PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**DEPAKENE®**

valproic acid

Oral solution, 250 mg/5 mL valproic acid (as sodium valproate), Oral

USP

Antiepileptic

BGP Pharma ULC

85 Advance Road

Etobicoke, Ontario

M8Z 2S6

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	02/2019
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	02/2019
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	02/2019
7 WARNINGS AND PRECAUTIONS	02/2019
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential	05/2021
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	03/2020
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DEPAKENE® (valproic acid) is indicated for:

- use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal, and is useful in primary generalized seizures with tonic-clonic manifestations.
- use adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2 to 15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity for statement regarding serious or fatal hepatic dysfunction.

1.1 Pediatrics

Pediatrics (< 18 years of age): When DEPAKENE® is used in children under the age of 2 years, it should be used with extreme caution and as a sole agent. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups. For a brief discussion, see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety and efficacy of DEPAKENE® in elderly patients with epilepsy has not been evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience with DEPAKENE® in this population. For a brief discussion, see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics, 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations, Dosing in Elderly Patients and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics.

2 CONTRAINDICATIONS

DEPAKENE® (valproic acid) is contraindicated in:

- Patients with known hypersensitivity to the drug, any ingredient in the formulation or component of the container. For a complete listing of ingredients (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- The treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilled (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

- Patients with hepatic disease or significant hepatic dysfunction (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hepatotoxicity and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity).
- 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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- Patients with known urea cycle disorders (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders).
- Patients with known porphyria.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Hepatotoxicity:** Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE® (valproic acid). These incidences usually occurred during the first 6 months of treatment with DEPAKENE®. Caution should be observed when administering DEPAKENE® 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. Experience has indicated that children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity).

- **Female children/Women of childbearing potential/Pregnancy (Teratogenicity):** DEPAKENE® can cause fetal harm. Because of its high teratogenic potential and risk of developmental disorders in infants exposed *in utero*, DEPAKENE® should not be used in female children, in women of childbearing potential, and pregnant women unless alternative treatments are ineffective or not tolerated. In women planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Female children/Women of childbearing potential/Pregnancy and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Pregnancy Exposure Risk Related to Valproate and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Risk in the neonate).

- **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 2 CONTRAINDICATIONS). 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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Patients with Mitochondrial Disease).

- **Pancreatitis:** Cases of life-threatening pancreatitis have been reported in both children and adults receiving DEPAKENE®. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Patients and guardians should be warned that abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt medical attention. If pancreatitis is diagnosed, DEPAKENE® should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated. Some cases have occurred shortly after initial use as well as after several years of use (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered (see 9 DRUG INTERACTIONS).

As the dosage of DEPAKENE® (valproic acid) is titrated upward, blood concentrations of phenobarbital, and/or phenytoin may be affected (see 9 DRUG INTERACTIONS).

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

Any changes in dosage and administration, or the addition or discontinuance of concomitant drugs, should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

When changing therapy involving drugs known to induce hepatic microsomal enzymes (e.g., carbamazepine) or other drugs with valproate interactions, (see 9 DRUG INTERACTIONS), it is advisable to monitor serum valproate concentrations.

Dosing in Elderly Patients:

Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, urinary tract infection, and other adverse events. Dose reductions or discontinuation of DEPAKENE® should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of clinical response (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics).

Dose-Related Adverse Events:

The frequency of adverse events (particularly elevated liver enzymes and thrombocytopenia) may be dose related. The probability of thrombocytopenia appears to increase significantly at total valproate concentration of ≥ 110 mcg/mL [females] or ≥ 135 mcg/mL [males] (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Dosing-related Adverse Reactions: Thrombocytopenia). Therefore, the benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse effects.

4.2 Recommended Dose and Dosage Adjustment

DEPAKENE® (valproic acid) is administered orally. The recommended initial dosage 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. When the total daily dose exceeds 250 mg, it should be given in a divided regimen (Table 1).

