DEPAKENE
Valproic Acid

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 Depakene 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). Depakene 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, Depakene should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakene 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

Depakene 50 mg/ml, syrup

Trademark is authorized as:
Depakene

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Valproic acid syrup is antiepileptic for oral administration. The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt.

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

Depakene 50 mg/mL syrup contains
Sucrose
Propylhydroxybenzoate E216
Methylhydroxybenzoate E218
Sorbitol Solution
Amaranth E123

3. PHARMACEUTICAL FORM

Depakene 50 mg/ml, syrup:
The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt. It is clear red-orange to raspberry red in color with a cherry flavor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Depakene may be used as sole or adjunctive therapy in the treatment of partial seizures (both elementary and complex) and absence seizures (petit mal seizures).

4.2 Posology and method of administration

DEPAKENE is administered orally. 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 a divided regimen.

Table 1 is a guide for the initial daily dose of DEPAKENE® (valproic acid) (15 mg/kg/day) :

Initial Daily Dose Guide					
Weight		Total Daily Dose (mg)	Number of Teaspoonfuls of Syrup		
(Kg)	(lb)		Dose 1	Dose 2	Dose 3
10 – 24.9	22 – 54.9	250	0	0	1
25 – 39.9	55 – 87.9	500	1	0	1
40 – 59.9	88 – 131.9	750	1	1	1
60 – 74.9	132 – 164.9	1.000	1	1	2
75 – 89.9	165 – 197.9	1.250	2	1	2

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of greater incidence of adverse reaction.

A good correlation has not been established between daily dose, serum level and therapeutic effect. However, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels of Phenobarbital and/or Phenytoin may affected.

As the DEPAKENE dosage is titrated upward, blood levels of Phenobarbital and/or Phenytoin may affected.

G.I. Irritation
Patients who experience G.I. Irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

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.

Valproic Acid is contraindicated in patients with known urea cycle disorders (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Urea Cycle Disorders*).

Valproic Acid is contraindicated in the following situation:
<u>Treatment of epilepsy</u>
• 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 Hepatotoxicity/ Hepatic dysfunction
<u>Conditions of occurrence</u>: 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, children, 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. In children, 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 nonspecific 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 (see 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, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.

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.

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. In clinical trials, there were two cases of pancreatitis without alternative etiology in 2,416 patients, representing 1,044 patient-years experience. 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, their caregivers, and families 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 (s*ee section* **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** – *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 *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.

<u>The treating physician must ensure that</u>
- 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 minimize 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 Divalproex sodium 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 Divalproex sodium 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.

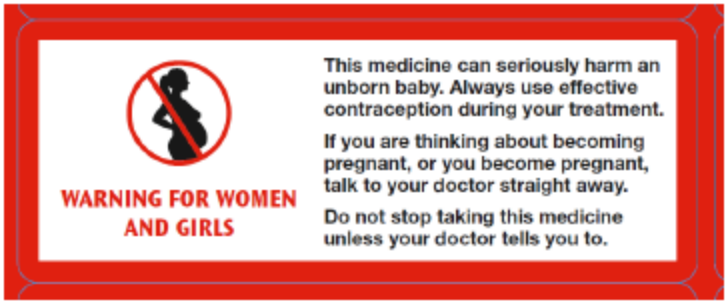
Pregnancy planning.
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess Valproic Acid therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment 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.

Educational 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 Divalproex sodium during pregnancy, the Marketing Authorization Holder has added a pictogram and warning to its outer packaging.



Use in male patients of reproductive potential

A retrospective observational study suggests indicates 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, bipolar disorder, or migraine.

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 p atients 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 valproate 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 section 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 section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE -** *Urea Cycle Disorders* and *Hyperammonemia*).

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 section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE -** H*yperammonemia 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 test:
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 Valproic Acid 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 Valproic Acid 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.

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** - *Usage in Pregnancy and* **FERTILITY, PREGNANCY AND LACTATION**).

Pediatric Use
Experience with oral valproate has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE -** *Hepatotoxicity*). 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 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.

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/m^2 basis.

Geriatric Use
In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. The discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

Somnolence in the elderly: A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE –** *Somnolence in the Elderly*). 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**).

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

Depakene 50mg/ml syrup:

- This medicinal product contains 3 g of sucrose per 5 ml dose sucrose. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- May be harmful to the teeth.
- This medicinal product contains Propylhydroxybenzoate E216 and Methylhydroxybenzoate E218. Those may cause allergic reactions (possibly delayed).
- This medicinal product contains Sorbitol Solution E420.
- Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- This medicinal product contains E123, amaranth. This may cause allergic reactions.

