

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)*].

NAME OF THE MEDICINAL PRODUCT

Depakene 50 mg/ml, syrup

Trademark is authorized as:
Depakene

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

PHARMACEUTICAL FORM

Depakene 50 mg/ml, syrup:

The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt.

CLINICAL PARTICULARS

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).

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 exceed 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 Teaspoonfulls 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
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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.

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.

Valproic Acid is contraindicated in patients with known hypersensitivity to the drug (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Multi-Organ Hypersensitivity Reactions**).

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

Valproic Acid is contraindicated in patients with known porphyria.

Valproic Acid is contraindicated in the following situation:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE and FERTILITY, PREGNANCY AND LACTATION**).
- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned in section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE and FERTILITY, PREGNANCY AND LACTATION** are met.

Valproic Acid is contraindicated in patients with porphyria.

Special warnings and precautions for use

Hepatotoxicity/Hepatotoxicity/ Hepatic dysfunction

Conditions of occurrence: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment.

Caution should be observed when administering Valproic acid products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, **children**, those with congenital metabolic disorders, 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. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug (see section **CONTRAINDICATIONS**).

Patients with known or suspected mitochondrial disease:

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

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.

In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, 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 (see 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 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **FERTILITY, PREGNANCY AND LACTATION**).
- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned below and in sections **CONTRAINDICATIONS** and **FERTILITY, PREGNANCY AND LACTATION** are met.

The treating physician must ensure that

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimize the risks.
- the potential for pregnancy is assessed for all female patients.
- 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*

- 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.

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.



Hyperammonemia

Hyperammonemia has been reported in association with valproic acid therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level measured.

Hyperammonemia should also be considered in patients who present with hypothermia (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hypothermia**). If ammonia is increased, valproic acid therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see section **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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

Urea Cycle Disorders (UCD): 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**).

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. 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 - Hyperammonemia and Encephalopathy**).

Associated with Concomitant Topiramate Use and Hyperammonemia). Consideration should be given to stopping valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

Brain Atrophy

There have been postmarketing 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 divalproex sodium be monitored for platelet count and coagulation parameters.

Since valproate may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration 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, which 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.

Patient with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate.

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.

Multi-Organ Hypersensitivity Reactions

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multi-organ hypersensitivity reactions have been rarely reported in close temporal association after the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported.

Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, hepatorenal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs not noted here may occur. If this reaction is suspected, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Information for Patients

Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia could be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.

Patients and guardians should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hyperammonemia**) and be told to inform the prescriber if any of these symptoms occur.

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 has indicated that pediatric patients 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/m² basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m² 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 **POSODOLOGY 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 **POSODOLOGY AND METHOD OF ADMINISTRATION**).

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.

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 of 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.

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

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

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.

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

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

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.

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 hydrolase, and glucuronyltransferases.

The following list provides information about the potential for an influence of valproate coadministration 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-Epoxyde - 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.

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.

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.

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

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.

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.

Topiramate and acetazolamide - Concomitant administration of valproate and topiramate or acetazolamide has been associated with hyperammonemia with and without encephalopathy. 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.

Oral Contraceptive Steroids - Administration of a single-dose of ethinylloestradiol (50 mcg) / levonorgestrel (250 mcg) to six women on valproate (200 mg b.i.d.) therapy for two months did not reveal any pharmacokinetic interaction.

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.

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

Both valproate monotherapy and valproic acid polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproic acid is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproic acid monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established 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 valproate may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function.

Developmental disorders

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 seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to 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 defects. 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 valproate 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 valproate *in utero* are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the general population.

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, valproate therapy should be reassessed
- *For epilepsy indication:* If a woman plans a pregnancy or becomes pregnant, valproate 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, tonic disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate 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.

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.

Undesirable effects

Epilepsy

Complex Partial Seizures (CPS)

The data described in the following section were obtained using divalproex sodium tablets. Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, divalproex sodium was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the divalproex sodium-treated patients (6%), compared to 1% of placebo-treated patients.

Table 2 lists treatment-emergent adverse events that were reported by $\geq 5\%$ of divalproex sodium-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to divalproex sodium alone, or the combination of divalproex sodium and other antiepilepsy drugs.