Table 1 - Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Teaspoonful of Oral Solution		
kg	lb		Dose 1	Dose 2	Dose 3
10 to 24.9	22 to 54.9	250	0	0	1
25 to 39.9	55 to 87.9	500	1	0	1
40 to 59.9	88 to 131.9	750	1	1	1
60 to 74.9	132 to 164.9	1,000	1	1	2
75 to 89.9	165 to 197.9	1,250	2	1	2

Therapeutic Blood Levels:

A good correlation has not been established between daily dose, total serum valproate concentration and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with epilepsy will range from 50 to 100 mcg/mL (350 to 700 micromole/L). Some patients may be controlled with lower or higher serum concentrations (see 7 WARNINGS AND PRECAUTIONS).

Conversion from DEPAKENE® to EPIVAL®:

EPIVAL® (divalproex sodium) enteric-coated tablets dissociate to the valproate ion in the gastrointestinal tract. EPIVAL® tablets are uniformly and reliably absorbed, however, because of the enteric coating, absorption is delayed by an hour when compared to DEPAKENE®.

In patients previously receiving DEPAKENE® therapy, EPIVAL® should be initiated at the same daily dosing schedule. After the patient is stabilized on EPIVAL®, a dosing schedule of two or three times a day may be chosen in selected patients. Changes in the dosing of EPIVAL® or concomitant medications should be accompanied by increased monitoring of plasma concentrations of valproate and other medications, as well as the patient's clinical status.

Female children, women of childbearing potential and pregnant women:

Valproic Acid treatment must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

In the exceptional circumstance when valproate is the only treatment option during pregnancy in epileptic women, valproic acid should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. During pregnancy, the daily dose immediate release formulations should be divided into at least two single doses.

Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. Therefore monotherapy should be favoured when possible.

4.4 Administration

DEPAKENE® may be taken with or without food.

Patients who experience gastrointestinal irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. Co-administration of DEPAKENE® with food should cause no clinical problems in the management of patients with epilepsy.

4.5 Missed Dose

The patient should not abruptly stop taking their medication because of the risk of increasing their seizures.

If the patient misses a dose, they should not try to make up for it by doubling up on their next dose. They should take their next regularly scheduled dose and try not to miss any more doses.

5 OVERDOSAGE

Overdosage with DEPAKENE® (valproic acid) may result in somnolence, muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, hypotension, metabolic acidosis, heart block, deep coma and circulatory collapse/shock. Cases of intracranial hypertension related to cerebral oedema have been reported. 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 a reported case of overdosage with DEPAKENE® after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram (EEG) recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

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. As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	oral solution / 250 mg/5 mL	artificial cherry flavor, FD&C Red No. 40, glycerin, hydrochloric acid*, methylparaben**, propylparaben**, purified water, sodium hydroxide*, sorbitol, sucrose***, vanillin.

* hydrochloric acid and sodium hydroxide are used for pH adjustment.

** methylparaben and propylparaben may cause allergic reactions (possibly delayed).

*** DEPAKENE® oral solution contains 3 g of sucrose per 5 mL dose.

DEPAKENE® (valproic acid) oral solution is a red-coloured liquid containing the equivalent of 250 mg valproic acid, as the sodium salt, per 5 mL (50 mg/mL) supplied in 240 mL bottles.

7 WARNINGS AND PRECAUTIONS

Pregnancy Prevention Program:

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for major congenital malformations and neurodevelopmental disorders (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

DEPAKENE ® is contraindicated in the treatment of epilepsy during pregnancy unless no other suitable alternative can be found (see 2 CONTRAINDICATIONS).

