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

This package insert is continually updated. Please read carefully before using a new pack

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Divalproex Gastro-resistant Tablets I.P.
DEPAKOTE® 250

Divalproex Gastro-resistant Tablets I.P.
DEPAKOTE® 500

Composition
DEPAKOTE® 250
Each enteric coated tablet contains Divalproex Sodium I.P. equivalent to valproic acid 250 mg
Colours: Sunset yellow Aluminium Lake & Titanium dioxide IP
DEPAKOTE® 500
Each enteric coated tablet contains Divalproex Sodium I.P. equivalent to valproic acid 500 mg
Colours: Ponceau 4R Aluminium Lake, Indigotine Aluminum Lake &Titanium Dioxide IP
INDICATIONS
BIPOLAR INDICATION
For the treatment of manic episodes in patients with bipolar disorders.

EPILEPSY INDICATION
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.

DOSAGE AND METHOD OF ADMINISTRATION
Method of Administration
Oral route

BIPOLAR INDICATION
In adults
Recommended initial dosage is 750 mg a day in 2 or 3 divided doses. Dosage should be increased as quickly as possible to reach minimum effective dose depending on the clinical effects sought. Daily dosage usually is between 1000 and 2000 mg. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.

In the elderly
Changes in pharmacokinetic parameters have been observed but they are of little clinical significance; thus dosage will be established depending on clinical response.

In children and adolescents
Safety and efficacy of Depakote® in the treatment of manic states have not been evaluated in patients under 18 years of age.

In patients with impaired renal or hepatic function:
See *"Contraindications" and "Warnings" or "Precautions"*.

EPILEPSY INDICATION
Depakote® has been studied as monotherapy and adjunctive therapy in complex partial seizures.
Monotherapy (Initial Therapy): Depakote® has not been systemically studied as initial therapy. Patient should initiate therapy at 10 to 15mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily optimal clinical response is achieved at daily doses below 60 mg/kg/day.

Conversion to Monotherapy : Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily optimal clinical response is achieved at daily doses below 60 mg/kg/day.

Concomitant therapy anti-epilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of Depakote® therapy or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of concomitant AED can be highly variable and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive therapy: Depakote® may be added to the patients regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily optimal clinical response is achieved at daily doses below 60 mg/kg/day. If the total daily dose exceeds 250 mg it should be given in divided doses.

Since valproate may interact with other concurrently administered AEDs as well as other drugs (see "*Interactions"*), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see "*Precautions"*).

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 (see "*Warnings"* and "*Pregnancy")* 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.

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. (See Section Interactions)

CONTRAINDICATIONS

- Hypersensitivity to Depakote®
- Acute or 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 (POLG, e.g. Alpers-Huttenlocher Syndrome) and in children under two years of age who are suspected of having a POLG-related disorder (see "Warnings").
- Patients with known urea cycle disorders (see "Precautions")

WARNINGS

- ***Severe liver damage***

-Conditions of occurrence:

Severe liver damage resulting sometimes in fatalities has exceptionally been reported.

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 or degenerative disease.

After the age of 3 years, the risk is significantly reduced and it progressively decreases with age.

In most cases, such liver damage occurred during the first 6 months of therapy.

-Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk *(*see *"Conditions of occurrence")*:

- Non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- In patients with epilepsy, recurrence of seizures.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.

-Detection :
Liver function tests should be performed before therapy and then periodically during the first 6 months of therapy. Among the usual investigations, tests which reflect protein synthesis particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Depakote® therapy. As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued since they follow the same metabolic pathway.

- ***Pancreatitis***

Severe pancreatitis, which may result in fatalities, has been very rarely reported. Young children are at particular risk but this risk decreases with increasing age. Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, valproate should be discontinued.

- ***Female children, female adolescents, women of childbearing potential and pregnant women***

Depakote® 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. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of child bearing potential treated with Depakote® plans a pregnancy or if she becomes pregnant.
Women of child-bearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Depakote® during pregnancy (see*"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. (See Section Interactions)

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, 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 the risks of developmental disorders.
• The need to use effective contraception.
• The 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.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see *"Pregnancy").*

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy or bipolar disorder.

- ***Suicidal ideation and behaviour***

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this effect is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

- ***Carbapenem agents***

The concomitant use of valproate and carbapenem agents is not recommended. (see *"Interactions").*

- ***Patients with known or suspected mitochondrial disease***

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear- encoded POLG gene. In particular, acute liver failure and liver-related deaths have been associated with valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial enzyme polymerase γ (POLG; e.g. Alpers-Huttenlocher Syndrome). POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to un-explained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see *"Contraindications"*).

