For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Abridged Prescribing Information

DEPAKOTE 250MG & 500MG
Divalproex Gastro-resistant Tablets I.P

COMPOSITION
DEPAKOTE ® 250: Each enteric coated tablet contains Divalproex Sodium IP equivalent to valproic acid 250mg
DEPAKOTE ® 500: Each enteric coated tablet contains Divalproex Sodium IP equivalent to valproic acid 500mg
THERAPEUTIC INDICATIONS : Treatment of manic episodes in bipolar disorders; monotherapy and adjunctive therapy in treatment of complex partial seizures, either in isolation or in association with other types of seizures.
DOSAGE & METHOD OF ADMINISTRATION:
Bipolar Disorders: Initial dosage 750mg / day in 2-3 divided doses. Usual daily dosage between 1000 and 2000mg. Maximum 2500mg/day. Not evaluated for patients under 18 years. Epilepsy: Complex Partial Seizures: Initiate therapy with 10-15mg/kg/day. Optimal clinical response is achieved at daily dose below 60mg/kg/day. Female children, female adolescents, women of childbearing potential and pregnant women: Depakote should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Depakote should 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 during pregnancy. Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
SAFETY-RELATED INFORMATION: Contraindications: Hypersensitivity to Depakote®; Acute and chronic hepatitis; Patient or family history of severe hepatitis, especially drug related; Hepatic porphyria; Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ and in children under two years of age who are suspected of having a POLG-related disorder; Patients with known urea cycle disorders.
Warnings: Severe liver damage resulting sometimes in fatalities has exceptionally been reported, severe pancreatitis which may result in fatalities has been very rarely reported.
Female children, female adolescents, women of childbearing potential and pregnant women : Valproate should not be used in female children, in female adolescents, in women of child-bearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. Children exposed in-utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and / or congenital malformations (in approximately 10% of cases). Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant. Women of child bearing potential must use effective contraception during treatment and be informed of the risks associated with the use of valproate during pregnancy. *Estrogen-containing products :* Valproate does not reduce efficacy of hormonal contraceptives: However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials to support her understanding of the risks. In particular the prescriber must ensure the patient understands :

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and risks of developmental disorders.
- need to use effective contraception;
- need for regular review of treatment;
- the need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

Valproate therapy must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.

Suicidal ideation and behavior : Patients should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered.

Carbapenem agents : Concomitant use of valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease : Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations or mitochondrial DNA as well as the nuclear-encoded POLG gene.

Aggravated convulsions : As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately.(see *Adverse Reaction*)

Precautions: Liver function tests should be carried out before therapy, and periodically during the first 6 months especially in patients at risk. Blood tests are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding. Potential benefit should be weighed against its potential risk in patients with systemic lupus erythematosus. When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate. Patients should be warned of the risk of weight gain at initiation and appropriate strategies should be adopted to minimize the risk. Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. Alcohol intake is not recommended during treatment. Monotherapy is recommended in children under the age of 3 years. Concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Patients with renal insufficiency should be closely monitored, it may be necessary to decrease the dosage.

Pregnancy : Not to be used during pregnancy and in women of child-bearing potential unless clearly necessary. Women of childbearing potential should be informed of the risks and benefits of use of valproate in pregnancy.

Lactation : Excretion of valproate in breast milk is low with a concentration of 1% to 10% of maternal serum levels. Based on literature breastfeeding can be envisaged taking into account the valproate safety profile especially hematological disorders**.**

Adverse Reactions: Very common (≥1%): tremor, nausea, Common (≥1% and<10%) : anaemia, thrombocytopenia, extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness, deafness, vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, abdominal pain upper, diarrhea, urinary incontinence , hypersensitivity, transient and /or dose related alopecia, nail and nail bed disorders, hyponatraemia, weight increased, haemorrhage, liver injury, dysmenorrhea, confusional state, hallucinations, aggression, agitation, disturbance in attention.

For full prescribing information, please contact Sanofi-Synthelabo (I) Pvt Ltd, Sanofi House, CT Survey No 117-B, L& T Business Park, Saki Vihar Road, Powai, Mumbai-400072

Source: CCDS version 23 dated 18th December 2017 , content of the DHPC

Updated: March 2018