- **Conditions of Pregnancy Prevention Program**

  The prescriber must ensure that:

  - individual circumstances are evaluated in each case and discussed with the patient. This is to guarantee the patient's engagement and understanding of the therapeutic options together with the risks and the measures needed to mitigate the risks.
  - the potential for pregnancy is assessed for all female patients.
  - the patient understands and acknowledges the risks of major congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
  - the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment with valproate as deemed necessary by the patient or treating physician. It is recommended that testing be done following a missed period, the failure of the selected method of contraception or as needed.
  - the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective and reliable contraception (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, Contraception), without interruption during the entire duration of treatment with valproate.
  - the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.
  - the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
  - the patient understands the need to **urgently** consult her physician if she becomes pregnant.
  - the patient has received the patient guide.
  - the patient has acknowledged that she has understood the risks associated with valproate use and necessary precautions to be taken during treatment (Annual Risk Acknowledgement Form).

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

  Pharmacist or other health care professional must ensure that:

  - the patient card is provided with every valproate dispensing and that the patients understand its content.
  - the patient is advised not to stop valproate treatment and to immediately contact a specialist in case of planned or suspected pregnancy.

- **Female Children**

- The prescriber must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child receiving valproate treatment experiences menarche.
- The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of major congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- In patients who have experienced menarche, the prescribing specialist must reassess the need for continuing valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the patient must use at least one effective and reliable method of contraception (preferably a user-independent form) or two complementary forms of contraception. Patient must also meet all other conditions of the Pregnancy Prevention Program. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

- **Pregnancy Test**

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

- **Contraception**

Women of childbearing potential who are prescribed valproate must use at least one form of effective and reliable contraception (preferably a user-independent form) or two complementary forms of contraception without interruption during the entire duration of treatment. 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. 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 and reliable contraception. At least 1 of these forms of contraception must be a primary form, which include tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and topical/injectable/insertable hormonal birth control products. Secondary or barrier forms of contraception include diaphragms, latex condoms, and cervical caps. A diaphragm and cervical cap must each be used with a spermicide.

Estrogen-containing hormonal contraceptives may result in decreased serum valproate levels and potentially lower valproate efficacy. Patients taking DEPAKENE® should be advised not to start or stop such products without consulting their physician. Prescribers should monitor valproate serum levels and clinical response when initiating or discontinuing estrogen-containing products (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Female children/Women of childbearing potential/Pregnancy and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3).

- **Annual Treatment Reviews by a Specialist**

The specialist should, at least annually, review whether valproate is the most suitable treatment option for the patient. The specialist should discuss the Annual Risk Acknowledgement Form, at initiation of treatment and during each annual review and ensure that the patient has understood its content.

- **Pregnancy Planning**

A specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women). If switching is not possible, the woman should receive further counselling regarding valproate risks for the unborn child to support her informed decision making regarding family planning.

- **In Case of Pregnancy**

If a woman receiving valproate treatment becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. Patients with ~~a~~ valproate exposed pregnancy and their partners should be referred to a specialist experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Where available, prenatal diagnostic testing to detect neural tube and other defects, should be offered to pregnant women receiving DEPAKENE® treatment.

- **Educational Materials**

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce related warnings and provide guidance regarding use of valproate in women of childbearing potential and details of the Pregnancy Prevention Program. A patient guide and patient card should be provided to <u>all women of childbearing potential</u> receiving valproate treatment.

A Risk Acknowledgement Form must be used at the time of treatment initiation and during each annual review of valproate treatment by the specialist, and when a woman is planning a pregnancy or has become pregnant. Specialist should reassess benefits and risks of valproate treatment and determine if the patient should continue to receive valproate therapy.

General:

Antiepileptic drugs (AEDs), including DEPAKENE® (valproic acid), should be withdrawn gradually to minimize the potential for seizures or increased seizure frequency (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

- **Interaction with Carbapenem Antibiotics**

Carbapenem antibiotics (ertapenem, imipenem, meropenem, doripenem) can reduce serum valproic acid concentrations to sub-therapeutic levels. This can result in loss of seizure control in epileptic patients or loss of efficacy in non-epileptics. In some cases of co-administration in epileptic patients, breakthrough seizures have occurred. Increasing valproic acid dose may not be sufficient to overcome this interaction. If co-administration is essential, serum valproic acid concentrations should be monitored daily after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3).