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 an inhibition ~~o~~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 coadministered.

Estrogen-Containing Hormonal Contraceptives - Valproate does not reduce efficacy of 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 (see section 4.4).

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-administrated, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum level 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 pharmacodynamics 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/nortriptyline 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 encelophalophaty 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 valproic acid 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 coadministered 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

Valproic acid is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproic acid is contraindicated for use in women of childbearing potential unless the measures for prevention of pregnancy as mentioned in sections **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** are met.

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 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 group. 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 study did not investigate the risk in children born to men who stopped using valproate more than 3 months before conception.

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 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 anti-epileptic polytherapy including Valproic Acid is higher than that of anti-epileptic 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 valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section POSOLOGY AND METHOD OF ADMINISTRATION).

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 exposures.

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.

Risk in the neonate

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate 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 hypoglycaemia 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 effect). 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

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using Valproic Acid (see section Undesirable effect). Valproic Acid administration may also impair fertility in men (see section Undesirable effect). 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 4.4 and 4.6)*	
	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[14], 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, Dyspnoea, Dysphonia, Epistaxis
	Unknown	Pleural effusion
Gastrointestinal disorders	*Very common*	Nausea[7]
	Common	Abdominal pain, Constipation, Diarrhoea, Dyspepsia[7], Flatulence, Vomiting[7]
	Uncommon	Anal incontinence, Anorectal disorder, Breath odour, Dry mouth, Dysphagia, Eructation, Gingival bleeding, Glossitis, Hematemesis, Melena, Pancreatitis[8], Rectal tenesmus, Salivary hypersecretion, Stomatitis
	Unknown	Gingival disorder, Gingival hypertrophy, Parotid gland enlargement
Renal and urinary disorders	*Uncommon*	Haematuria, Micturition urgency, Pollakiuria, Urinary incontinence, Dysuria

	Unknown	Enuresis, Fanconi syndrome[9], Renal failure, Tubulointerstitial nephritis
Skin and tissue disorders	*Common*	Alopecia[10], Ecchymosis, Pruritus, Rash maculo-papular
	Uncommon	Acne, Angioedema, Dermatitis exfoliative, Dry skin, Eczema, Erythema nodosum, Hyperhidrosis, Nail disorder, Petechiae, Seborrhoea
	Unknown	Cutaneous vasculitis, Drug Rash with Eosinophilia and Systemic Symptoms syndrome (DRESS) (see section 4.4), Erythema multiforme, Hair disorder, Hyperpigmentation, Nail bed disorder, Photosensitivity reaction, Stevens-Johnson syndrome, Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	*Uncommon*	Muscle spasm, Muscle twitching, Muscular weakness, Arthralgia, Myalgia
	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	Hyperkalaemia, Hypernatremia, Hypoglycaemia, Hyponatremia, Hypoproteinaemia
	Unknown	Biotin deficiency, Dyslipidemia, Hyperammonemia, Hypocarnitinemia (see section 4.3 and 4.4), Insulin resistance, Obesity
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Uncommon*	Haemangioma of skin
	Unknown	Myelodysplastic syndrome
Vascular disorders	*Uncommon*	Orthostatic hypotension, Pallor, Peripheral vascular disorder, Vasodilatation, Hypotension
	Very common	Asthenia

General disorders and administration site conditions	*Common*	Gait disturbance, Oedema peripheral
	Uncommon	Chest pain, Chills, Face oedema, Injection site inflammation[13], Injection site pain[13], Injection site reaction[13], Pyrexia, Back pain, Neck pain, Malaise
	Unknown	Hypothermia
Hepatobiliary disorders	*Unknown*	Hepatotoxicity
Reproductive system and breast disorders	*Uncommon*	Amenorrhea, Dysmenorrhea, Erectile dysfunction, Menorrhagia, Menstrual disorder, Metrorrhagia, Vaginal haemorrhage, Vaginitis
	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 behaviour, Aggression, Emotional distress, Learning disorder, Psychotic disorder
Cardiac disorders	*Uncommon*	Bradycardia, Cardiac arrest, Cardiac failure congestive, Tachycardia, Hypertension, Palpitation
Eye disorders	*Common*	Amblyopia, Diplopia
	Uncommon	Chromatopsia, Dry eye, Eye disorder, Eye pain, Lacrimation disorder, Miosis, Photophobia, Visual impairment, Conjunctivitis
Immune system disorders	*Unknown*	Anaphylactic reaction, Hypersensitivity
Infections and infestations	*Common*	Infection
	Uncommon	Bronchitis, Furuncle, Gastroenteritis, Herpes simplex, Influenza, Rhinitis, Sinusitis, Pharyngitis

