DEPAKOTE IV
Valproic Acid
Solution for Infusion
500mg/ 5 mL

WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity

General Population: **Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months *[see Warnings and Precautions (5.1)]*.**

Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When Depakote is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Patients with Mitochondrial Disease: **There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g. Alpers Huttenlocher Syndrome). Depakote is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder *[see Contraindications (4)]*. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakote should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakote for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice *[see Warnings and Precautions (5.1)]*.**

Fetal Risk

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

Valproate should only be used to treat pregnant women with epilepsy if other medications have failed to control their symptoms or are otherwise unacceptable.

Valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using valproate *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

A Medication Guide describing the risks of valproate is available for patients [*see Patient Counseling Information (17)*].

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated *[see Warnings and Precautions (5.5)]*.

1. NAME OF THE MEDICINAL PRODUCT
Depakote IV, Valproic Acid Injection 500mg/5 mL
Trademark is authorized as Depakote

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each mL contains: Valproic Acid 100 mg. Excipients include 0.4 mg of Edetate Disodium and Water for Injection q.s. to 1 mL. The pH is adjusted to 7-9 with sodium hydroxide and/or hydrochloric acid.

Excipients with known effect in injection:
Valproic acid injection contains Sodium hydroxide E524.

For the full list of excipients, see section list of excipients.

3. PHARMACEUTICAL FORM

Depakote IV 500mg/5 mL, Injection:
Clear, colorless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epilepsy
Valproic acid injection is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

Valproic acid injection is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible. See section **Special Warnings and Precautions for Use** for statement regarding fatal hepatic dysfunction.

4.2 Posology and Method of Administration

General
Valproic acid injection is for intravenous use only.

Valproic acid injection is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of ten years, and in simple and complex absence seizures.

Use of Valproic acid injection for periods of more than 14 days has not been studied. Patients should be switched to oral valproate products as soon as it is clinically feasible.

Valproic acid injection should be administered as a 60-minute infusion (but not more than 20 mg/min) with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Administration Guidelines
Rapid infusion of Valproic acid injection has been associated with an increase in adverse events. Infusion times of less than 60 minutes or rates of infusion > 20 mg/min have not been studied in patients with epilepsy (*see section* **Undesirable Effects**).

Valproic acid injection should be administered intravenously as a 60-minute infusion, as noted above. It should be diluted with at least 50 mL of a compatible diluent. Any unused portion of the vial contents should be discarded.

Initial Exposure to Valproate
The following dosage recommendations were obtained from studies utilizing oral divalproex sodium products.

Complex Partial Seizures (CPS)
For adults and children ten years of age or older.

Monotherapy (Initial Therapy)
Valproic acid has not been systematically studied as initial therapy. 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. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions (*see section* **Special Warnings and Precautions for Use**–*Thrombocytopenia*).

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. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every two weeks. This reduction may be started at initiation of divalproex sodium therapy, or delayed by one to two weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy
Valproic acid may be added to the patient's 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 satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium, no adjustment of carbamazepine or phenytoin dosage was needed (*see section* –**Pharmacodynamics Properties-***Clinical Studies*). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (*see section* **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Simple and Complex Absence Seizures
The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures will range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations (*see section* **Pharmacological Properties**).

As the Valproic acid dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (*see section* **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Replacement Therapy
When switching from oral valproate products, the total daily dose of Valproic acid injection should be equivalent to the total daily dose of the oral valproate product (*see section* **Pharmacological Properties**), and should be administered as a 60 minute infusion (but not more than 20 mg/min) with the same frequency as the oral products, although plasma concentration monitoring and dosage adjustments may be necessary. Patients receiving doses near the maximum recommended daily dose of 60 mg/kg/day, particularly those not receiving enzyme-inducing drugs, should be monitored more closely. If the total daily dose exceeds 250 mg, it should be given in a divided regimen. However, the equivalence shown between Valproic acid injection and oral valproate products (divalproex sodium) at steady state was only evaluated in any every six-hour regimen. Whether, when Valproic acid injection is given less frequently (i.e., twice or three times a day), trough levels fall below those that result from an oral dosage form given via the same regimen, is unknown. For this reason, when Valproic acid injection is given twice or three times a day, close monitoring of trough plasma levels may be needed.

General Dosing Advice
Geriatric
Due to a decrease in clearance of unbound valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (*see section* **Special Warnings and Precautions for Use**- *Somnolence in the Elderly and section* **Pharmacological Properties-** *Geriatric*).

Dose-Related Adverse Events
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males) (*see section* **Special Warnings and Precautions for Use**- *Thrombocytopenia*). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Compatibility and Stability
Valproic acid injection was found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or flexible plastic container at room temperature below 30°C.
- Dextrose (5%) Injection

- Sodium Chloride (0.9%) Injection
- Lactated Ringer's Injection

4.3 Contraindications

Valproic acid should not be administered to patients with hepatic disease or significant hepatic dysfunction (*see section* **Special Warnings and Precautions for Use**- *Hepatotoxicity*).

Valproic acid is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g. Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder (*see section* **Special Warnings and Precautions for Use**- *Hepatotoxicity*).

Valproic acid is contraindicated in Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia *(see section* **Special Warnings and Precautions for Use***: Patients at risk of hypocarnitinemia).*

Valproic acid is contraindicated in patients with known hypersensitivity to the drug (*see section* **Special Warnings and Precautions for Use** - *Multi-Organ Hypersensitivity Reactions*).

Valproic acid is contraindicated in patients with known urea cycle disorders (*see section* **Special Warnings and Precautions for Use** - *Hyperammonemia***,** *Urea Cycle Disorders*).

Valproic acid is contraindicated in the following situation:
Treatment of epilepsy
- in pregnancy unless there is no suitable alternative treatment (*see section* **Special Warnings and Precautions for Use** *and* **Fertility, Pregnancy and Lactation**).
- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned in section **Special Warnings and Precautions for Use** and **Fertility, Pregnancy and Lactation** are met.

Valproic acid is contraindicated in patients with porphyria.

4.4 Special Warnings and Precautions for Use
Hepatotoxicity/ Hepatic dysfunction
Conditions of occurrence: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment.
Caution should be applied when administering valproic acid products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, those with congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations *(see section* **Special Warnings and Precautions for Use***),* those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of three years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy (seizure control) should be

weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Suggestive signs: Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms.

Detection: Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months of therapy, especially in patients at risk (refer to section **Interaction with other Medicinal Products and Other Forms of Interaction**). However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug *(see section* **Contraindications***)*.

Patients with known or suspected mitochondrial disease
Valproate induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes (*see section* **Contraindications**).

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 unexplained 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.
In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, divalproex sodium should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with valproic acid for the development of acute liver injury with regular clinical assessments and liver function test monitoring.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproic acid. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. Patients and guardians experiencing abdominal pain, nausea, vomiting, and/or anorexia should be warned that these could be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Suicidal Behavior and Ideation
An increase in the risk of suicidal thoughts or behavior in patients taking antiepileptic drugs (AEDs) for any indication has been reported. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing valproic acid or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and an increase risk of suicidal thoughts and behavior. Should suicidal thoughts and behaviors emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients (and caregivers of patients) should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thought about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Interaction with Carbapenem Antibiotics
The concomitant use of INN and carbapenem agents is not recommended *(see section* **Interaction with Other Medicinal Products and other Forms of Interactions** - *Carbapenem Antibiotics)*.

Thrombocytopenia - (*see section* Special Warnings and Precautions for Use - *General)*

Female children/Female adolescents/Women of childbearing potential/Pregnancy:
Valproic Acid has a high teratogenic potential and children exposed *in utero* to Valproic Acid have a high risk for congenital malformations and neurodevelopmental disorders (see section **Fertility, Pregnancy and Lactation**).

Valproic Acid is contraindicated in the following situations:
Treatment of epilepsy
- in pregnancy unless there is no suitable alternative treatment *(see section* **Special Warnings and Precautions for Use** *and* **Fertility, Pregnancy and Lactation***)*.
- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned below and in sections **Contraindications** and **Fertility, Pregnancy and Lactation** are met.

The treating physician must ensure that
- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise 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 Valproic Acid in utero.
- the patient understands and acknowledges the risk of lower weight at birth for the gestational age for children exposed to Valproic Acid in utero. (See section 4.6 Pregnancy).
- 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 (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with Valproic Acid.
- the patient understands the need for regular (at least annual) review of treatment by the treating physician, preferably by a specialist experienced in the management of epilepsy.
- 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 hazards and necessary precautions associated with Valproic Acid use and the need to urgently consult her physician in case of pregnancy.
- The patient has received the patient guide.