- **Effects of Valproate on HIV and CMV Viruses Replication**

  There are *in vitro* studies that suggest valproate stimulates the replication of the HIV (Human Immunodeficiency Virus) and CMV (Cytomegalovirus) viruses under certain experimental conditions. The clinical relevance of these *in vitro* data is unknown. 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.

Carcinogenesis and Mutagenesis:

Long-term animal toxicity studies indicate that valproic acid is a weak carcinogen or promoter in rats and mice. The significance of these findings for humans is unknown at present (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and 16 NON-CLINICAL TOXICOLOGY, Genotoxicity).

Driving and Operating Machinery:

DEPAKENE® may produce central nervous system (CNS) depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Endocrine and Metabolism:

- **Urea Cycle Disorders**

  DEPAKENE® (valproic acid) is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of DEPAKENE® in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to initiation of DEPAKENE®, evaluation for urea cycle disorders (UCD) should be considered in the following patients:

  - 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;
  - those with signs and symptoms of UCD, for example, cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen (BUN), protein avoidance;
  - those with a family history of UCD or a family history of unexplained infant deaths (particularly males);

- those with other signs or symptoms of UCD. Patients receiving DEPAKENE® who develop symptoms of unexplained hyperammonemic encephalopathy should receive prompt treatment (including discontinuation of DEPAKENE®) and be evaluated for underlying urea cycle disorders (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and Encephalophathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin).

- **Hyperammonemia**

  Hyperammonemia has been reported in association with DEPAKENE® 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 as a possible cause and serum ammonia level should be measured. Hyperammonemia should also be considered in patients with hypothermia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothermia). If serum ammonia is increased, DEPAKENE® should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and Encephalopathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin).

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

- **Hyperammonemia and Encephalopathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin**

  Concomitant administration of topiramate, acetazolamide, phenobarbital or phenytoin and DEPAKENE® 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 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, 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, acetazolamide, phenobarbital or phenytoin 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, acetazolamide, phenobarbital or phenytoin and DEPAKENE® may exacerbate existing defects or unmask deficiencies in susceptible persons (see 2 CONTRAINDICATIONS **and** 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders **and** 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia**).**

- **Hypothermia**

  Hypothermia, defined as an unintentional drop in core body temperature to < 35°C (95°F), has been reported in association with DEPAKENE® both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with DEPAKENE® after starting topiramate treatment or after increasing the daily dose of topiramate (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3). Hypothermia 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. Consideration should be given to stopping DEPAKENE® in patients who develop hypothermia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia).

- **Sucrose or Fructose Intolerance**

  DEPAKENE® oral solution contains sucrose, which may be harmful to the teeth. Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

  When prescribing to diabetic patients, the sucrose content should be taken into account (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

  DEPAKENE® oral solution contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Hematologic:

- **Thrombocytopenia**

  Because of reports of thrombocytopenia and inhibition of the second 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. It is recommended that patients receiving DEPAKENE® be monitored for platelet count and coagulation parameters prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE® dosage or withdrawal of therapy (see also 7 WARNINGS AND PRECAUTIONS, Hematologic, Dosing-related Adverse Reactions: Thrombocytopenia).

  In addition, the findings from a crossover clinical trial conducted with EPIVAL® ER (divalproex sodium extended-release tablets), in 44 epilepsy patients, indicate that the frequency of treatment-emergent mild thrombocytopenia (platelet count between 100 to150 x 10^9/L) was significantly higher after 12 weeks of treatment with EPIVAL® ER than after 12 weeks of treatment with EPIVAL® (7 versus 3 low counts, respectively).

- **Dosing-related Adverse Reactions: Thrombocytopenia**

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

Hepatic/Biliary/Pancreatic:

- **Serious or Fatal Hepatotoxicity**

  Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE® and its derivatives. These incidences usually have occurred during the first 6 months of treatment with DEPAKENE®. Caution should be observed when administering DEPAKENE® 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.