	Unknown	Otitis media, Pneumonia, Urinary tract infection, Cystitis
Injury, poisoning and procedural complications	*Common*	Injury

1 may reflect potentially serious hepatotoxicity (see section 4.4)
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 4.4). Encephalopathy in the absence of elevated ammonia levels was also observed.
3 here, consider aggravated seizure and reference to section 4.4
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 4.4)
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 4.6)
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. Young children are at particular risk of pancreatitis. These risks decrease with increasing age (See 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

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 antiepileptic 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
For all formulations

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 4 presents the findings.

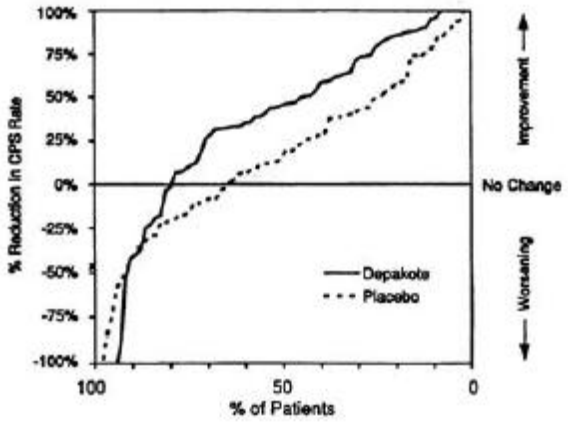
Table 4
Adjunctive Therapy Study
Median Incidence of CPS per 8 Weeks

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 ≤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.

Figure 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 5 presents the findings for all patients randomized who had at least one post-randomization assessment.

Table 5
Monotherapy Study
Median Incidence of CPS per 8 Weeks

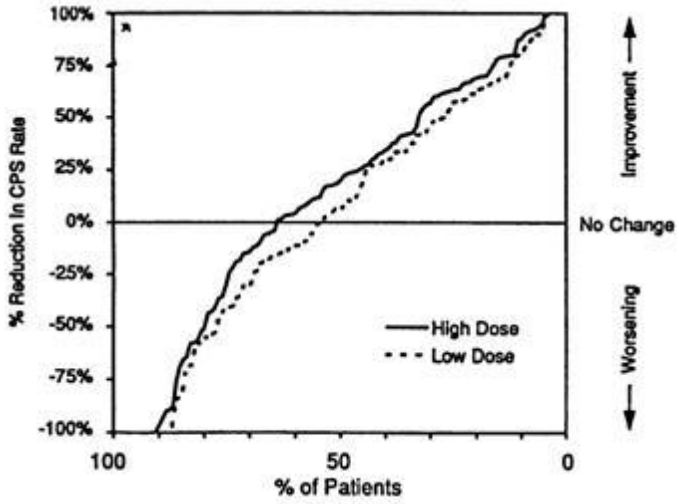
Treatment	**Number of Patients**	**Baseline Incidence**	**Randomized Phase Incidence**
High Dose Divalproex Sodium	131	13.2	10.7*
Low Dose Divalproex Sodium	134	14.2	13.8

* Reduction from baseline statistically significantly greater for high dose than low dose at $p \leq 0.05$ 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.

Figure 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.

5.2 Pharmacokinetic properties

Absorption
Equivalent oral doses of divalproex sodium (Depakote) products and valproic acid (Depakene) capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy. However, it is possible that differences among the various valproate products in T_{max} and C_{max} could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate

of absorption of the tablet (increase in T_{max} from 4 to 8 hours) than on the absorption of the sprinkle capsules (increase in T_{max} from 3.3 to 4.8 hours).

While the absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Co-administration of oral valproate products with food and substitution among the various divalproex sodium and valproic acid formulations should cause no clinical problems in the management of patients with epilepsy (see section **POSOLOGY AND METHOD OF ADMINISTRATION**). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

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 **POSOLOGY AND METHOD OF ADMINISTRATION**).

Pediatric

Pediatric patients up to the age of 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.

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.

Hepatic Impairment

See section **CONTRAINDICATIONS** and **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.

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.

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 published literature, behavioral abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure to clinically relevant doses/exposures of valproate. In mice, behavioral changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute *in utero* exposure of the first generation. The relevance of these findings for humans is unknown.