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

Female children

- The treating physician must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using Valproic Acid experiences menarche.

The treating physician 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 Valproic Acid *in utero*.

The prescriber must also inform them about the risk of lower weight at birth for the gestational age for children exposed to Valproic Acid in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for Valproic Acid therapy annually and consider alternative treatment options. If Valproic Acid is the only suitable treatment, the need for using effective contraception and all other measures as described in section **Contraindications**, **Special Warnings and Precautions for Use** and **Fertility, Pregnancy and Lactation** should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach child bearing potential.

Pregnancy must be excluded before start of treatment with Valproic Acid.

Contraception

Women of childbearing potential who are prescribed Valproic Acid must use effective contraception, without interruption during the entire duration of treatment with Valproic Acid. 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 preferably by a specialist

The treating physician should at least annually review whether Valproic acid is the most suitable treatment for the patient.

The treating physician should ensure the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to Valproic Acid *in utero*.

Pregnancy planning

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess Valproic acid 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 **Fertility, Pregnancy and Lactation**). If switching is not possible, the woman should receive further counselling regarding the Valproic Acid risks for the unborn child to support her informed decision making regarding family planning.

In case of pregnancy

In case of pregnancy, the patient should immediately contact a specialist/physician to re-evaluate treatment and consider alternative options.

Pharmacist must ensure that

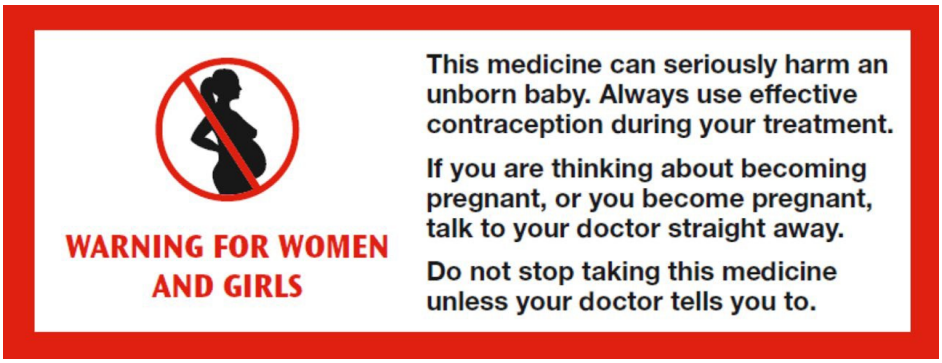
- the patients are advised not to stop Valproic Acid medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Education materials

In order to assist healthcare professionals and patients in avoiding exposure to Valproic Acid during pregnancy, the Marketing Authorization Holder has provided educational materials like a physician guide to reinforce the warnings and provide guidance regarding use of Valproic Acid in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide should be provided to all women of childbearing potential using Valproic Acid.

Visual Reminder on outer packaging

In order to inform and remind patients about avoiding exposure to Valproic Acid, during pregnancy, the Marketing Authorization Holder has added a pictogram and warning to its outer packaging.



Use in males of reproductive potential

A retrospective observational study suggests an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared with the risk in those born to men treated with lamotrigine or levetiracetam (see section Pregnancy).

Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk and consider whether valproate remains the most appropriate treatment.

The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment.

The study did not evaluate the risk of neurodevelopmental disorders in children born to fathers who stopped using valproate more than 3 months before conception.

The male patient should be advised:

- not to donate sperm during treatment and for 3 months after stopping the treatment,
- of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,
- that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception.

The treatment in male patient should be initiated and supervised by a specialist in the management of epilepsy.

There is the need for regular reviews by physician to assess if valproate remains the most appropriate treatment for the patient and discuss suitable treatment alternatives with the patient. This is particularly important if the male patient is planning to conceive a child and, in this case, before discontinuing contraception.

The Marketing Authorization Holder provides educational materials to healthcare professionals. A patient guide should be provided to all men of reproductive potential using valproate.

Hyperammonemia
Hyperammonemia has been reported in association with valproic acid therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level measured. Hyperammonemia should also be considered in patients who present with hypothermia (*see section* **Special Warnings and Precautions for Use**–*Hypothermia*). If ammonia is increased, valproic acid therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (*see section* **Contraindications** *and* **Special Warnings and Precautions for Use**).

Asymptomatic elevations of ammonia are more common and, when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproic acid therapy should be considered.

Urea Cycle Disorders (UCD) hyperammonemia: Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (*see section* **Contraindications** *and* **Special Warnings and Precautions for Use** - *Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use, Patients at risk of hypocarnitinemia and Hepatotoxicity/ Hepatic dysfunction).*

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. Carnitine supplementation should be considered in these patients. (see also sections **Interaction with Other Medicinal Products and Other Forms of Interaction**, **Undesirable Effects** and **Overdose**).

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use
Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia (*see section* **Special Warnings and Precautions for Use** – *Hypothermia*). In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

It is not known if topiramate monotherapy is associated with hyperammonemia.

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons (*see section* **Contraindications** *and* **Special Warnings and Precautions for Use**).

Hypothermia
Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with valproic acid therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproate after starting topiramate treatment or after increasing the daily dose of topiramate (*see section* **Interaction with Other Medicinal Products and Other Forms of Interaction** - *Topiramate and* **Special Warnings and Precautions for Use** - *Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use* and *Hyperammonemia*). Consideration should be given to stopping valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

Brain Atrophy
There have been post marketing reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use valproate products; in some cases, patients recovered with permanent sequelae (*see section* **Undesirable Effects**). The motor and cognitive functions

of patients on valproate should be routinely monitored and drug should be discontinued in the presence of suspected or apparent signs of brain atrophy. Reports of cerebral atrophy with various forms of neurological problems including developmental delays and psychomotor impairment have also been reported in children who were exposed in-utero to valproate products (*see section* **Fertility, Pregnancy and Lactation**).

General

Laboratory tests:

Because of reports of thrombocytopenia (*see* **Special Warnings and Precautions for Use**-*Thrombocytopenia*), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters (e.g., low fibrinogen), platelet counts, and coagulation tests are recommended before initiating therapy and at periodic intervals. Prior to planned surgery it is recommended that patients receiving valproic acid be monitored for platelet count and coagulation parameters. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since divalproex sodium/valproate sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy (*see section* **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Valproic acid is partially eliminated in the urine as a keto-metabolite that may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Recommendations:

Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since divalproex sodium/valproate sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy (*see section* **Interaction with Other Medicinal Products and Other Forms of Interaction**).

There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The therapeutic benefit that may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

It seems prudent not to use valproate sodium in patients with acute head trauma for the prophylaxis of post-traumatic seizures until further information is available.

Severe Cutaneous Adverse Reactions and Angioedema
Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

Information for Female patients

Since valproic acid has been associated with certain types of birth defects and developmental risk, female patients of childbearing age considering the use of valproic acid should be advised of the risks associated with the use of valproic acid during pregnancy (*see section* **Special Warnings and Precautions for Use**).

Pediatric Use
When valproic acid injection is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, valproic acid should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with valproic acid for the development of acute liver injury with regular clinical assessments and liver function test monitoring.
The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m2 basis.

The safety of valproic acid injection has not been studied in individuals below the age of two years.

Geriatric Use
Somnolence in the elderly: A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence. The starting dose should be reduced in these

patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (*see section* **Posology and Method of Administration**). In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (*see section* **Posology and Method of Administration**).

No unique safety concerns were identified in the 19 patients > 65 years of age receiving valproic acid in clinical trials.

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.

Estrogen-containing products
Valproate does not reduce efficacy of hormonal contraceptives (see section 4.5).

Information related to excipients
This medicinal product contains 3.5 mmol (141 mg) sodium hydroxide per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Effects of Co-Administered Drugs on Valproate Clearance
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases (such as ritonavir), may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.
In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.
Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme-inducing drugs are introduced or withdrawn.
The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs For Which a Potentially Important Interaction Has Been Observed

Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and in

inhibition if metabolism of valproate. Valproate free fraction was increased four-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Carbapenem Antibiotics - A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics (ertapenem, imipenem, meropenem) and may result in loss of seizure control. The mechanism of this interaction is not well understood. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates.

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

Estrogen-Containing Hormonal Contraceptives: Estrogen-containing hormonal contraceptives may increase the clearance of valproate, which may result in decreased concentration of valproate and potentially increased seizure frequency. Prescribers should monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products, preferably during on-off intervals of the hormonal contraceptive cycle.