  Experience has indicated that children under the age of 2 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. The risk in this age group decreased considerably in patients receiving DEPAKENE® as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only DEPAKENE®. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patients. No deaths have been reported in patients over 10 years of age who received DEPAKENE® alone.

  If DEPAKENE® is to be used in children 2 years old or younger, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risk (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

  Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia, and vomiting. Patients should be monitored closely for appearance of these symptoms. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking DEPAKENE®.

  Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 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.

  In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decreases in concentration and serum ammonia for increases in concentration. If changes occur, DEPAKENE® should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

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. The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may increase with increasing dose. The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects (see 2 CONTRAINDICATIONS).

- **Patients with 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 2 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. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders.

  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 liver function test monitoring.

  In the presence of significant hepatic dysfunction, suspected or apparent, DEPAKENE® should be discontinued and alternative therapy initiated. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

- **Pancreatitis**

  Cases of life-threatening pancreatitis have been reported in both children and adults receiving DEPAKENE®. Some of the cases have been described as hemorrhagic with a 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 DEPAKENE®. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2,416 patients, representing 1,044 patient-years experience. 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, DEPAKENE® should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Monitoring and Laboratory Tests:

Since DEPAKENE® 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 and whenever enzyme-inducing drugs are introduced or withdrawn (see 9 DRUG INTERACTIONS).

- **Monitoring Valproate Concentrations**

  Protein binding of valproate is reduced in the elderly, in patients with renal impairment, and in the presence of other drugs (e.g., acetylsalicylic acid). Accordingly, measurements of plasma levels of valproate may be misleading in these patients, as actual drug exposure may be higher than measured values (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics; 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia; 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3).

Musculoskeletal/Rhabdomyolysis:

Rare cases of rhabdomyolysis, independent of neuroleptic malignant syndrome, have been reported to occur in patients treated with DEPAKENE. Cases have included renal failure and fatalities.

Patients should be carefully monitored for muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever or tea-coloured urine. Blood creatine phosphokinase (CPK) levels should be assessed in patients experiencing these symptoms and DEPAKENE therapy should be discontinued if markedly elevated CPK levels are measured or if the patient develops signs and symptoms indicative of rhabdomyolysis.

Caution should be exercised in prescribing DEPAKENE to patients with predisposing/risk factors, including: prior history of muscular disorders such as CPT II deficiency (carnitine palmitoyltransferase type II); uncontrolled hypothyroidism; hepatic or renal impairment; concomitant medications that are known to be associated with rhabdomyolysis (e.g., statins, antipsychotics, diuretics, some antidepressants).

Neurologic:

- **Brain Atrophy**

  There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy with neurological symptoms, in children, adults, and the elderly, receiving valproate therapy. A temporal relationship between valproate therapy and the development of cerebral atrophy and associated signs and symptoms was also demonstrated. In some cases, symptoms disappeared after valproate discontinuation but patients recovered with permanent sequelae (see 8 ADVERSE REACTIONS). 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.

- **Neurological Problems in Children after *in utero* Exposure to Valproate**

  Reports of cerebral atrophy with various forms of neurological problems including cognitive developmental delays, psychomotor impairment and decreased IQ scores have been reported in children who were exposed *in utero* to valproate products (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

- **Aggravated convulsions**

  As with other antiepileptic drugs, some patients may experience a worsening of convulsion frequency and severity, or the onset of new types of convulsions with valproate. Postmarketing reports of serious aggravated seizures have been reported for valproic acid including status epilepticus and death. In case of aggravated convulsions, patients should be advised to consult their physician immediately.

Psychiatric:

- **Suicidal Behaviour and Ideation**

  Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

  All patients treated with antiepileptic drugs (AEDs), irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

  An FDA meta-analysis of randomized placebo controlled trials, in which AEDs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

  There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (AED or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (AED or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more AED). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on AEDs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (AED or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking AEDs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct AED treatment in both arms.