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

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

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

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
Depakene 50 mg/ml, syrup:
Sucrose (sugar granulated)
Methylparaben
Propylparaben
Sorbitol solution
Glycerin
Vanillin crystals
Dye, Red, FD&C, No 40
Flavor, Cherry, Artificial, No. 59.456/A
Sodium hydroxide
Hydrochloric acid

Incompatibilities
Not applicable

Shelf life
Expiry date is indicated on the packaging

Special precautions for storage
Do not store above 30°C

Special precautions for disposal and other handling
No special requirements.

HARUS DENGAN RESEP DOKTER
HOW SUPPLIED
Depakene® 250 mg/5 ml syrup
Bottle of 120 ml
Reg. No. DKL7800201637A1

Depakene® 250 mg/5 ml syrup
Plastic Bottle of 120 mL
Reg. No. DKL7800201637A2

LEGAL STATUS
POM (Prescription-Only Medicine)

MANUFACTURED BY:
PT. Abbott Indonesia
Jl. Raya Jakarta – Bogor Km. 37, Depok, Indonesia
Under license of Abbott Laboratories, ILL., USA

Refer to RDCCDS000637 ver. 26.0 and ver. 27.0
L029/11/24
Date of revision : 16 June 2025

BROSUR INFORMASI UNTUK PASIEN
Sirup Depakene
(Asam Valproat)

Baca seluruh isi brosur ini secara seksama sebelum Anda mulai minum 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 Depakene dan apa kegunaannya

Sirup Depakene adalah obat resep dokter yang digunakan secara tunggal atau bersama dengan obat lain untuk mengobati epilepsi, yaitu kejang parsial kompleks dan kejang absans (kejang *petit mal*).

2. Apa yang perlu Anda ketahui sebelum mengonsumsi sirup Depakene

Jangan gunakan obat ini jika Anda;
- memiliki penyakit hati atau gangguan fungsi hati
- memiliki kelainan genetik yang disebabkan oleh gangguan pada bagian dari sel tubuh (mitokondria), contohnya seperti sindrom *Alpers-Huttenlocher*
- menderita porfiria (kondisi metabolik langka)
- alergi terhadap Asam Valproat. Lihat bagian akhir brosur ini untuk mengetahui daftar lengkap bahan-bahan yang terdapat di dalam Depakene.
- memiliki masalah genetik yang disebut gangguan siklus urea (*urea cycle disorder*)
- memiliki resiko hipokarnitinemia
- sedang hamil atau mungkin menjadi hamil karena Anda tidak menggunakan alat kontrasepsi yang efektif

Jangan minum obat ini jika Anda mengalami salah satu kondisi di atas. Jika Anda tidak yakin, konsultasikan dengan dokter Anda sebelum mengonsumsi Depakene.

Peringatan dan tindakan keselamatan
- Sejumlah kecil orang yang diobati dengan antiepilepsi seperti valproat pernah berpikir untuk menyakiti diri sendiri atau bunuh diri. Jika sewaktu-waktu Anda memiliki pikiran ini, segera hubungi dokter Anda.

DISETUJUI OLEH BPOM : 21/10/2025
ID : EREG10034612500010
EREG10034612500011

- Seperti halnya obat antiepilepsi lain, kejang dapat menjadi lebih parah atau terjadi lebih sering saat mengonsumsi obat ini. Jika ini terjadi, segera hubungi dokter Anda.
- Jika Anda yang mengonsumsi Depakene mengalami masalah dengan keseimbangan dan koordinasi, merasa lesu atau kurang waspada, muntah, segera beri tahu dokter Anda. Ini mungkin disebabkan oleh peningkatan jumlah amonia dalam darah.

Beritahukan pada dokter atau apoteker Anda sebelum menggunakan obat ini;
- memiliki kelainan genetik yang disebabkan oleh gangguan pada bagian dari sel tubuh (mitokondria), contohnya seperti sindrom *Alpers-Huttenlocher*
- minum alkohol
- sedang hamil atau kemungkinan hamil. Depakene dapat membahayakan janin Anda.
- sedang menyusui. Depakene dapat masuk ke ASI. Bicaralah dengan penyedia layanan kesehatan Anda tentang cara terbaik untuk memberi asupan bayi Anda jika Anda menggunakan Depakene.
- memiliki kondisi medis lainnya
- berjenis kelamin pria dan berencana menjadi ayah dari seorang anak. Depakene dapat menyebabkan masalah kesuburan pada pria. Beritahu dokter Anda jika Anda berencana memiliki keturunan.

Jika Anda harus menjalani jenis operasi apa pun, termasuk prosedur gigi yang memerlukan anestesi, beri tahu dokter bahwa Anda sedang mengonsumsi Depakene.