Felbamate - A study involving the co-administration of 1,200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentrations by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2,400 mg/day increased the mean valproate peak concentrations to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

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

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

Rifampin - A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after five nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral

clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Drugs For Which Either No Interaction or a Likely Clinically Unimportant Interaction Has Been Observed

Antacids - A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine - A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg b.i.d.) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol - A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg b.i.d.) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine - Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyltransferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamincs of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs For Which a Potentially Important Valproate Interaction Has Been Observed

Amitriptyline/Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (ten males and five females) who received valproate (500 mg b.i.d.) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortripytline in the presence of valproate.

Carbamazepine/carbamazepine-10,11-Epoxide - Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11- epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam - The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam - Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1,500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide - Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1,600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine - In a steady-state study involving ten healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital - Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg b.i.d. for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Phenytoin - Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg t.i.d.) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate.
In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.
Valproic acid metabolites 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.

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 Section **Special Warnings and Precautions for Use** 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.

Primidone - Primidone is metabolized into a barbiturate and therefore, may also be involved in a similar interaction with valproate as phenobarbital.

Propofol- A clinically significant interaction between valproate and propofol may occur leading to an increased blood level of propofol. Therefore, when co-administered with valproate, the dose of propofol should be reduced.

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

Tolbutamide - From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Cannabidiol - 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.
Drug Interaction between valproate and cannabidiol may result in an increased risk of elevation of liver transaminases (see section **Special Warnings and Precautions for Use**).
Appropriate liver monitoring should be exercised when valproate is used with cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters.

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.

Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. Blood ammonia levels should be measured in patients with reported onset of hypothermia (*see section* **Special Warnings and Precautions for Use**).

Warfarin - In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if divalproex sodium therapy is instituted in patients taking anticoagulants.

Zidovudine - In six patients, who were seropositive for HIV, the clearance of zidovudine (100 mg every eight hours) was decreased by 38% after administration of valproate (250 or 500 mg every eight hours); the half-life of zidovudine was unaffected.

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

Drugs For Which Either No Interaction or a Likely Clinically Unimportant Interaction Has Been Observed

Acetaminophen - Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine - In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium - Co-administration of valproate (500 mg b.i.d.) and lithium carbonate (300 mg t.i.d.) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam - Concomitant administration of valproate (500 mg b.i.d.) and lorazepam (1 mg b.i.d.) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

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.

4.6 Fertility, Pregnancy and Lactation

Treatment of epilepsy

- Valproic Acid is contraindicated during pregnancy, unless there is no suitable alternative treatment.
- Valproic Acid is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions).

Teratogenicity and Developmental Effects from female and male exposure.

Pregnancy Exposure Risk related to valproate

Valproate was shown to cross the placental barrier both in animal species and in humans (see section **Pharmacokinetic Properties**).

Pregnancy Exposure Risk related to **valproic acid**

In females, both Valproic Acid monotherapy and valproic acid polytherapy are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both Valproic Acid monotherapy and polytherapy (concomitantly with other antiepileptic drugs) compared to the population not exposed to Valproic Acid.

Risk to children of fathers treated with Valproic Acid
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 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% 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 1.50 (95% CI: 1.09, 2.07). 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.

The study data on male patients had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times.

The data showed that around 5 out of 100 children had a neurodevelopmental disorder when born to fathers treated with valproate compared with around 3 out of 100 when born to fathers treated with lamotrigine or levetiracetam. The study did not investigate the risk in children born to men who stopped using valproate more than 3 months before conception.
The possible risk in children born to men treated with valproate in the 3 months before conception is lower than the previously confirmed risk in children born to women treated with valproate during pregnancy.
Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential regularly (see section Warnings and 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 valproic acid monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (about 2-3%). The risk of major congenital malformations in children after *in utero* exposure to antiepileptic polytherapy including Valproic Acid is higher than that of antiepileptic drugs polytherapy not including Valproic Acid. This risk is dose-dependent in Valproic Acid monotherapy, and available data suggest it is dose-dependent in Valproic Acid polytherapy. However, a threshold dose below which no risk exists cannot be established based on available data.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and 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 Valproic Acid may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

In utero exposure to Valproic Acid 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. Monitoring of signs and symptoms of ototoxicity is recommended.

Neurodevelopmental disorders from in utero exposure
Data have shown that exposure to valproic acid 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 Valproic Acid is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When Valproic Acid 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 Valproic Acid is administered in monotherapy, studies in preschool children exposed in utero to valproic acid 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, possibly indicating neurodevelopmental disorders.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of Valproic Acid 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 valproic acid that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data show that children exposed to Valproic Acid in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.
Available data suggest that children exposed to Valproic Acid in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the general population.

Lower weight at birth for the gestational age from *in utero* exposure
In utero exposure to valproate can lead to a lower weight at birth for the gestational age.
In preclinical studies a dose-related fetal weight decrease was demonstrated in animals exposed to valproate *in utero* compared to unexposed animals (see section 5.3 Preclinical safety data).

Epidemiological studies have reported a decrease in mean birth weight, and higher risk of being born with a low birth weight (<2500 grams) or small for gestational age (defined as birth weight below the 10th percentile corrected for their gestational age, stratified by gender) for children exposed to valproate *in utero* in comparison to unexposed or lamotrigine-exposed children. Available data in human do not allow to conclude on a potential dose-related effect.

Female children, female adolescents and woman of childbearing potential (see above and section **Special Warnings and Precautions for Use***)*
If a Woman wants to plan a Pregnancy

- *For epilepsy indication*: During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
- *For epilepsy indication*: In women planning to become pregnant or who are pregnant, Valproic Acid therapy should be reassessed
- *For epilepsy indication:* If a woman plans a pregnancy or becomes pregnant, Valproic Acid therapy should be stopped.
- *For epilepsy indication:* In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

If a woman plans a pregnancy

For the indication epilepsy, if a woman is planning to become pregnant, a specialist (preferably) experienced in the management of epilepsy, must reassess Valproic Acid 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 **Special Warnings and Precautions for Use**). If switching is not possible, the woman should receive further counselling regarding the Valproic Acid risks for the unborn child to support her informed decision making regarding family planning.

Pregnant women

Valproic Acid as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections **Contraindications** and **Special Warnings and Precautions for Use**), as evaluated and decided by the treating physician.

If a woman using Valproic Acid becomes pregnant, she must be immediately referred to a specialist (preferably) 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 Valproic Acid in pregnancy and after careful consideration of alternative treatment preferably by the specialist, in exceptional circumstances a pregnant woman must receive Valproic Acid for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of Valproic Acid 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 (*see section* **Posology and Method of Administration**).

All patients with a Valproic Acid exposed pregnancy and their partners should consider specialized prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.

The available evidence does not suggest that folate supplementation before the pregnancy may prevent the risk of neural tube defects which may occur in all pregnancies.

<u>Risk in the neonate</u>

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken Valproic Acid during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a 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 hypoglycemia have been reported in neonates whose mothers have taken Valproic Acid during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken Valproic Acid during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken Valproic Acid during the last trimester of their pregnancy.

Breastfeeding
Valproic Acid is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (*see section* **Undesirable Effects**).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from divalproex sodium therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using Valproic Acid (*see section* **Undesirable Effects**). Valproic Acid administration may also impair fertility in men (*see section* **Undesirable Effects**).

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.