- **Behavioural Disorders**

  There have been postmarketing reports of behavioural disorders, including aggression, agitation, abnormal behaviour, disturbance in attention, and learning disorders. Although patients of all ages were affected, including the elderly and those exposed to valproate products *in utero*, a large number of cases were reported in children. There was no clear trend with respect to valproate dose. In some cases, patients improved or recovered following valproate discontinuation.

Renal:

- **Renal Impairment**

Renal impairment is associated with an increase in the unbound fraction of valproate. In several studies, the unbound fraction of valproate in plasma from renally impaired patients was approximately double that for subjects with normal renal function. Accordingly, monitoring of total concentrations in patients with renal impairment may be misleading since free concentrations may be substantially elevated whereas total concentrations may appear to be normal. Hemodialysis in renally impaired patients may remove up to 20% of the circulating valproate.

Reproductive Health: Female and Male Potential:

- **Fertility**

Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using valproate.

The effect of DEPAKENE® on the development of the testis in humans is unknown (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, Fertility for results in animal studies). Valproate administration has been associated with reduced semen quality in humans and thus may impair fertility in men (see 8 ADVERSE REACTIONS). Discontinuation or dose reduction of valproate may be associated with the improvement of impaired male fertility markers and could be linked with successful conception, as observed in some case reports.

Sensitivity/Resistance:

- **Multi-organ Hypersensitivity Reaction**

Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of DEPAKENE® 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, hepato-renal 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, DEPAKENE® 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.

Skin:

- **Serious Skin Reactions**

The dose of lamotrigine should be reduced when co-administered with DEPAKENE®. Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and DEPAKENE® administration (see Lamotrigine Product Monograph for details on lamotrigine dosing with concomitant DEPAKENE® administration).

7.1 Special Populations

7.1.1 Pregnant Women

Female children/Women of childbearing potential/Pregnancy:

DEPAKENE® can cause fetal harm when administered to pregnant women. DEPAKENE® use during pregnancy is associated with an increased risk of severe birth defects such as neural tube defects (e.g., *spina-bifida*), craniofacial defects, cleft palate, cardiovascular malformations (e.g., atrial septal defect), hypospadias, etc. In some cases, fatal outcomes have been reported (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Birth Defects**).**

DEPAKENE® should not be used to treat female children, women of childbearing potential, and pregnant women unless alternative treatments are ineffective or not tolerated. The benefit and risk should be carefully re-assessed, at least annually, at puberty, and urgently when a woman of childbearing potential plans a pregnancy or becomes pregnant. Since some of the congenital malformations occur in the first trimester of pregnancy before many women know that they are pregnant, all women of childbearing potential should be informed of the potential hazard to the fetus from exposure to DEPAKENE®. Women of childbearing potential must use at least one effective and reliable method of contraception (preferably a user-independent form) or two complementary forms of contraception during treatment with DEPAKENE® (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

Valproate does not reduce the efficacy of hormonal contraceptives. However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially increased seizure frequency. Patients taking DEPAKENE should be advised not to start or stop estrogen-containing products (including oral contraceptives) without consulting their physician. Prescribers should monitor valproate plasma levels and clinical response (seizure control) when initiating, or discontinuing estrogen-containing products (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3).

Pregnancy Exposure Risk Related to Valproate:

Both valproate adjunctive and monotherapy are frequently associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate may also be associated with a greater risk of congenital malformations than valproate monotherapy.

Tests to detect neural tube and other defects using current accepted procedures should be considered as part of routine prenatal care in pregnant women receiving DEPAKENE®.

- **Pregnancy Registry**

  Pregnant patients taking DEPAKENE® should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the following website: http://www.aedpregnancyregistry.org/.

- **Pregnancy Prevention Program**

Information on the Pregnancy Prevention Program including educational resources, as well as to report suspected embryo-fetal exposure to valproate, can be found at the following website: www.depakene.ca.

