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.

Only for Bipolar indication
In children and adolescents
The efficacy of Depakote® in the treatment of manic states has not been established in patients aged less than 18 years
See also sections Warnings/Precautions and Adverse reactions for safety information

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, women of childbearing potential and pregnant women
Depakote® must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, *"Warnings"* and *"Pregnancy")*
Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (PPP Section Warnings).
In the exceptional circumstance when valproate is the only treatment option during pregnancy in epileptic women, Depakote® should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose of non-prolonged release formulations should be divided into at least two single doses during pregnancy (See section 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
Depakote is contraindicated in following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see Sections Warnings and Pregnancy).
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see Sections Warnings and Pregnancy).

Treatment of bipolar disorder

• in pregnancy (see Sections Warnings and Pregnancy).

• in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see Sections Warnings and Pregnancy).

All indications

- 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")
- Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia (see "Precautions" *Patients at risk of hypocarnitinemia*)

WARNINGS

Pregnancy Prevention Program

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see Section Pregnancy).

Depakote is contraindicated in the following situations:

Treatment of epilepsy

• in pregnancy unless there is no suitable alternative treatment (see Sections Contraindications and Pregnancy).
• in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see Sections Contraindications and Pregnancy).

Treatment of bipolar disorder

• in pregnancy (see Sections Contraindications and Pregnancy).
• in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see Sections Contraindications and Pregnancy).

Conditions of Pregnancy Prevention Program:

The prescriber must ensure that
• Individual circumstances are evaluated in each case and discussed with the patient. This is to guarantee the patient's engagement and understanding of the therapeutic options together with the risks and the measures needed to mitigate the risks.
• the potential for pregnancy is assessed for all female patients.
• the patient understands and acknowledges the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
• the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
• the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (see subsection contraception of this warning), without interruption during the entire duration of treatment with valproate.
• the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders.
• the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
• the patient understands the need to urgently consult her physician in case of pregnancy.
• the patient has received the patient guide.
• the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Pharmacist or other health care professional must ensure that
• the patient card is provided with every valproate dispensing and that the patients understand its content.
• the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Female children
• The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
• The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
• In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention program should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test
Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception
Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user-independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist
The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning
For the epilepsy indication, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess the valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section Pregnancy). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the bipolar disorder indication, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate exposed

pregnancy and their partners should be referred to a specialist experienced in <teratology>/ pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see section Pregnancy).

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention program. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

A risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist, and when a woman is planning a pregnancy or is pregnant.

- ***Use in males of reproductive potential***

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 (see section Pregnancy).

As a precautionary measure, the prescriber should inform the male patients of this potential risk and consider alternative therapeutic options with the patient. In men initiating or remaining on valproate treatment, the need for effective contraception should be discussed with the patient, at least annually. The prescriber should ensure the male patient has acknowledged the risk and precautions associated with valproate use (Annual Risk Acknowledgement Form).

The Marketing Authorization Holder has provided educational materials to remind the warnings and provide guidance regarding use of valproate in men of reproductive potential. A patient guide should be provided to all men of reproductive potential using valproate. 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.

- ***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 disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see "Precautions") 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, especially in patients at risk (see also Section "*Interactions*"). 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.

- ***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, ophthalmoplegia, 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"*).

- ***Urea cycle disorders and risk of hyperammonemia***

When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate (see *"Contraindications"* and *"Precautions" Patients at risk of hypocarnitinemia and Severe liver damage*).

- ***Patients at risk of hypocarnitinemia***

Valproate administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine *(*see also Warnings on *Patients with known or suspected mitochondrial disease* and *urea cycle disorders and risk of hyperammonemia),* impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.

Patients should be warned to report immediately any signs of hyperammonemia such as ataxia, impaired consciousness, vomiting for further investigation. Carnitine supplementation should be considered when symptoms of hypocarnitinemia are observed.

Patients with known systemic primary carnitine deficiency and corrected for hypocarnitinemia should be treated with valproate only if the benefits of valproate treatment outweigh the risks in these patients and there is no suitable therapeutic alternative. In these patients, close monitoring for recurrence of hypocarnitinemia should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate (see*"Contraindications").* Carnitine supplementation should be considered in these patients.
See also *"*Interactions*"*, *"*Adverse Reactions*"* and *"*Overdose*"*).

- ***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.

- ***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)

- ***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 Depakote® and carbapenem agents is not recommended. (see *"Interactions").*

- ***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* and see also *"Interactions"*).*"*). 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.

- ***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")*

- ***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"* and see also *"Interactions").).*
The concomitant use of salicylates should be avoided in children under 3 years of age 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 estroprogestative agents in women receiving hormonal contraception.

- ***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.