4.7 Effects on Ability to Drive and Use Machines

Since Valproic Acid may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

4.8 Undesirable Effects

The following adverse reactions possibly related to valproates are displayed by MedDRA system organ class classification. Frequency groupings are classified according to the subsequent conventions: very common (≥1/10), Common (≥1/100 to <1/10), Uncommon

(≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and Not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Congenital, familial and genetic disorders	Congenital malformations and developmental disorders *(see section* **Special Warnings and Precautions for Use** *and* **Fertility, Pregnancy and Lactation***)*	
	Unknown	Porphyria acute
Blood and lymphatic system disorders	*Common*	Thrombocytopenia
	Uncommon	Anemia, Hypochromic anemia, Leukopenia, Thrombocytopenic purpura
	Unknown	Agranulocytosis, Anemia folate deficiency, Anemia macrocytic, Aplastic anemia, Bone marrow failure, Eosinophilia, Hypofibrinogenemia, Lymphocytosis, Macrocytosis, Pancytopenia, Platelet aggregation inhibition,
Investigations	*Common*	Weight decreased, Weight increased
	Uncommon	Alanine aminotransferase increased[1], Aspartate aminotransferase increased[1], Blood creatinine increased, Blood folate decreased, Blood lactate dehydrogenase increased[1], Blood urea increased, Drug level increased, Liver function test abnormal[1], Protein bound iodine increased, White blood cell count decreased,
	Unknown	Acquired Pelger-Huet morphology, Blood bilirubin increased[1], Carnitine decreased, Thyroid function test abnormal
Nervous system disorders	*Very common*	Somnolence, Tremor
	Common	Amnesia, Ataxia, Dizziness, Dysgeusia, Headache, Nystagmus, Paresthesia, Speech disorder
	Uncommon	Aphasia, Coordination abnormal, Dysarthria, Dystonia, Encephalopathy[2], Hyperkinesia, Hyperreflexia, Hypertonia, Hypoesthesia, Hyporeflexia, Seizure[3], Stupor, Tardive dyskinesia, Visual field defect

	Unknown	Asterixis, Cerebellar atrophy[4], Cerebral atrophy[4], Cognitive disorder, Coma, Extrapyramidal disorder, Disturbance in attention, Memory impairment, Parkinsonism, Psychomotor hyperactivity, Psychomotor skills impaired, Sedation[5]
Ear and labyrinth disorders	*Common*	Tinnitus
	Uncommon	Deafness[6], Ear disorder, Hyperacusis, Vertigo
	Unknown	Ear pain
Respiratory, thoracic and mediastinal disorders	*Uncommon*	Cough, Dyspnea, Dysphonia, Epistaxis
	Unknown	Pleural effusion
Gastrointestinal disorders	*Very common*	Nausea[7]
	Common	Abdominal pain, Constipation, Diarrhea, Dyspepsia[7], Flatulence, Vomiting[7]
	Uncommon	Anal incontinence, Anorectal disorder, Breath odor, Dry mouth, Dysphagia, Eructation, Gingival bleeding, Glossitis, Hematemesis, Melena, Pancreatitis[8], Rectal tenesmus, Salivary hypersecretion
	Unknown	Gingival disorder, Gingival hypertrophy, Parotid gland enlargement
Renal and urinary disorders	*Uncommon*	Hematuria, Micturition urgency, Pollakiuria, Urinary incontinence
	Unknown	Enuresis, Fanconi syndrome[9], Renal failure, Tubulointerstitial nephritis
Skin and tissue disorders	*Common*	Alopecia[10], Ecchymosis, Pruritus, Rash
	Uncommon	Acne, Angioedema, Dermatitis exfoliative, Dry skin, Eczema, Erythema nodosum, Hyperhidrosis, Nail disorder, Petechiae, Seborrhea
	Unknown	Cutaneous vasculitis, Drug Rash with Eosinophilia and Systemic Symptoms syndrome (DRESS) *(see section* **Special Warnings and Precautions for Use***)*, Erythema multiforme, Hair disorder, Hyperpigmentation, Nail bed disorder, Photosensitivity reaction, Stevens-Johnson syndrome, Toxic epidermal necrolysis
Musculoskeletal and connective tissue	*Uncommon*	Muscle spasm, Muscle twitching, Muscular weakness

disorders	*Unknown*	Bone density decreased, Bone pain, Osteopenia, Osteoporosis, Rhabdomyolysis, Systemic lupus erythematosus
Endocrine disorders	*Unknown*	Hyperandrogenism[11], Hypothyroidism, Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	*Common*	Decreased appetite, Increased appetite
	Uncommon	Hyperkalemia, Hypernatremia, Hypoglycemia, Hyponatremia, Hypoproteinemia
	Unknown	Biotin deficiency, Dyslipidemia, Hyperammonemia, Hypocarnitinemia *(see section* **Contraindications** *and* **Special Warnings and Precautions for Use***)*, Insulin resistance, Obesity
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Uncommon*	Hemangioma of skin
	Unknown	Myelodysplastic syndrome
Vascular disorders	*Uncommon*	Orthostatic hypotension, Pallor, Peripheral vascular disorder, Vasodilatation
General disorders and administration site conditions	*Very common*	Asthenia
	Common	Gait disturbance, Edema peripheral
	Uncommon	Chest pain, Chills, Face edema, Injection site inflammation[13], Injection site pain[13], Injection site reaction[13], Pyrexia
	Unknown	Hypothermia
Hepatobiliary disorders	*Unknown*	Hepatotoxicity
Reproductive system and breast disorders	*Uncommon*	Amenorrhea, Dysmenorrhea, Erectile dysfunction, Menorrhagia, Menstrual disorder, Metrorrhagia, Vaginal hemorrhage
	Unknown	Breast enlargement, Galactorrhea, Infertility male[12], Menstruation irregular, Polycystic ovaries
Psychiatric disorders	*Common*	Abnormal dreams, Affect lability, Confusional state, Depression, Insomnia, Nervousness, Thinking abnormal
	Uncommon	Agitation, Anxiety, Apathy, Catatonia, Delirium, Euphoric mood, Hallucination, Hostility, Personality disorder
	Unknown	Abnormal behavior, Aggression, Emotional distress, Learning disorder, Psychotic

		disorder
Cardiac disorders	*Uncommon*	Bradycardia, Cardiac arrest, Cardiac failure congestive, Tachycardia
Eye disorders	*Common*	Amblyopia, Diplopia
	Uncommon	Chromatopsia, Dry eye, Eye disorder, Eye pain, Lacrimation disorder, Miosis, Photophobia, Visual impairment
Immune system disorder	*Unknown*	Anaphylactic reaction, Hypersensitivity
Infection and infestations	*Common*	Infection
	Uncommon	Bronchitis, Furuncle, Gastroenteritis, Herpes simplex, Influenza, Rhinitis, Sinusitis
	Unknown	Otitis media, Pneumonia, Urinary tract infection
Injury, poisoning and procedural complications	*Common*	Injury

1 may reflect potentially serious hepatotoxicity *(see section* **Special Warnings and Precautions for Use***)*

2 encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders-*(see section* **Special Warnings and Precautions for Use***)*. Encephalopathy in the absence of elevated ammonia levels was also observed.

3 here, consider aggravated seizure and reference to section **Special Warnings and Precautions for Use**

4 reversible and irreversible. Cerebral atrophy seen in children exposed to valproate in utero led to various forms of neurological events, including developmental delays and psychomotor impairment *(see section* **Special Warnings and Precautions for Use***)*

5 noted in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication

6 either reversible or irreversible

7 these effects are usually transient and rarely require discontinuation of therapy

8 includes acute pancreatitis including fatalities

9 occurring primarily in children

10 reversible

11 with events of hirsutism, virilism, acnea, male pattern alopecia, androgen increased

12 including azoospermia, abnormal semen analysis, decreased sperm count, spermatozoa morphology abnormal, aspermia, and decrease spermatozoa motility (see section **Fertility, Pregnancy and Lactation**)

13 ADRs specific to sodium valproate injection

14 Isolated cases of acquired Pelger-Huet anomaly. Recognizing it is crucial for discontinuing valproates as discontinuation is the only treatment if drug induced and further avoiding

unnecessary over-diagnosing neoplastic disorders such as myelodysplastic syndrome. This morphology anomaly may be associated with other cytopenias as well

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 three years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section **Pharmacological Properties**).

Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR
or via pv.indonesia@abbott.com

4.9 Overdose
Overdosage with valproate may result in somnolence, heart block, hypotension and circulatory collapse/shock, and deep coma. Fatalities have been reported; however, patients have recovered from valproate levels as high as 2,120 mcg/mL.

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

In case of valproate overdose resulting in hyperammonemia, carnitine can be given through IV route to attempt to normalize ammonia levels.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Anticonvulsant and mood-stabilizing drug
ATC-Code: N03AG01

Valproic acid is a carboxylic acid. Other chemical names for this compound are 2-propylpentanoic acid, 2 propylvaleric acid and n-dipropylacetic acid. Valproic acid (pKa 4.8) is a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/mL) and very soluble in organic solvents. Its empirical formula is C8H1602 and has a molecular weight of 144.

Mechanism of action and Pharmacodynamic properties

Valproic acid dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Description of clinical studies

Epilepsy

Complex Partial Seizures (CPS)

The studies described in the following section were conducted using divalproex sodium tablets.
The efficacy of divalproex sodium in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials.
In one, multiclinic, placebo controlled study employing an add-on design (adjunctive therapy), 144 patients who continued to suffer eight or more CPS per eight weeks during an 8-week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range," were randomized to receive, in addition to their original antiepilepsy drug (AED), either divalproex sodium or placebo. Randomized patients were to be followed for a total of 16 weeks. Table 1 presents the findings.

