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. Only for Bipolar indication – In children and adolescents the efficacy of Depakote® in the treatment of manic states has not been established in patients under 18 years of age. 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. Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia (see "Precautions" Patients at risk of hypocarnitinemia)
Warnings: Severe liver damage resulting sometimes in fatalities has exceptionally been reported, severe pancreatitis which may result in fatalities has been very rarely reported.
Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.
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). Monitoring of signs and symptoms of ototoxicity is recommended.

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.
In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos). These have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.
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.
Metamizole: Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.
Methotrexate: Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.
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 of age. Concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity. Appropriate liver monitoring should be exercised when valproate is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters Patients with renal insufficiency should be closely monitored, it may be necessary to decrease the dosage. A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate at time of conception compared to those treated with lamotrigine or levetiracetam. T he prescriber should inform the male patients of this potential risk and consider alternative therapeutic options with the patient as precautionary measure. An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the prescriber.

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.

Neurodevelopmental disorders from in utero exposure: Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when valproate is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated epileptic mothers.

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. . *Pediatric population*- Experience indicates that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see "Precautions") or degenerative disease..Young children are also at particular risk of pancreatitis. These risks decrease with increasing age. Psychiatric disorders such as abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

For full prescribing information, please contact Sanofi Healthcare India Private Limited, Sanofi House, CT Survey No 117-B, L& T Business Park, Saki Vihar Road, Powai, Mumbai-400072

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