- ***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

Liver function tests should be carried out before therapy (see *"Contraindications"*), and periodically during the first 6 months especially in patients at risk (see *"Warnings"*). As with most antiepileptic drugs, a slight increase in liver enzymes may be noted, particularly at the beginning of the therapy; they are transient and isolated. More extensive biological investigations (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

- Haematological tests

  Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see *"Adverse Reaction*").

- ***Patients with systemic lupus erythematosus***

Although immune disorders have been noted only exceptionally during the use of Depakote®, the potential benefit of Depakote® should be weighed against its potential risk in patients with systemic lupus erythematosus.

- ***Urea cycle disorders***

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate (see *"Contraindications"*)

- ***Weight gain***

Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimize the risk. *(*see *"Adverse Reaction")*

- ***Carnitine palmitoyltransferase (CPT) type II deficiency***

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. (see*"Contraindications")*

- ***Alcohol***

Alcohol intake is not recommended during treatment with valproate.

- ***Children*:**

  Monotherapy is recommended in children under the age of 3 years when prescribing Depakote®, but the potential benefit of Depakote® should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy *(*see *"Warnings").*

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity.

- ***Renal insufficiency*:**

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

INTERACTIONS

Effects of valproate on other drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

Depakote® may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore clinical monitoring is advised and dosage should be adjusted when appropriate.

- ***Lithium***

Depakote has no effect on serum lithium levels.

- ***Phenobarbital***

Depakote® increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Depakote® increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of a combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Depakote® decreases phenytoin total plasma concentration. Moreover, Depakote® increases the phenytoin free form with possible overdose symptoms (valproic acid displaces phenytoin from its

plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***

Clinical toxicity has been reported when valproate was co-administered with carbamazepine as valproate may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Depakote reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Zidovudine***

Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Felbamate***

Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Olanzapine***

Valproic acid may decrease the olanzapine plasma concentration.

- ***Rufinamide***

Valproic acid may lead to an increase in plasma level of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population

- ***Propofol***

Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- ***Nimodipine***

Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50 %.

Effects of other drugs on valproate

- ***Antiepileptics***

Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of felbamate and valproate decreases valproic acid clearance by 22% to 50%, and consequently increase the valproic acid plasma concentrations. Valproate dosage should be monitored.

Valproic acid serum levels may be increased in case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia.

- ***Mefloquine***

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy.

- ***Highly protein bound agents***

In case of concomitant use of valproate and highly protein bound agents (aspirin), valproate free serum levels may be increased.

- ***Vitamin K dependent factor anticoagulant***

Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent factor anticoagulant.

- ***Cimetidine or Erythromycin***

Valproic acid serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

- ***Carbapenem agents***

Carbapenem (panipenem, meropenem, imipenem…): Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100% decrease in valproic acid levels within two days sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, coadministration of carbapenem agents in patients stabilized on valproic acid should be avoided. If treatment with these antibiotics cannot be avoided, close monitoring of Depakote® blood level should be performed.

- ***Rifampicin***

Rifampicin may decrease the valproate acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

- **Protease inhibitors**

Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma level when co-administered.

- **Cholestyramine**

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

- **Estrogen-containing products**

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 adding, or discontinuing estrogen-containing products. Consider monitoring of valproate plasma levels

Valproate usually has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

Other Interactions

Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.

- ***Quetiapine***

Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.

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PREGNANCY

- ***Risk associated with seizures***

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.

- ***Risk associated with Depakote®***

In animals: Teratogenic effects have been demonstrated in the mice, rats and rabbits.

Congenital malformations

In humans: Available data suggest an increased incidence of minor or major malformations including, in particular, neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in off spring born to mothers treated with valproate, when compared to the incidence for certain other antiepileptic drugs. Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73%. (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established

Developmental disorders

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.

There are data to show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (estimated 3- to 5-fold increased risk), including childhood autism.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

In view of the above data the following recommendations should be taken into consideration:
This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a woman of child bearing potential treated with Depakote plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

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. (See Section Interactions)

Women of childbearing potential should be informed in detail of the risks and benefits of the use of valproate during pregnancy.

If a woman plans a pregnancy or becomes pregnant, Depakote® therapy should be reassessed whatever the indication.

- In bipolar disorders indication, cessation of Depakote® therapy should be considered.

- In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Depakote® treatment is to be continued during the pregnancy, it is recommended to use Depakote® in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.

- In addition, if appropriate, folate supplementation should be started before pregnancy and at relevant dosage (5 mg daily) as it may minimize the risk of neural tube defects. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

- Specialized prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

- ***Risk in the neonate***

Exceptional cases of hemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenis, hypofibrinogenemia and/or to decrease in other coagulation factors; afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitterness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of pregnancy.