<u>Other Interactions</u>

- ***Risk of liver damage***

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see Section *Warnings/Precautions*- "Severe liver damage" and "children").

Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see Section *Warnings/Precautions*- "Severe liver damage" and "children").

In patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19% of patients. 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 (see Section "*Warnings/Precautions*").

- ***Topiramate and acetazolamide***

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.

- ***Pivalate-conjugated medicines***

Concomitant administration of valproate and pivalate-conjugated medicines that decrease carnitine levels (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) may trigger occurrence of hypocarnitinemia (see "Precautions" *Patients at risk of hypocarnitinemia*). Concomitant administration of these medicines with valproate is not recommended. Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinemia.

- ***Quetiapine***

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

PREGNANCY

Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled (see Sections Contraindications and Warnings).

Teratogenicity and Developmental Effects from female and male exposure
Valproate was shown to cross the placental barrier both in animal species and in humans

Pregnancy Exposure Risk related to valproate
In females, both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data how an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate
In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits.

Risk to children of fathers treated with valproate
A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate at time of conception compared to those treated with lamotrigine or levetiracetam.
The adjusted cumulative risk of NDDs ranged between 5.6% to 6.3% in the valproate group versus between 2.5% to 3.6% in the composite lamotrigine/levetiracetam monotherapy exposure. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.47 (95% CI: 1.10, 1.96).
Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. Further investigations are needed. Alternative therapeutic options and the need for effective contraception should be discussed with male patients of reproductive potential, at least annually (see section Warnings/Precautions).

Congenital malformations from in utero exposure
A meta-analysis (including registries and cohort studies) showed that about 11% of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformations.
This is a greater than the risk of major malformations the general population, about 2-3%. The risk of major congenital malformations in children after in utero exposure to anti-epileptic polytherapy including valproate is higher than that of anti-epileptic drugs polytherapy not including valproate. This risk is dose dependent in valproate monotherapy, and available data suggest it is dose-dependent in valproate polytherapy. However a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor or major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip palate, craniostenosis, cardiac, renal and urogenital defects, limb defects(including bilateral aplasia of the radius, and multiple anomalies involving various body systems.

In utero exposure to valproate may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases had not resolved. Monitoring of signs and symptoms of ototoxicity is recommended.

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.

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.

The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

When valproate is administered in monotherapy 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.

Available data from a study conducted using registries in Denmark show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately 3 -fold), and childhood autism(approximately 5 fold) compared to the unexposed population.

Available data from a second study conducted using registries in Denmark show that children exposed to valproate in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

If a woman plans a pregnancy
For the epilepsy indication, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess the valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see Section Warnings). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the bipolar disorder indication, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered**.**

Pregnant women

Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see Sections Contraindications and Warnings).

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

• Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist *experienced in <teratology> / pre-natal medicine* for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation (5 mg daily) before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure**.**

- ***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 thrombocytopenia, 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, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of 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)

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").*

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"*). In the few cases in which valproate was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed.

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.

Eye disorders
Not known: diplopia

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), *Urea cycle disorders and risk of hyperammonemia and patients at risk of hypocarnitinemia*).
Not known: hypocarnitinemia (see "Contraindications" and "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.

Pediatric population

The safety profile of valproate in the pediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the pediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section Warnings/Precautions). Psychiatric disorders such as aggression, agitation, disturbance in attention,

abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric 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.
In case of valproate overdose resulting in hyperammonemia, carnitine can be given through IV route to attempt to normalize ammonia levels.

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.

GENOTOXICITY

Valproate was not mutagenic in bacteria (Ames test), or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay), and did not induce DNA repair activity in primary culture of rat hepatocytes. After oral administration, valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice.
In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand-breaks, chromosomal aberrations or micronuclei) have been reported in rodents. However, the relevance of the results obtained with the intraperitoneal route of administration is unknown.
Statistically significant higher incidences of sister-chromatid exchange (SCE) have been observed in patients exposed to valproate as compared to healthy subjects not exposed to valproate. However, these data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with valproate versus untreated epileptic patients, provided contradictory results. The biological significance of an increase in SCE frequency is not known.

CARCINOGENICITY

The 2-year carcinogenicity studies were conducted in mice and rats given oral valproate doses of approximately 80 and 160 mg/kg/day (which are the maximum tolerated doses in these species but less than the maximum recommended human dose based on body surface area). Subcutaneous fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to those in registries of historical controls.

REPRODUCTIVE & DEVELOPMENTAL TOXICITY

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits. In published literature, behavioral abnormalities have been reported in first generation offspring of mice and rats after in utero exposure to clinically relevant doses/exposures of valproate. In mice,

behavioral changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility

In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Relevance of the testicular findings to paediatric population is unknown.

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