Table 2		
Adverse Events Reported by $\geq 5\%$ of Patients Treated with Divalproex Sodium During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures		
Body System / Adverse Event	DVPX* (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Abnormal	5	1
Respiratory System		

Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0
*DVPX = Divalproex Sodium		

Table 3 lists treatment-emergent adverse events that were reported by $\geq 5\%$ of patients in the high dose divalproex sodium group, and for which the incidence was greater than in the low dose group, in a controlled trial of divalproex sodium monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to divalproex sodium alone, or the combination of divalproex sodium and other antiepilepsy drugs.

Table 3		
Adverse Events Reported by $\geq 5\%$ of Patients in the High Dose Group in the Controlled Trial of Divalproex Sodium Monotherapy for Complex Partial Seizures		
Body System / Adverse Event	High Dose (%) (n = 131)	Low Dose (%) (n = 134)
Body as a Whole		
Asthenia	21	10
Digestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal Pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/ Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18
Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		

Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1
¹ Headache was the only adverse event that occurred in $\geq 5\%$ of patients in the high dose group and at an equal or greater incidence in the low dose group.		

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with divalproex sodium in controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.

Cardiovascular System: Tachycardia, hypertension, palpitation.

Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.

Hemic and Lymphatic System: Petechia.

Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.

Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.

Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.

Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.

Skin and Appendages: Rash, pruritus, dry skin.

Special Senses: Taste perversion, abnormal vision, deafness, otitis media.

Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Other Patient Populations

Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal

The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Obesity has been as well reported in rare cases in the framework of the post marketing experience.

Diarrhea, abdominal cramps, constipation and gingival disorder (mainly gingival hyperplasia) have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

CNS Effects

Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, memory impairment, cognitive disorder, and extrapyramidal disorders including parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Urea Cycle Disorders, Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use, and Hyperammonemia**). Additionally, there have been reports of encephalopathy in the absence of elevated ammonia levels.

There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use of valproate products. In some cases the patients recovered with permanent sequelae (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Brain Atrophy**). Cerebral atrophy seen in children exposed to valproate in utero led to various forms of neurological events, including developmental delays and psychomotor impairment. Congenital malformations and developmental disorders have been as well reported (see section **FERTILITY, PREGNANCY AND LACTATION**).

There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use of valproate products. In some cases the patients recovered with permanent sequelae (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). 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 **FERTILITY, PREGNANCY AND LACTATION**).

Dermatologic

Transient hair loss, hair disorders (such as hair texture abnormal, hair colour changes, hair growth abnormal) skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a six-month-old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35-year-old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**). Nail and nail bed disorders have been as well reported in the framework of the post marketing experience.

Psychiatric

Emotional upset, depression, psychosis, aggression, psychomotor hyperactivity, hostility, agitation, disturbance in attention, abnormal behavior, learning disorder and behavioral deterioration.

Musculoskeletal

Weakness.

Reports have been received of decreased bone mass, potentially leading to osteoporosis and osteopenia, during long-term therapy with anticonvulsant medications, including valproate. Some studies have indicated that supplemental calcium and vitamin D may be of benefit to patients who are on chronic valproate therapy.

Hematologic

Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and hemorrhage (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - General** and section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**) - Warfarin). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

Hepatic

Minor elevations of transaminase (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hepatotoxicity**).

Endocrine

Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased). Abnormal thyroid function tests including hypothyroidism (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - General**). There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic

Acute pancreatitis including fatalities (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Pancreatitis**).

Metabolic

Hyperammonemia (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hyperammonemia**), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is unknown.

Hyperglycinemia (elevated plasma glycine concentration) has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Insulin resistance and dyslipidemia have been as well reported in the framework of the post marketing experience.

Genitourinary

Enuresis, renal failure, tubulointerstitial nephritis and urinary tract infection.

Reproductive

Male infertility including azoospermia, abnormal semen analysis, decreased sperm count, spermatozoa morphology abnormal, aspermia, and decrease spermatozoa motility have been reported.

Special Senses

Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Myelodysplastic syndrome

Respiratory, thoracic and mediastinal disorders

Pleural effusion

Other

Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, rhabdomyolysis, biotin deficiency/biotinidase deficiency, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

Mania

Although valproic acid has not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of divalproex sodium tablets.

