syrup

250mg TABLETS:

Composition:

Each enteric coated tablet contains:
Divalproex Sodium (USP) eq. to
Valproic acid 250mg.

(Product complies USP Specifications).

500mg TABLETS:

Composition:

Each enteric coated tablet contains:
Divalproex Sodium (USP) eq. to
Valproic acid 500mg.

(Product complies USP Specifications).

DIVALPRO SYRUP

Composition:

Each 5ml contains:
Sodium valproate (BP) eq. to
Valproic acid 250mg

(Product complies USP Specs).

ڈائیپرو
(ڈائیپروکس سوڈیم)

WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity:

In 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.

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.

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).

Fetal Risk:

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

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.

CLINICAL PHARMACOLOGY:

Pharmacodynamics:

Divalpro exerts its effects mainly on the central nervous system. The most likely mode of action is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness in acute mania was demonstrated in two, 3 week, double-blind, placebo-controlled trials conducted in bipolar patients. It was initiated at a dose of 250 mg TID and subsequently titrated up to a maximum daily dose not exceeding 2500 mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

Pharmacokinetics:

Following oral administration, the absolute bioavailability of valproic acid approaches 100%. Mean terminal half-life is about 14 hours, steady-state conditions usually being achieved within 3 - 4 days. Peak plasma concentrations are achieved within 3 - 5 hours.

Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Distribution:

Plasma protein binding ranges from 85 - 94% over plasma drug concentrations of 40 - 100 µg/ml. It is concentration-dependent, and the free fraction increases non-linearly with plasma drug concentration.

Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism:

It is extensively metabolized in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 - 0.6 L/h and is independent of hepatic blood flow.

The major pathway of valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9, and UGT2B7.

Elimination:

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Hemodialysis reduces serum valproic acid concentrations by about 20%.

Interaction with estrogen-containing products.

Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.

Indications:

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded for acute mania.

Divalpro 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 in epilepsy. Divalpro is indicated in prophylaxis of migraine headaches.

Method of administration and Posology:

Syrup

This syrup is for oral administration. Daily dosage requirements vary according to age and body weight. Syrup may be given twice daily. If it is necessary to dilute the Syrup, the recommended diluent is Syrup BP, but syrup containing SO₂ as a preservative should not be used. The diluted product will have a 14-day shelf life.

Tablet

This tablet is for oral administration.

Mania: Recommended initial dose is 25mg/kg/day, once daily. Maximum recommended dosage is 60mg/kg/day.

Epilepsy: Complex Partial Seizures (For adults and children 10 years of age or older): Monotherapy (Initial Therapy) with 10-15mg/kg/day.

Conversion to Monotherapy: Initiate therapy at 10-15mg/kg/day. Concomitant anti-epileptic drug to be reduced by approximately 25% every 2 weeks.

Adjunctive Therapy: Initiate therapy at 10-15mg/kg/day.

Simple and Complex Absence Seizures: Recommended initial dose is 15mg/kg/day.

Maximum recommended dosage is 60mg/kg/day.

DOSEAGE:

Usual requirements are as follows:

Adults:

Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1000 - 2000 mg per day, i.e.

20 - 30 mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg:

The Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20 - 30 mg/kg body weight per day.

Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg:

20 mg/kg of body weight per day; in severe cases, this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and hematological parameters should be monitored.

Use in the elderly:

Although the pharmacokinetics are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of the free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency:

It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

In patients with hepatic insufficiency:

Salicylates should not be used concomitantly since they employ the same metabolic pathway.

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid.

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition, in conjunction with, concomitant use in children under 3 years can increase the risk of liver toxicity.

Female children and women of childbearing potential:

Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme. The benefits and risks should be carefully reconsidered at regular treatment reviews.

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged-release formulation. The daily dose should be divided into at least two single doses.

OVERDOSAGE:

Signs of acute massive overdose, i.e. plasma concentration 10 - 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension, and circulatory collapse/shock. A favorable outcome is usual, however, some deaths have occurred following massive overdose.

Symptoms may, however, be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties). Cases of intracranial hypertension related to cerebral edema have been reported.

The presence of sodium in the sodium valproate formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 - 12 hours following ingestion. Haemodialysis and haemoperfusion have been used successfully.

Before using this medicine, be sure to tell your doctor and pharmacist

Do not take divalpro and tell your doctor if:

- You are allergic (hypersensitive) to sodium valproate or any of the other ingredients.
- Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You have liver problems or you or your family have a history of liver problems caused by taking medicine.
- You have a rare illness called porphyria which affects your metabolism.
- You have a known metabolic disorder, i.e. a urea cycle disorder.
- You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).
- You are pregnant. If you are a woman able to have a baby you must not take unless you use an effective method of birth control (contraception) at all times during your treatment