Jika Anda tidak yakin apakah salah satu hal di atas berlaku untuk Anda, bicarakan dengan dokter Anda sebelum mengonsumsi Depakene.

Bicarakan dengan dokter Anda meskipun Anda tidak lagi memiliki kondisi ini, tetapi pernah mengalaminya di masa lalu.

Mengonsumsi Depakene dapat membuat Anda bertambah berat badan. Bicarakan dengan dokter Anda tentang bagaimana hal ini akan memengaruhi Anda.

Dokter Anda dapat meminta tes darah dan tes fungsi hati sebelum dan selama pengobatan Anda dengan obat ini. Depakene dapat mengubah kadar enzim hati yang ditunjukkan dalam tes darah.

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).

Beritahu penyedia layanan kesehatan Anda tentang semua obat yang Anda gunakan, termasuk obat resep dan non-resep, vitamin, suplemen herbal, dan obat yang Anda minum untuk jangka waktu singkat.

Minum Depakene bersama dengan obat-obatan lain tertentu dapat menyebabkan efek samping atau mempengaruhi khasiatnya. Jangan memulai atau menghentikan obat lain tanpa berbicara dengan penyedia layanan kesehatan Anda.

Ketahui obat-obatan yang Anda minum. Catat daftarnya dan tunjukkan catatan ini kepada penyedia layanan kesehatan dan apoteker Anda setiap kali Anda membeli obat baru.

Depakene dapat menyebabkan kantuk dan pusing. Jangan minum alkohol atau minum obat lain yang membuat Anda mengantuk atau pusing bersamaan dengan minum Depakene, sampai Anda berbicara dengan dokter Anda. Minum Depakene bersama dengan alkohol atau obat-obatan yang menyebabkan kantuk atau pusing dapat memperparah kantuk atau pusing Anda.

Interaksi Depakene 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:

- Aspirin – Metabolisme asam valproat dapat menurun apabila dikombinasikan dengan Aspirin. Harus diperhatikan jika valproat dan aspirin diberikan bersama.
- Antibiotik Karbapenem – Konsentrasi serum asam valproat dapat menurun bila dikombinasikan dengan antibiotik karbapenem (ertapenem, imipenem, meropenem) dan dapat menyebabkan hilangnya kontrol kejang.
- Cholestyramine – Dapat menyebabkan penurunan kadar plasma valproat saat digunakan bersama.
- Kontrasepsi Hormonal yang Mengandung Estrogen – Valproat tidak mengurangi efektivitas kontrasepsi hormonal. Dapat meningkatkan klirens valproat, yang dapat menyebabkan penurunan konsentrasi valproat dan berpotensi meningkatkan frekuensi kejang.
- Felbamate – Konsentrasi serum asam valproat dapat meningkat bila dikombinasikan dengan Felbamate. Penurunan dosis valproat mungkin diperlukan saat terapi felbamate dimulai.
- Metamizole – Dapat menurunkan kadar serum valproat saat digunakan bersama, yang dapat mengakibatkan potensi penurunan efikasi klinis valproat.
- Methotrexate – Konsentrasi serum asam valproat dapat menurun bila dikombinasikan dengan metotreksat.
- Protease inhibitors – Konsentrasi serum asam valproat dapat menurun bila dikombinasikan dengan Protease inhibitors (lopinavir, ritonavir).
- Rifampin – Metabolisme asam valproat dapat meningkat bila dikombinasikan dengan Rifampin.
- Amitriptyline/Nortriptyline – Metabolisme asam valproat dapat menurun bila dikombinasikan dengan Amitriptyline. Pemantauan kadar Amitriptyline harus dipertimbangkan untuk pasien yang memakai valproate bersamaan dengan amitriptyline. Pertimbangan harus diberikan untuk menurunkan dosis amitriptyline/nortriptyline dengan adanya valproate.
- Carbamazepine – Konsentrasi serum carbamazepine-10,11 epoksida (CBZ-E), metabolit aktif Carbamazepine, dapat meningkat bila digunakan dalam kombinasi dengan asam valproat.
- Clonazepam/ Diazepam – Risiko atau tingkat keparahan depresi SSP dapat meningkat bila Asam valproat dikombinasikan dengan Clonazepam/ Diazepam.
- Ethosuximide – Konsentrasi serum asam valproat dapat menurun bila dikombinasikan dengan Ethosuximide.
- Lamotrigine - Asam valproat dapat menurunkan laju ekskresi Lamotrigin yang dapat menghasilkan kadar serum yang lebih tinggi. Dosis Lamotrigin harus dikurangi saat diberikan bersamaan dengan valproat.
- Phenobarbital – Konsentrasi serum fenobarbital dapat meningkat bila digunakan dalam kombinasi dengan asam valproat.