Table 1
Adjunctive Therapy Study
Median Incidence of CPS per 8 Weeks

Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
Divalproex Sodium	75	16.0	8.9*
Placebo	69	14.5	11.5

* Reduction from baseline statistically significantly greater for divalproex sodium than placebo at $p \leq 0.05$ level.

Figure 1 presents the proportion of patients (X-axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y-axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement

was consistently higher for divalproex sodium than for placebo. For example, 45% of patients treated with divalproex sodium had a ≥ 50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

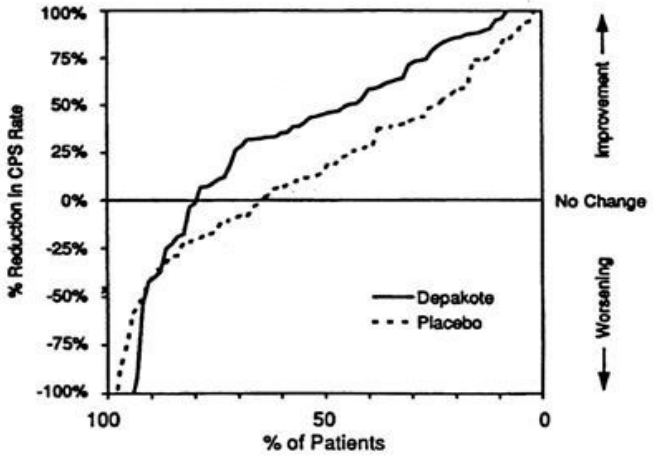


Fig 1

The second study assessed the capacity of divalproex sodium to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if: 1) they continued to experience two or more CPS per four weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone); and 2) they made a successful transition over a two week interval to divalproex sodium. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to divalproex sodium monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 mcg/mL in the low dose and high dose groups, respectively.

Table 2 presents the findings for all patients randomized who had at least one post-randomization assessment.

Table 2
Monotherapy Study
Median Incidence of CPS per 8 Weeks

Treatment	**Number of Patients**	**Baseline Incidence**	**Randomized Phase Incidence**
High Dose Divalproex Sodium	131	13.2	10.7*
Low Dose Divalproex Sodium	134	14.2	13.8

* Reduction from baseline statistically significantly greater for high dose than low dose at p ≤ 0.05 level.

Figure 2 presents the proportion of patients (X-axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y-axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose divalproex sodium than for low dose divalproex sodium. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose divalproex sodium monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose divalproex sodium.

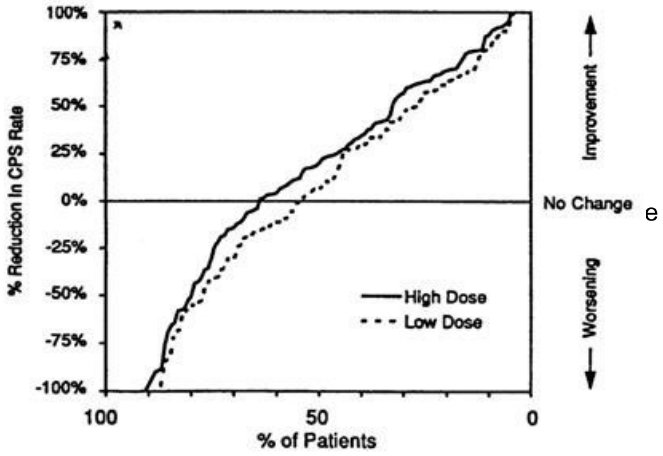


Fig 2

In a clinical trial of divalproex sodium as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 x 10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males).

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age was 83 years old), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN.

A study was conducted to evaluate the effect of IV valproate in the prevention of post-traumatic seizures in patients with acute head injuries. Patients were randomly assigned to receive either IV valproate given for one week (followed by oral valproate products for either one or six months per random treatment assignment) or IV phenytoin given for one week (followed by placebo). In this study, the incidence of death was found to be higher in the two groups assigned

to valproate treatment compared to the rate in those assigned to the IV phenytoin treatment group (13% versus 8.5%, respectively). Many of these patients were critically ill with multiple and/or severe injuries, and evaluation of the causes of death did not suggest any specific drug-related causation. Further, in the absence of a concurrent placebo control during the initial week of intravenous therapy, it is impossible to determine if the mortality rate in the patients treated with valproate was greater or less than that expected in a similar group not treated with valproate, or whether the rate seen in the IV phenytoin treated patients was lower than would be expected.

5.2 Pharmacokinetic Properties

Absorption/ Bioavailability

Equivalent doses of intravenous (IV) valproate and oral valproate products are expected to result in equivalent C_{max}, C_{umin}, and total systemic exposure to the valproate ion. However, the rate of valproate ion absorption may vary with the formulation used. These differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

Administration of divalproex sodium (Depakote) tablets and IV valproate (given as a one hour infusion), 250 mg every six hours for four days to 18 healthy male volunteers resulted in equivalent AUC, C_{max}, C_{umin} at steady state, as well as after the first dose. The T_{max} after IV valproate sodium occurs at the end of the one hour infusion, while the T_{max} after oral dosing with divalproate sodium occurs at approximately four hours. Because the kinetics of unbound valproate are linear, bioequivalence between valproate sodium and divalproex sodium up to the maximum recommended dose of 60 mg/kg/day can be assumed. The AUC and C_{max} resulting from administration of IV valproate 500 mg as a single one hour infusion and a single 500 mg dose of valproic acid syrup to 17 healthy male volunteers were also equivalent.
Patients maintained on valproic acid doses of 750 mg to 4,250 mg daily (given in divided doses every six hours) as oral divalproex sodium alone (n=24) or with another stabilized antiepileptic drug [carbamazepine (n=15), phenytoin (n=11), or phenobarbital (n=1)], showed comparable plasma levels for valproic acid when switching from oral divalproex sodium to IV valproate (1-hour infusion).

Distribution

Protein Binding

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide) (*see section* **Interaction with Other Medicinal Products and Other Forms of Interaction** *for more detailed information on the pharmacokinetic interactions of valproate with other drugs*).

CNS Distribution

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Placental transfer (see section **Fertility, Pregnancy and Lactation**)
Valproate crosses the placental barrier in animal species and in humans:
- In animal species, valproate crosses the placenta, to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism
Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30 to 50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β−oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15 to 20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Excretion
Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1,000 mg.
The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations
Geriatric
The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction of valproate is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly (see section **Posology and Method of Administration**).

Pediatric
Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults.
Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. Based on published literature, in pediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In children aged 2-10 years, valproate clearance is 50% higher than in adults.

Gender
There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m^2, respectively).

Ethnicity
The effects of ethnicity on the kinetics of valproate have not been studied.

Hepatic impairment
See section **Contraindications** and section **Special Warnings and Precautions for Use-** *Hepatotoxicity*.
Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in seven patients with cirrhosis and by 16% in four patients with acute hepatitis, compared to six healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal impairment
A slight reduction (27%) in the clearance of unbound valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading. For further guidance please refer to section **Posology and Method of Administration**.

Plasma Levels and Clinical Effect
The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate that affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy
The therapeutic range in epilepsy is commonly considered to be 50 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations. Equivalent doses of valproate sodium and divalproex sodium yield equivalent plasma levels of the valproate ion.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis, Reproductive and Developmental Toxicity and Impairment of Fertility

Carcinogenesis

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 historical control data.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. 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. It did not induce either chromosome aberrations in rat bone marrow or dominant lethal effects in mice after oral administration.

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.

Reproductive and Developmental Toxicity

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits.

In mice, rats, and rabbits, in utero exposure to valproate induced a dose-related decrease in fetal weight, intra-uterine growth restriction and reduction in crown rump length compared to unexposed animals.

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 pediatric population is unknown.

However, male infertility has been identified as an undesirable effect in humans (see sections **Fertility, Pregnancy and Lactation** and **Undesirable Effects**).