Body as a Whole: Chills, neck pain, neck rigidity.

Cardiovascular System: Hypotension, postural hypotension, vasodilation.

Digestive System: Fecal incontinence, gastroenteritis, glossitis.

Musculoskeletal System: Arthrosis.

Nervous System: Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.

Skin and Appendages: Furunculosis, maculopapular rash, seborrhea.

Special Senses: Conjunctivitis, dry eyes, eye pain.

Urogenital System: Dysuria.

Other patient population

Extrapyramidal disorders and encephalopathy in the absence of elevated ammonia levels have been reported in post-marketing data.

Migraine

Although valproic acid has not been evaluated for safety and efficacy in the treatment of prophylaxis of migraine headaches, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of divalproex sodium tablets.

Body as a Whole: Face edema.

Digestive System: Dry mouth, stomatitis.

Urogenital System: Cystitis, metrorrhagia, vaginal hemorrhage.

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 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 the national reporting system.

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 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 overdose. Because naloxone could theoretically also reverse the antiepileptic effects of valproate it should be used with caution in patients with epilepsy.

PHARMACOLOGICAL PROPERTIES

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 C₈H₁₆O₂ 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

Epilepsy

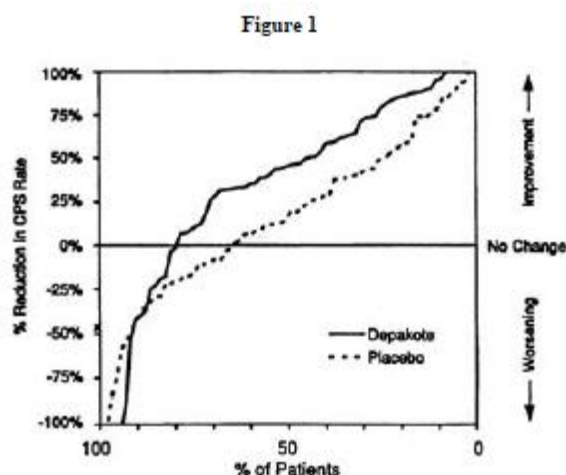
Complex Partial Seizures (CPS)

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.



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.

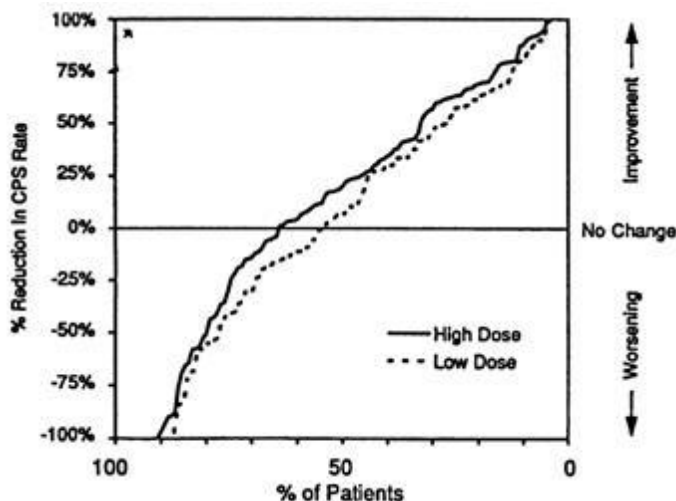
Table 5 presents the findings for all patients randomized who had at least one post-randomization assessment.

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 $\leq 75 \times 10^9/L$. 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.

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 divalproex sodium tablet (increase in T_{max} from four to eight hours) than on the absorption of the divalproex sodium 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 **POSODOLOGY 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 m² and 11 L/1.73 m², respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m² and 92 L/1.73 m². 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 **POSODOLOGY 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 m², 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%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

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 with 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 which 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.

Preclinical safety data

Carcinogenesis, Mutagenesis, 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 sisterchromatid 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.

Impairment of Fertility and development toxicity

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m² basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m² basis). Segment I fertility studies in rats have shown oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m² basis) for 60 days to have no effect on fertility. 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.

PHARMACEUTICAL PARTICULARS

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

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

MANUFACTURED BY:

PT. Abbott Indonesia

Jl. Raya Jakarta – Bogor Km. 37, Depok, Indonesia

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