- Phenytoin – Kadar serum asam valproat dapat meningkat jika digunakan bersamaan dengan fenitoin atau fenobarbital. Oleh karena itu, pasien yang diobati dengan kedua obat tersebut harus dipantau secara hati-hati untuk tanda dan gejala hiperamonemia.
- Cefditoren pivoxil, adefovir dipivoxil, pivmecillinam dan pivampicillin – Pemberian obat-obat tersebut bersama dengan valproate tidak direkomendasikan karena dapat menyebabkan berkurangnya kadar carnitine dalam darah.
- Propofol – Konsentrasi serum Propofol dapat meningkat bila dikombinasikan dengan asam valproat. Oleh karena itu, ketika diberikan bersamaan dengan valproat, dosis propofol harus dikurangi.
- Nimodipine – Pengobatan bersamaan nimodipine dengan asam valproat dapat meningkatkan konsentrasi plasma nimodipine sebesar 50%.
- Tolbutamide – Metabolisme Tolbutamide dapat menurun bila dikombinasikan dengan asam valproat.
- Cannabidiol – Interaksi obat antara valproate dan cannabidiol dapat mengakibatkan peningkatan risiko peningkatan transaminase hati. Pemantauan hati yang tepat harus dilakukan ketika valproate digunakan dengan cannabidiol.
- Topiramate dan acetazolamide – Pemberian bersama valproate dan topiramate atau acetazolamide telah dikaitkan dengan hiperamonemia dengan dan tanpa ensefalopati. Pasien yang diobati dengan kedua obat tersebut harus dipantau secara hati-hati untuk tanda dan gejala ensefalopati hiperamonemia.
- Warfarin – Konsentrasi serum Warfarin dapat meningkat bila dikombinasikan dengan asam valproat.
- Zidovudine – Konsentrasi serum Zidovudine dapat ditingkatkan bila dikombinasikan dengan asam valproat.
- Quetiapine – Penggunaan bersama valproat dan quetiapine dapat meningkatkan risiko neutropenia/leucopenia.

Jika Anda memerlukan tes darah untuk memeriksa fungsi tiroid, mohon informasikan hal ini kepada dokter Anda, karena pengobatan dengan Depakene dapat menyebabkan diagnosis hipotiroidisme yang salah (produksi hormon tiroid yang tidak mencukupi).

Jika Anda harus menjalani jenis operasi apa pun, termasuk prosedur gigi yang memerlukan anestesi, beri tahu dokter bahwa Anda sedang mengonsumsi Depakene.

Kehamilan, menyusui dan kesuburan

<u>Kehamilan</u>

- Anda tidak boleh menggunakan Depakene jika Anda sedang hamil, kecuali dua orang dokter spesialis telah sepakat bahwa kondisi Anda tidak merespons pengobatan lain dan manfaat pengobatan lebih besar daripada risikonya.
- Jangan berhenti mengonsumsi Depakene atau kontrasepsi Anda, sampai Anda membicarakan hal ini dengan dokter Anda.
- Segera hubungi dokter jika Anda berencana untuk memiliki bayi atau sedang hamil.
- Valproat mengandung risiko jika dikonsumsi selama kehamilan. Semakin tinggi dosisnya, semakin tinggi pula risikonya, tetapi semua dosis mengandung risiko, termasuk jika valproat digunakan dalam kombinasi dengan obat lain untuk mengobati epilepsi.
- Valproat dapat menyebabkan cacat lahir yang serius dan dapat memengaruhi perkembangan fisik dan mental anak saat ia tumbuh setelah lahir dan dapat menyebabkan

kecacatan permanen. Jika Anda mengonsumsi valproat selama kehamilan, Anda memiliki risiko lebih tinggi daripada wanita lain untuk memiliki anak dengan cacat lahir yang memerlukan perawatan medis.
  - Cacat lahir yang paling sering dilaporkan meliputi spina bifida (tulang belakang tidak berkembang dengan baik); malformasi wajah dan tengkorak; malformasi jantung, ginjal, saluran kemih, dan organ seksual; cacat anggota tubuh dan berbagai malformasi terkait yang memengaruhi beberapa organ dan bagian tubuh. Cacat lahir dapat mengakibatkan kecacatan yang mungkin parah dan/atau permanen.
  - Masalah pendengaran atau tuli dilaporkan pada anak yang terpapar valproat selama kehamilan.
  - Malformasi mata dilaporkan pada anak yang terpapar valproat selama kehamilan yang berkaitan dengan malformasi kongenital lainnya. Malformasi mata ini dapat memengaruhi penglihatan.