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Edetate disodium
Sodium hydroxide (E524)
Hydrochloric acid (E507)
Charcoal, activated
Water for injection

6.2 Incompatibilities
Not Applicable

6.3 Shelf Life
The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage
Store below 30°C.

6.5 Nature and Contents of Container
Box of 10 units single dose glass vial @ 5mL. Reg. No.: DKIxxx

6.6 Special Precautions for Disposal and Other Handling
Store below 30°C.

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
Olic (Thailand) Limited
166 Bangpa-in Industrial Estate
Udomsorayuth Road, Moo 16, Bangkrason
Bangpa-in, Ayutthaya, 13160, Thailand

Registered by:
PT Abbott Indonesia
Jl. Raya Bogor, Km. 37, Depok, Indonesia

Refer to RDCCDS000637/27
L003/02/24
Last revision : 08 July 2026

BROSUR INFORMASI UNTUK PASIEN
Depakote IV
Valproic Acid
Solution for Infusion
500mg/ 5 mL

Baca seluruh isi brosur ini secara seksama sebelum Anda mulai menggunakan obat ini dan setiap kali Anda membeli lagi karena brosur ini berisi informasi penting bagi Anda dan mungkin ada informasi baru.
- Simpan brosur ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Hal ini dapat membahayakan mereka, bahkan jika gejalanya sama dengan Anda.
- Jika Anda mengalami efek samping, sampaikan kepada dokter atau apoteker Anda. Termasuk kemungkinan efek samping yang tidak tercantum di dalam brosur ini. Lihat bagian 4.

Apa yang ada di dalam brosur ini:

1. Apa yang dimaksud dengan Depakote IV dan apa kegunaannya?
2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Depakote IV
3. Bagaimana cara pemberian Depakote IV
4. Kemungkinan efek samping
5. Bagaimana cara menyimpan Depakote IV
6. Isi kemasan dan informasi lainnya

1. Apa yang dimaksud dengan Depakote IV dan apa kegunaannya

Injeksi Asam Valproat digunakan sebagai pengobatan terapi tunggal maupun tambahan untuk menangani kejang tipe absans sederhana dan kompleks, serta sebagai terapi tambahan pada pasien yang memiliki beberapa jenis kejang termasuk kejang absans.

- Kejang absence sederhana adalah kondisi ketika seseorang tiba-tiba tampak “melamun” atau kehilangan kesadaran selama beberapa detik tanpa gejala lain yang terlihat.
- Kejang absence kompleks adalah kondisi yang mirip, tetapi disertai gejala lain, misalnya gerakan otomatis atau perubahan perilaku singkat.

Injeksi Asam Valproat diberikan sebagai alternatif intravena pada pasien yang sementara waktu tidak bisa minum produk valproat secara oral.

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Depakote IV

Jangan menggunakan Injeksi Asam Valproat dan beri tahu dokter atau perawat Anda jika:
- Anda alergi (hipersensitif) terhadap asam valproat atau salah satu bahan lain dari Injeksi Asam Valproat (tercantum di bagian 6) Tanda-tanda reaksi alergi meliputi: ruam, masalah menelan atau bernapas, pembengkakan pada bibir, wajah, tenggorokan, atau lidah
- Anda diketahui mempunyai kelainan metabolik, misalnya kelainan siklus urea
- Anda mempunyai penyakit liver atau Anda atau keluarga Anda mempunyai riwayat penyakit liver, terutama jika disebabkan oleh obat-obatan
- Anda menderita penyakit langka yang disebut porfiria yang mempengaruhi metabolisme Anda

- Anda memiliki masalah genetik yang disebabkan oleh kelainan mitokondria (misalnya sindrom Alpers-Huttenlocher)
- memiliki resiko hipokarnitinemia
- Anda sedang hamil, kecuali jika tidak ada cara lain yang berhasil untuk Anda (lihat "Kehamilan, menyusui, dan kesuburan" di bawah).

Jangan menggunakan obat ini jika salah satu gejala di atas berlaku pada Anda. Jika Anda tidak yakin, bicarakan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan Injeksi Asam Valproat.

Kehamilan, menyusui dan kesuburan

Kehamilan

- Anda tidak boleh menggunakan Injeksi Asam Valproat jika Anda sedang hamil, kecuali jika dokter spesialis Anda telah menentukan bahwa tidak ada pengobatan alternatif yang berhasil untuk Anda.
- Jika Anda seorang wanita yang dapat memiliki bayi, Anda tidak boleh menggunakan Injeksi Asam Valproat kecuali Anda menggunakan metode kontrasepsi yang efektif setiap saat selama seluruh perawatan Anda dengan Injeksi Asam Valproat.
- Jangan berhenti pengobatan Valproat atau alat kontrasepsi Anda, sampai Anda membicarakan hal ini dengan dokter spesialis Anda. Spesialis Anda akan memberi saran lebih lanjut.

Risiko valproate bila dikonsumsi selama kehamilan (terlepas dari penyakit yang menggunakan valproate):

- Segera bicarakan dengan dokter jika Anda berencana memiliki bayi atau sedang hamil
- Valproate mempunyai risiko jika dikonsumsi selama kehamilan. Semakin tinggi dosisnya, semakin tinggi risikonya namun semua dosis mempunyai risiko, termasuk bila valproate digunakan dalam kombinasi dengan obat lain untuk mengobati epilepsi.
- Hal ini dapat menyebabkan cacat lahir yang serius dan dapat mempengaruhi perkembangan fisik dan mental anak seiring pertumbuhannya setelah lahir. Jika Anda menggunakan valproate selama kehamilan, Anda memiliki risiko lebih tinggi dibandingkan wanita lain untuk memiliki anak dengan cacat lahir yang memerlukan perawatan medis. Karena valproate telah digunakan selama bertahun-tahun, kita tahu bahwa pada wanita yang menggunakan valproate, sekitar 11 dari setiap 100 bayi akan mengalami cacat lahir. Bandingkan dengan 2-3 bayi dari setiap 100 bayi yang dilahirkan oleh perempuan pada populasi umum.
    - Cacat lahir yang paling sering dilaporkan adalah spina bifida (tulang belakang tidak berkembang dengan baik); malformasi wajah dan tengkorak; kelainan jantung, ginjal, saluran kemih dan organ seksual; cacat anggota badan dan berbagai malformasi terkait yang mempengaruhi beberapa organ dan bagian tubuh. Cacat lahir dapat mengakibatkan kecacatan yang mungkin parah
    - Masalah pendengaran atau ketulian telah dilaporkan terjadi pada anak-anak yang terpapar valproate selama kehamilan
    - Malformasi mata telah dilaporkan pada anak-anak yang terpapar valproate selama kehamilan sehubungan dengan malformasi kongenital lainnya. Malformasi mata ini dapat mempengaruhi penglihatan
- Diperkirakan 30-40% anak yang ibunya menggunakan valproate selama kehamilan mungkin mengalami masalah perkembangan anak usia dini. Anak-anak yang terkena

dampaknya mungkin lambat berjalan dan berbicara, kurang mampu secara intelektual dibandingkan anak-anak lain, dan mengalami kesulitan dalam bahasa dan ingatan.

- Autisme dan gangguan terkait lebih sering didiagnosis pada anak-anak yang terpapar valproate selama kehamilan dan terdapat beberapa bukti bahwa anak-anak yang terpapar valproate selama kehamilan berisiko lebih tinggi terkena *Attention Deficit Hyperactivity Disorder* (ADHD).
- Sebelum meresepkan obat ini kepada Anda, dokter spesialis Anda akan menjelaskan apa yang mungkin terjadi pada bayi Anda jika Anda hamil saat menggunakan valproate. Jika Anda kemudian memutuskan ingin memiliki bayi, Anda tidak boleh berhenti minum obat atau metode kontrasepsi (kontrasepsi) sampai Anda membicarakan hal ini dengan dokter spesialis Anda.
- Jika Anda adalah orang tua atau pengasuh dari anak perempuan yang diobati dengan valproate, Anda harus menghubungi dokternya setelah anak Anda yang menggunakan valproate mengalami menstruasi pertama (menarche)
- Beberapa pil KB (pil KB yang mengandung estrogen) dapat menurunkan kadar valproat dalam darah Anda. Pastikan Anda berkonsultasi dengan dokter mengenai metode kontrasepsi (kontrasepsi) yang paling tepat untuk Anda
- Tanyakan kepada dokter atau perawat mengenai konsumsi asam folat saat berencana memiliki bayi. Asam folat dapat menurunkan risiko umum spina bifida dan keguguran dini yang terjadi pada semua kehamilan. Namun, hal ini kecil kemungkinannya akan mengurangi risiko cacat lahir yang terkait dengan penggunaan valproate.

Menyusui

Sangat sedikit valproate yang masuk ke dalam ASI. Namun, konsultasikan dengan dokter apakah Anda harus menyusui bayi Anda. Mintalah saran dari dokter atau apoteker sebelum mengonsumsi obat apapun.