If a woman is planning a pregnancy:

A specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

- **Pregnant Women**

  Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

  If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

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

  - Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day;
  - Consider the use of a prolonged release formulation of DEPAKENE®, which may be preferable to immediate-release formulations in order to avoid high peak plasma concentrations.

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

  Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Program are fulfilled (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

- **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 can be fatal. However, this syndrome must be distinguished from the decrease of vitamin-K factors induced by phenobarbital and other enzymes. Therefore, in neonates, platelet count, plasma levels of fibrinogen, coagulation tests and coagulation factors should be investigated.

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

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (symptoms include: agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur, in the days following birth, in neonates whose mothers have taken valproate during the last trimester of pregnancy.

- **Birth Defects**

  Summary:

  - Valproate can cause fetal harm when administered to pregnant women;
  - Maternal valproate use can cause neural tube defects (e.g., *spina-bifida*) and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations such as atrial septal defect, hypospadias, limb malformations such as club foot and polydactyly);
  - The rate of congenital malformations among babies born to mothers using valproate

    monotherapy is about four times higher than the rate among babies born to epileptic mothers using other anti-epileptic monotherapies. This risk is dose-dependent but a threshold dose below which no risk exists cannot be established.

  Data:

  Data described below were gained almost exclusively from women who received valproate to treat epilepsy. Data from Pregnancy Registries indicate an increased risk of congenital anomalies in infants exposed to DEPAKENE® monotherapy during the first trimester of pregnancy as compared to other antiepileptic drugs. Based on Pregnancy Registry data and the United States Centers for Disease Control (CDC), the estimated risk of valproate-exposed women having children with *spina-bifida*, oral clefts, neural tube defects, and hypospadias is approximately 1 to 2% as compared to the risk of *spina-bifida* in the general population which is about 0.06 to 0.07%.

  In a study using NAAED Pregnancy Registry data, 16 cases of major malformations following prenatal valproate exposure were reported among offspring of 149 enrolled women who used valproate during pregnancy. Three of the 16 cases were neural tube defects; the remaining cases included craniofacial defects, cardiovascular malformations and malformations of varying severity involving other body systems. The NAAED Pregnancy Registry has reported a major malformation rate of 10.7% in the offspring of women exposed to valproate monotherapy during pregnancy (average daily dose: 1000 mg; range: 500 – 2000 mg/day) as compared to major malformation rate of 2.9% among 1,048 epileptic women who received any other antiepileptic drug monotherapy during pregnancy. These data show a four-fold increased risk for any major malformation following

valproate exposure *in utero* compared to the risk following exposure *in utero* to any other antiepileptic drug monotherapy.

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate 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.

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 various therapeutic doses of valproate, during any trimester of pregnancy, can also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. All cases to date were reported as serious and included both unilateral and bilateral deafness or hearing impairment. When outcomes were reported, the majority of the cases remained unresolved. In 58% of the cases, the age of diagnosis of hearing impairment or deafness was within the first 4 weeks following birth. Monitoring of signs and symptoms of ototoxicity is recommended.

- **Risk of Neurological Problems from *in utero* Exposure**

  Cerebral Atrophy:

  Exposure *in utero* to valproate products has been associated with cerebral atrophy with varying degrees/manifestations of neurological compromise, including developmental delays and psychomotor impairment (see 8 ADVERSE REACTIONS and 7 WARNINGS AND PRECAUTIONS, Neurologic, Brain Atrophy).

- **Developmental Delays**

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

  Studies in preschool children exposed to valproate *in utero* 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.

- **Decreased IQ**

  Valproate can cause decreased Intelligence Quotient (IQ) scores in children following *in utero* exposure. Although it is not known exactly when during pregnancy cognitive effects in valproate-exposed children occur, there is a risk that it may occur early in pregnancy.

  IQ measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics. There is evidence in

children exposed to valproate that the risk of intellectual impairment may be independent of maternal IQ.