- ***Fertility***

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see *"Adverse Reactions"*). Valproate administration may also impair fertility in men (see *"Adverse Reactions"*).
Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

LACTATION

Excretion of valproate in breast milk is low, with a concentration between 1% to 10% of maternal serum levels. Based on literature and clinical experience, breastfeeding can be envisaged, taking into account the Depakote® safety profile, especially hematological disorders. (see *"Adverse Reactions").*

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

The patient should be warned of the risk of somnolence especially in cases of anticonvulsant polytherapy or association with benzodiazepines *(*see *"Interactions")*

ADVERSE REACTIONS
The following CIOMS frequency rating is used when applicable:
Very common ≥ 10%; Common ≥1 and <10%; Uncommon ≥0.1 and <1; Rare ≥0.01 and <0.1;
Very rare <0.01, Unknown (cannot be estimated from available data)

*Congenital, familial and genetic disorders (*see *"Pregnancy")*

Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia. (see *"Precautions"***)**
Uncommon: pancytopenia, leucopenia
Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.

Investigations
Common:
Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see also "Precautions" and *"Pregnancy")*
biotin deficiency/biotinidase deficiency

Nervous system disorders
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus, dizziness (for intravenous injection, dizziness may occur within few minutes and it usually resolves spontaneously within a few minutes.)
Uncommon: coma*, encephalopathy*, lethargy*(see below), reversible parkinsonism, ataxia, paresthesia
Uncommon: Aggravated convulsions (see *"Warnings").*

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.
*Stupor and lethargy sometimes leading to transient coma /encephalopathy; they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage. These cases mostly occurred during combined therapy (in particular with phenobarbital or topiramate) or after a sudden increase in valproate doses.

Ear and labyrinth disorders
Common: deafness

Respiratory, thoracic and mediastinal disorders
Uncommon : pleural effusion

Gastrointestinal disorders
Very common : nausea
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, abdominal pain upper, diarrhea frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing the treatment.Uncommon: pancreatitis, sometimes lethal. (see *"Warnings"*)

Renal and urinary disorders
Common: urinary incontinence
Uncommon: renal failure
Rare : enuresis. tubulointerstitial nephritis
reversible Fanconi syndrome but the mode of action is as yet unclear.

Skin and subcutaneous tissue disorders
Common: hypersensitivity, transient and /or dose related alopecia, nail and nail bed disorders.

Uncommon: angioedema, rash, hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal)
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Musculoskeletal and connective tissue disorders
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with sodium valproate. The mechanism by which sodium valproate affect bone metabolism has not been identified.
Rare: systemic lupus erythematosus (see Precautions) rhabdomyolysis(see precautions)

Endocrine disorders
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acnea, male pattern alopecia, and/or androgen increased)
Rare: hypothyroidism (see Pregnancy).

Metabolism and nutrition disorders
Common: hyponatraemia, weight increased.
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see Section "Precautions").
Rare: hyperammonaemia (see section Precautions), obesity
*Cases of isolated and moderate hyperammonemia without change in liver function tests may frequently occur and should not cause treatment discontinuation. Hyperammonemia associated with neurological symptoms has also been reported. In such cases, further investigations should be considered (see Precautions)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Rare: myelodysplastic syndrome

Vascular disorders
Common: haemorrhage (see Warnings & Pregnancy)
Uncommon: vasculitis

General disorders and administration site conditions
Uncommon: hypothermia**,** non severe oedema peripheral

Hepatobiliary disorders
Common: liver injury (see *"Warnings"*).

Reproductive system and breast disorders
Common: dysmenorrhea
Uncommon : amenorrhea
Rare: male infertility, polycystic ovaries

Psychiatric disorders
Common : confusional state , hallucinations aggression*,agitation*,disturbance in attention*
Rare: abnormal behaviour*,psychomotor hyperactivity*,learning disorder*
*These ADRs are principally observed in the paediatric population.

OVERDOSE
Signs and Symptoms
Signs of acute massive overdose usually include a coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis. hypotension and circulatory collapse/shock

Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral edema have been reported.
The presence of sodium content in the valproate formulations may lead to hypernatraemia when taken in overdose

Management:
Hospital management of overdose should be symptomatic: gastric lavage may be useful up to 10 to 12 hours following ingestion, cardio-respiratory monitoring.

Naloxone has been successfully used in a few isolated cases. In case of massive overdose, hemodialysis and hemoperfusion have been used successfully.

Interference with Laboratory and Diagnostic Test
Since valproate is excreted mainly through the kidney partly in the forms of ketone bodies, ketone body excretion test may give false positive results in diabetic patients.

Manufactured by:
Windlas Biotech Limited (Plant 2)
Khasra No. 141-143 & 145,
Mohabewala Industrial Area,
Dehradun-248 110 Uttarakhand.

Marketed by:
Sanofi-Synthelabo (India) Pvt. Ltd.
Sanofi House, CT Survey No 117-B,
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Powai, Mumbai 400072.

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