- Jika Anda mengonsumsi valproat selama kehamilan, berat badan bayi Anda mungkin lebih rendah dari yang diharapkan untuk usianya saat lahir.
- Jika Anda mengonsumsi Depakene selama kehamilan karena kondisi medis apapun, anak Anda berisiko memiliki IQ lebih rendah dibandingkan anak-anak lain dan mungkin berisiko mengalami autisme atau gangguan pemusatan perhatian/hiperaktivitas.
- Sebelum meresepkan obat ini kepada Anda, dua orang dokter spesialis akan menyetujui bahwa kondisi Anda tidak merespons pengobatan lain dan manfaat pengobatan lebih besar daripada risikonya, dan dokter spesialis Anda akan menjelaskan apa yang mungkin terjadi pada bayi Anda jika Anda hamil saat mengonsumsi valproat.
- Jika Anda memutuskan untuk memiliki bayi di kemudian hari, Anda tidak boleh berhenti mengonsumsi obat atau metode kontrasepsi Anda hingga Anda membicarakannya dengan dokter spesialis Anda.
- Jika Anda adalah orang tua atau pengasuh anak perempuan yang diobati dengan valproat, Anda harus menghubungi dokter setelah anak Anda yang menggunakan valproat mengalami menstruasi pertama (*menarche*) untuk memutuskan apakah valproat adalah satu-satunya pengobatan yang harus diresepkan.
- Beberapa pil KB (pil KB yang mengandung estrogen) dapat menurunkan kadar valproat dalam darah Anda. Pastikan Anda berbicara dengan dokter Anda tentang metode kontrasepsi yang paling tepat untuk Anda.
- Tanyakan kepada dokter Anda tentang mengonsumsi asam folat saat mencoba untuk hamil. Asam folat dapat menurunkan risiko umum spina bifida dan keguguran dini yang terjadi pada semua kehamilan. Namun, kecil kemungkinannya bahwa asam folat akan mengurangi risiko cacat lahir yang terkait dengan penggunaan valproat.

<u>Menyusui</u>
Sangat sedikit valproat 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.

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

3. Cara minum sirup Depakene

- Minum Depakene persis seperti yang diberitahukan kepada Anda oleh penyedia layanan kesehatan Anda. Penyedia layanan kesehatan Anda akan memberitahu Anda berapa banyak Depakene yang harus diminum dan kapan harus meminumnya.
- Penyedia layanan kesehatan Anda mungkin mengubah dosis Anda.
- Jangan mengubah dosis Depakene Anda tanpa berbicara dengan penyedia layanan kesehatan Anda.
- **Jangan berhenti mengonsumsi Depakene tanpa terlebih dahulu berbicara dengan penyedia layanan kesehatan Anda**. Menghentikan pemakaian Depakene secara tiba-tiba dapat menyebabkan masalah serius. Menghentikan obat kejang secara tiba-tiba pada penderita epilepsi dapat menyebabkan kejang yang tidak kunjung berhenti (status epileptikus).

Jika Anda mengonsumsi Depakene lebih banyak dari yang seharusnya
Overdosis obat ini dapat berbahaya. Jika Anda merasa telah mengonsumsi Depakene lebih banyak dari yang seharusnya, segera hubungi dokter Anda atau memeriksakan diri ke instalasi gawat darurat rumah sakit terdekat. Bawalah bungkus obat bersama Anda. Dengan demikian, dokter akan mengetahui apa yang telah Anda konsumsi. Efek yang dapat terjadi antara lain: mual, sakit kepala, penglihatan kabur karena pupil mata mengecil, pusing berputar, penurunan refleks tubuh, kebingungan, kehilangan ingatan, dan kelelahan. Kemungkinan lainnya yang dapat terjadi ialah kelemahan otot, kejang, kehilangan kesadaran, perubahan perilaku, dan kesulitan bernapas seperti napas cepat, sesak napas, atau nyeri dada.

Jika Anda lupa mengonsumsi Depakene
Jika Anda lupa mengonsumsi satu dosis pada waktu yang tepat, minumlah segera setelah Anda ingat, kecuali jika sudah mendekati waktu untuk dosis berikutnya. Kemudian lanjutkan seperti sebelumnya. Jangan minum dosis ganda untuk mengganti dosis yang terlupakan.