Saran penting untuk pasien pria

- Dokter spesialis Anda akan menjelaskan kepada Anda tentang risiko infertilitas pria yang diketahui dan risiko potensial pada anak yang lahir dari ayah yang diobati dengan valproat.
- Kemungkinan risiko gangguan perkembangan saraf pada anak lahir dari ayah yang mengonsumsi obat Valproat. Pasien pria disarankan untuk tidak mendonorkan sperma selama pengobatan dan selama 3 bulan setelah menghentikan pengobatan, konsultasikan dengan dokter Anda untuk mendiskusikan pilihan pengobatan segera setelah berencana untuk memiliki anak, dan sebelum menghentikan kontrasepsi. Jika terjadi kehamilan saat pasien menggunakan Valproat atau Valproat sudah di hentikan dalam 3 bulan sebelum pembuahan, pasien pria dan pasangan wanitanya harus segera menghubungi dokter.

Interaksi Depakote IV dengan obat-obat lain

Beritahu dokter atau apoteker Anda jika Anda sedang meminum/menggunakan, baru-baru ini telah meminum/menggunakan atau mungkin akan meminum/menggunakan obat lainnya. Hal ini sangat penting jika Anda menggunakan salah satu dari berikut ini:

- Beberapa obat yang digunakan untuk nyeri dan peradangan (salisilat) seperti aspirin
- Beberapa obat lain yang digunakan untuk mengobati serangan (epilepsi). Ini termasuk obat-obatan seperti fenobarbital, primidon, fenitoin, karbamazepin, rufinamide, topiramate, acetazolamide, lamotrigin dan felbamate.

- Obat-obatan yang digunakan untuk menenangkan gangguan kesehatan emosional dan mental (termasuk skizofrenia, gangguan bipolar, dan depresi) seperti quetiapine, diazepam, dan olanzapine
- Antikoagulan – seperti warfarin – digunakan untuk mengencerkan darah dan mencegah penggumpalan. Dokter Anda mungkin mengubah dosis obat pengencer darah Anda dan memantau pengobatan Anda dengan cermat
- Zidovudine dan protease inhibitor seperti lopinavir dan ritonavir – digunakan untuk mengobati infeksi HIV dan AIDS
- Agen karbapenem (antibiotik yang digunakan untuk mengobati infeksi bakteri) seperti panipenem, imipenem, meropenem, rifampisin dan eritromisin. Kombinasi Injeksi Asam Valproat dan karbapenem sebaiknya dihindari karena dapat menurunkan efek obat Anda
- Cimetidine - digunakan untuk mengobati sakit maag
- Nimodipine – digunakan untuk mengobati pendarahan di otak (perdarahan subarachnoid)
- Propofol – digunakan untuk anestesi
- Produk yang mengandung estrogen (termasuk beberapa pil KB)
- Metamizole – digunakan untuk mengobati nyeri dan demam.

Obat-obatan lain dan Injeksi Asam Valproat
Beri tahu dokter, perawat, atau apoteker Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi, atau mungkin mengonsumsi obat lain. Ini termasuk obat-obatan yang Anda beli tanpa resep, termasuk obat-obatan herbal. Ini karena Injeksi Asam Valproat dapat mempengaruhi cara kerja beberapa obat lain. Juga beberapa obat dapat mempengaruhi cara kerja Injeksi Asam Valproat.

Injeksi Asam Valproat dengan makanan dan minuman
Asupan alkohol tidak dianjurkan selama perawatan

Mengemudi dan mengoperasikan mesin
Anda mungkin merasa mengantuk saat mengonsumsi Depakote. Jika hal ini terjadi pada Anda, jangan menyetir mobil atau mengoperasikan mesin yang berbahaya sampai Anda mengetahui bagaimana efek Depakote IV terhadap Anda. Depakote IV dapat memperlambat kemampuan berpikir dan motorik Anda.

3. Cara pemberian Depakote IV
Injeksi Asam Valproat hanya untuk penggunaan intravena.
Penggunaan Injeksi Asam Valproat untuk jangka waktu lebih dari 14 hari belum diteliti. Pasien harus dialihkan ke produk valproat oral segera setelah memungkinkan secara klinis.

Injeksi Asam Valproat sebaiknya diberikan melalui infus selama 60 menit (tidak lebih cepat dari 20 mg per menit) dengan frekuensi yang sama seperti obat minum. Namun, pemeriksaan kadar obat dalam darah dan penyesuaian dosis mungkin diperlukan. Sebelum diberikan, produk obat parenteral harus dicek secara visual untuk memastikan tidak ada partikel atau perubahan warna, jika memungkinkan.

Pemberian infus terlalu cepat dapat meningkatkan risiko efek samping. Waktu infus kurang dari 60 menit atau kecepatan lebih dari 20 mg per menit belum pernah diteliti pada pasien epilepsi.

Injeksi Asam Valproat dapat dicampurkan dengan cairan infus berikut dan tetap stabil hingga setidaknya 24 jam jika disimpan pada suhu ruangan di bawah 30°C dalam wadah kaca atau kantong plastik infus:
- Larutan Glukosa 5%
- Larutan Natrium Klorida (garam fisiologis) 0,9%
- Larutan Ringer Laktat

4. Kemungkinan efek samping
- Sejumlah kecil orang yang diobati dengan obat antiepilepsi seperti natrium valproat pernah berpikir untuk melukai atau membunuh diri mereka sendiri. Jika suatu saat Anda mempunyai pemikiran tersebut, segera hubungi dokter Anda
- Seperti obat antiepilepsi lainnya, kejang mungkin menjadi lebih parah atau lebih sering terjadi saat menggunakan obat ini. Jika hal ini terjadi segera hubungi dokter Anda.

Bicaralah dengan dokter, perawat atau apoteker Anda sebelum menggunakan Injeksi Asam Valproat jika:
- Anda menderita penyakit otak atau kondisi metabolik yang mempengaruhi otak Anda
- Anda mempunyai masalah dengan pankreas Anda
- Anda menderita diabetes atau sedang menjalani tes diabetes. Obat ini mungkin mempengaruhi hasil tes urine
- Anda menderita defisiensi karnitin palmitoyltransferase (CPT) tipe II
- Anda mempunyai masalah ginjal. Dokter Anda mungkin memantau valproate Anda tingkatkan atau sesuaikan dosis Anda
- Anda mengalami 'gangguan siklus urea' yang menyebabkan terlalu banyak amonia menumpuk di dalam tubuh
- Anda menderita penyakit yang disebut '*systemic lupus erythematosus* (SLE)' – penyakit langka pada sistem kekebalan tubuh yang menyerang kulit, tulang, sendi, dan organ dalam
- Anda mengetahui bahwa ada masalah genetik yang disebabkan oleh kelainan mitokondria di keluarga Anda.

Jika Anda tidak yakin apakah hal-hal di atas berlaku pada Anda, bicarakan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan Injeksi Asam Valproat.

Tes darah
Dokter Anda mungkin melakukan tes darah dan tes fungsi hati sebelum dan selama perawatan Anda dengan obat ini. Injeksi Asam Valproat dapat mengubah kadar enzim hati yang ditunjukkan dalam tes darah. Ini bisa berarti hati Anda atau anak Anda tidak berfungsi dengan baik.

Jika Anda memerlukan tes darah untuk memeriksa fungsi tiroid, mohon informasikan hal ini kepada dokter Anda, karena pengobatan dengan Depakote dapat menyebabkan diagnosis hipotiroidisme yang salah (produksi hormon tiroid yang tidak mencukupi).
Beri tahu dokter umum, spesialis, atau apoteker Anda, jika Anda mengalami salah satu efek samping berikut:

Sangat umum (dapat memengaruhi lebih dari 1 dari 10 orang):
- gemetar tak terkendali atau gerakan gemetar di satu atau lebih bagian tubuh Anda (tremor)

- rasa kantuk yang berlebihan
- mual
- kondisi tubuh yang terasa lemah

Umum (dapat memengaruhi hingga 1 dari 10 orang):
- trombosit rendah
- penambahan berat badan
- penurunan berat badan
- pusing, sakit kepala
- gangguan daya ingat / kehilangan ingatan
- gangguan koordinasi gerak tubuh
- gangguan rasa / perubahan persepsi rasa
- mata berkedut (nistagmus)
- sensasi geli/kesemutan atau kebas
- gangguan bicara / kesulitan berbicara
- bunyi berdenging di telinga
- nyeri perut
- muntah, diare, atau sembelit
- perut kembung, rasa tidak nyaman di perut
- nafsu makan menurun
- nafsu makan meningkat
- ruam kulit / bercak merah, gatal
- memar / lebam
- kerontokan rambut
- gangguan cara berjalan / langkah tidak stabil
- pembengkakan pada tungkai atau kaki
- mimpi yang tidak biasa / mimpi aneh
- perubahan emosi yang cepat / emosi tidak stabil
- kebingungan / kondisi bingung
- gangguan suasana hati / perasaan sedih berkepanjangan
- sulit tidur / gangguan tidur
- rasa gugup / cemas
- pola pikir tidak wajar / gangguan berpikir
- penglihatan kabur pada satu mata / mata malas
- penglihatan ganda
- infeksi / masuknya kuman ke tubuh
- cedera / luka akibat benturan atau kecelakaan