Jika Anda berhenti mengonsumsi Depakene
Jika Anda ingin berhenti mengonsumsi Depakene, konsultasikan dengan dokter Anda terlebih dahulu. Jangan berhenti mengonsumsi Depakene hanya karena Anda merasa lebih baik, karena hal ini dapat menyebabkan kekambuhan segera dan kondisi Anda mungkin bertambah buruk.

Jika Anda memiliki pertanyaan lebih lanjut terhadap penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. Kemungkinan efek samping

Seperti obat pada umumnya, obat ini dapat memberikan efek samping, meskipun tidak semua orang mengalaminya. Harap perhatikan bahwa daftar berikut mencakup semua efek samping yang dilaporkan – bahkan yang sangat jarang terjadi.

Sangat penting bagi Anda untuk segera memberi tahu dokter Anda atau pergi ke rumah sakit segera jika Anda mengalami salah satu gejala berikut, karena tindakan medis yang mendesak mungkin diperlukan:
- Perubahan dalam darah, yang dapat meningkatkan risiko lemas, pendarahan atau memar, dan kemungkinan infeksi.
- Nyeri perut hebat atau terus-menerus, mual dan/atau muntah (ini mungkin gejala dari kerusakan hati berat atau radang pankreas, yang dapat mengancam jiwa).
- Muntah, gangguan koordinasi gerakan dan kesadaran menurun secara progresif (ini mungkin merupakan tanda-tanda peningkatan kadar amonia dalam darah).
- Reaksi kulit yang serius (terkadang mengancam jiwa) dengan lepuh pada kulit, mulut, mata atau alat kelamin.

Seperti obat antiepilepsi lainnya, Depakene dapat menyebabkan pikiran atau tindakan bunuh diri. Hubungi penyedia layanan kesehatan segera jika Anda memiliki salah satu dari gejala-gejala ini, terutama jika gejala tersebut baru, memburuk, atau membuat Anda khawatir:
- pikiran tentang bunuh diri atau mati
- percobaan bunuh diri
- depresi yang baru atau memburuk
- kecemasan yang baru atau memburuk
- merasa takut atau gelisah
- serangan panik
- gangguan tidur (insomnia)
- lekas marah yang baru atau memburuk
- bertindak agresif, marah, atau kasar
- bertindak atas dorongan yang berbahaya
- peningkatan ekstrim pada aktivitas dan berbicara (mania)
- perubahan perilaku atau suasana hati yang tidak biasa lainnya

Bagaimana saya dapat melihat gejala-gejala awal pikiran dan tindakan bunuh diri? Perhatikan setiap perubahan, terutama perubahan suasana hati, perilaku, pikiran, atau perasaan yang tiba-tiba. Pertahankan semua kunjungan tindak lanjut dengan penyedia layanan kesehatan Anda sesuai jadwal. Pikiran atau tindakan bunuh diri dapat disebabkan oleh hal-hal selain obat-obatan. Jika Anda memiliki pikiran atau tindakan bunuh diri, penyedia layanan kesehatan Anda mungkin memeriksa penyebab-penyebab lainnya.

Untuk pasien lanjut usia: Obat ini bisa menyebabkan rasa kantuk berlebihan pada lansia, terutama yang memiliki demensia. Jika Anda merasa sangat mengantuk atau mengalami penurunan nafsu makan dan minum dari biasanya, segera beri tahu dokter. Dokter mungkin akan memulai pengobatan dengan dosis yang lebih rendah dan memantau kondisi Anda secara berkala.

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 Depakene. 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 sirup Depakene
Jangan disimpan di atas suhu 30°C. Jauhkan obat ini dari penglihatan dan jangkauan anak-anak. Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada kemasan.

6. Isi kemasan dan informasi lainnya
Bahan aktif: asam valproat
Bahan tidak aktif: pewarna merah FD&C Red No. 40, gliserin, metilparaben, propilparaben, sorbitol, sukrosa, vanilin, air, natrium hidroksida, asam klorida, dan perisa ceri buatan.

Seperti apa penampakan sirup Depakene dan isi kemasannya
Depakene 50 mg/ml, sirup:
Sirup mengandung setara dengan 250 mg asam valproat per 5 mL sebagai garam natrium.
Cairan merah-oranye bening hingga merah raspberry bebas dari partikel dengan rasa dan aroma ceri.

Ukuran kemasan:
Dus, 1 botol @ 120 mL sirup. Reg. No.: DKL7800201637A1
Dus, 1 botol plastik @ 120 mL sirup. Reg. No.: DKL7800201637A2

HARUS DENGAN RESEP DOKTER

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DISETUJUI OLEH BPOM : 21/10/2025
ID : EREG10034612500010
EREG10034612500011