Tidak umum (dapat memengaruhi hingga 1 dari 100 orang):
- gangguan artikulasi bicara
- gerakan otot tidak terkendali / kejang otot
- gangguan fungsi otak
- gerakan tubuh berlebihan / tidak terkendali
- refleks tubuh berlebihan
- ketegangan otot berlebihan
- penurunan sensasi / rasa pada kulit
- refleks tubuh menurun
- kejang
- penurunan kesadaran / respon sangat lambat
- gerakan wajah/tubuh tidak terkendali akibat obat

- gangguan pada lapang pandang
- gangguan pendengaran / tuli
- gangguan telinga
- sensitivitas berlebihan terhadap suara
- rasa berputar (vertigo)
- batuk, radang tenggorokan
- sesak napas
- gangguan suara / suara serak
- mimisan
- tidak bisa menahan buang air besar
- gangguan pada anus dan rektum
- bau mulut
- mulut kering
- sulit menelan
- sendawa
- gusi berdarah
- radang lidah
- muntah darah
- tinja berwarna hitam akibat perdarahan saluran cerna
  radang pankreas
- rasa ingin buang air besar terus-menerus
- produksi air liur berlebihan
- infeksi bernanah pada gusi
- kencing berdarah
- rasa ingin buang air kecil yang mendesak
- sering buang air kecil
- tidak bisa menahan buang air kecil
- radang vagina
- jerawat
- pembengkakan jaringan bawah kulit
- kulit mengelupas akibat peradangan
- kulit kering, kulit pucat
- eksim / peradangan kulit
- benjolan merah dan nyeri di bawah kulit
- keringat berlebihan
- gangguan pada kuku
- bintik-bintik merah kecil di kulit akibat perdarahan
- produksi minyak berlebihan di kulit
- nyeri otot, nyeri sendi, kejang otot, kedutan otot, kelemahan otot
- kadar kalium darah tinggi
- kadar natrium darah tinggi
- kadar natrium darah rendah
- kadar protein darah rendah
- gula darah rendah
- tumor pembuluh darah di kulit
- tekanan darah turun saat berdiri (hipotensi ortostatik)
- gangguan pembuluh darah tepi
- pelebaran pembuluh darah
- nyeri punggung
- rasa tidak enak badan / lemas

- nyeri dada
- menggigil
- wajah bengkak
- demam
- tidak haid, nyeri haid, gangguan haid
- perdarahan di luar siklus haid
- perdarahan dari vagina
- disfungsi ereksi / kesulitan ereksi
- haid terlalu banyak
- gelisah / tidak tenang, cemas
- tidak peduli / kurang respons emosional
- tidak bergerak dan tidak responsif
- bingung berat disertai perubahan kesadaran
- perasaan sangat senang berlebihan
- halusinasi / melihat atau mendengar sesuatu yang tidak nyata
- sikap bermusuhan / agresif
- gangguan kepribadian
- detak jantung lambat
- henti jantung
- gagal jantung kongestif
- detak jantung cepat, jantung berdebar, tekanan darah tinggi
- gangguan persepsi warna
- mata kering
- gangguan mata, nyeri mata
- gangguan produksi air mata
- pengecilan pupil mata
- silau terhadap cahaya
- gangguan penglihatan
- radang saluran napas
- bisul
- radang lambung dan usus / muntaber
- infeksi virus herpes
- flu, radang hidung, radang sinus

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia):
- gangguan metabolisme akut yang memengaruhi saraf dan pencernaan
- jumlah sel darah putih sangat rendah
- anemia akibat kekurangan folat
- anemia dengan sel darah merah berukuran besar
- anemia akibat sumsum tulang tidak menghasilkan sel darah
- gagal fungsi sumsum tulang
- kadar eosinofil tinggi dalam darah
- kadar fibrinogen darah rendah
- kadar limfosit tinggi dalam darah
- sel darah merah berukuran besar
- penurunan semua jenis sel darah
- hambatan penggumpalan trombosit
- perubahan bentuk sel darah putih akibat kondisi tertentu
- kadar bilirubin darah meningkat
- kadar karnitin rendah dalam darah

- hasil tes fungsi tiroid tidak normal
- gerakan tangan tidak terkendali
- penyusutan otak kecil (serebelum)
- penyusutan jaringan otak
- gangguan fungsi berpikir / kognitif
- tidak sadar total / koma
- gangguan gerak tubuh akibat masalah saraf
- gangguan konsentrasi
- gangguan daya ingat
- gejala mirip penyakit Parkinson
- gerakan berlebihan yang tidak terkendali
- gangguan kemampuan gerak motorik
- efek penenang / rasa kantuk akibat obat
- nyeri telinga
- penumpukan cairan di rongga paru
- gangguan pada gusi
- pembesaran gusi dan kelenjar ludah
- tidak bisa menahan kencing saat tidur
- gangguan ginjal yang menyebabkan kehilangan zat penting
- gagal ginjal, radang pada jaringan dan saluran kecil ginjal
- peradangan pembuluh darah di kulit
- reaksi alergi berat terhadap obat yang menyerang banyak organ
- ruam kulit berbentuk lingkaran / bercak khas akibat infeksi atau obat
- gangguan pada rambut (misalnya rontok, rapuh)
- penggelapan warna kulit / kulit lebih gelap dari biasanya
- gangguan pada dasar kuku
- reaksi kulit terhadap sinar matahari
- reaksi kulit berat akibat obat, bisa mengancam nyawa
- kerusakan kulit parah akibat reaksi obat
- penurunan kepadatan tulang, tulang rapuh / keropos
- nyeri tulang
- kerusakan otot berat yang bisa memengaruhi ginjal
- lupus / penyakit autoimun sistemik
- kadar hormon pria berlebihan pada wanita
- fungsi tiroid menurun / hormon tiroid rendah
- gangguan pengaturan cairan tubuh akibat hormon ADH berlebihan
- kekurangan vitamin B7 (biotin)
- gangguan kadar lemak darah
- kadar amonia darah tinggi
- kekurangan karnitin dalam darah
- tubuh tidak merespons insulin dengan baik
- kegemukan / obesitas
- gangguan produksi sel darah di sumsum tulang
- suhu tubuh terlalu rendah
- kerusakan hati akibat zat tertentu
- pembesaran payudara
- keluar ASI tanpa menyusui
- gangguan kesuburan pria
- kista di ovarium / gangguan hormonal wanita
- gangguan psikotik / kehilangan kontak dengan realitas

- radang telinga tengah
- infeksi paru / radang paru
- infeksi saluran kemih

Ini belum semua efek samping yang mungkin dari Depakote. Untuk informasi lebih lanjut, tanyakan kepada penyedia layanan kesehatan atau apoteker Anda. Beritahu penyedia layanan kesehatan Anda jika Anda memiliki efek samping yang mengganggu Anda atau yang tidak kunjung hilang.

Pelaporan efek samping
Jika Anda mengalami efek samping apapun, bicarakan dengan dokter atau apoteker Anda. Ini mencakup kemungkinan efek samping yang tidak tercantum dalam brosur ini. Anda juga dapat melaporkan efek samping secara langsung ke: pv.indonesia@abbott.com

Dengan melaporkan efek samping Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara menyimpan Depakote IV
Simpan pada suhu di bawah 30°C.

6. Isi kemasan dan informasi lainnya
Bahan aktif: asam valproat
Bahan tidak aktif: *edetate disodium*, natrium hidroksida, asam klorida, *charcoal*, Air untuk injeksi

Seperti apa penampakan Depakote IV dan isi kemasannya
Cairan jernih dan tidak berwarna.
Setiap 1 mL mengandung 100 mg Asam Valproat sebagai zat aktif. Bahan lainnya meliputi Edetat Dinatrium dan air untuk injeksi. Tingkat keasaman (pH) produk diatur pada kisaran 7 – 9 menggunakan natrium hidroksida dan/atau asam klorida.

Dus, 10 vial @ 5 mL
Reg. No.: xxx

HARUS DENGAN RESEP DOKTER

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