- **Autism and/or Autism Spectrum Disorders**

  There are limited data on long term outcomes. A population-based study was conducted in Denmark based on various national patient registries including the Danish Medical Birth Register. This study showed that children exposed to valproate *in utero* are at increased risk of autism spectrum disorders (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the children of unexposed epileptic women in the same study.

- **Attention Deficit Hyperactivity Disorder (ADHD)**

  Another population-based study in Denmark was also conducted based on various national patient registries including the Danish Medical Birth Register. This study showed that children exposed to valproate *in utero* are at increased risk of developing ADHD compared to the children of unexposed epileptic women in the same study. Data show that 8.4% of the children exposed to valproate *in utero* were diagnosed with ADHD compared to 3.2% of unexposed children in the same study.

  Although available studies have some limitations, the weight of the evidence supports a causal association between valproate exposure *in utero* and subsequent adverse effects on neurodevelopment, including increases in the occurrence of autism spectrum disorders.

- **Coagulation Abnormalities**

  There have been reported postmarketing cases of coagulation abnormalities in patients of all ages receiving valproate therapy. These include thrombocytopenia, hypofibrinogenemia, and/or decrease in other coagulation factors, which can lead to bleeding and other complications, especially in the cases of decrease in factors VII, VIII and XIII. These abnormalities may not necessarily be dose-dependent. Some of the hemorrhage manifestations may include mucosal bleeding (e.g., menorrhagia, epistaxis, hematuria, melena), easy-bruising, soft-tissue hematoma, hemarthrosis, and intracranial hemorrhage. Caution should be taken in patients taking valproate and anticoagulants and in cases of injury or surgery to avoid life-threatening or fatal bleeding (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia).

  Pregnant women taking DEPAKENE® may also develop coagulation abnormalities, which may result in hemorrhagic complications in the neonate including death (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia). If DEPAKENE® is used in pregnancy, the coagulation parameters should be monitored carefully.

- **Hepatic Failure**

  Hepatic failure, resulting in the death of a newborn and of an infant has been reported following the use of valproate during pregnancy.

- **Hypoglycemia**

  Serious postmarketing reports of hypoglycemia have been received for neonates whose mothers received DEPAKENE® treatment during pregnancy. In most cases, DEPAKENE® was the only reported antiepileptic drug (AED). Most of these neonates also displayed other congenital anomalies including hypospadias, complex facial dysmorphism, limb anomalies, severe cardiac anomalies, etc. Therefore, if a decision has been made to use DEPAKENE® during pregnancy, or if

the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

- **Thyroid Gland Abnormalities**

  Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy. There have also been reported cases of increased serum thyroid stimulating hormone or decreased serum thyroxine levels in children receiving valproate therapy. In addition, there have been reported cases of hypothyroidism and hyperthyroidism in adults and children receiving valproate monotherapy.

- **Teratogenicity in Animals**

  Animal studies have demonstrated valproic acid induced teratogenicity (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology), and studies in human females have demonstrated placental transfer of the drug. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 mcg/mL (2.3 times the upper limit of the human therapeutic range for epilepsy) during susceptible periods of embryonic development.

  Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m^2 basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 mcg/mL or greater (3.4 times the upper limit of the human therapeutic range for epilepsy or greater). Behavioural deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy.

  An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following

  administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 mcg/mL (2.8 times the upper limit of the human therapeutic range for epilepsy).

7.1.2 Breast-feeding

DEPAKENE® is secreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of maternal serum concentrations. Women should not breastfeed during DEPAKENE® treatment and for one month after discontinuation of the drug. Based on literature and clinical experience, hematological disorders have been shown in breastfed newborns/infants of treated women.

7.1.3 Pediatrics

Experience has indicated that children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity). 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 (see 2 CONTRAINDICATIONS).

Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

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. (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Patients with Mitochondrial Disease).

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproate concentrations. The variability in free fraction limits the clinical usefulness of monitoring total serum valproate concentrations. Interpretation of valproate concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

7.1.4 Geriatrics

Alterations in the kinetics of unbound valproate in the elderly (≥ 65 years of age) indicate that the initial dosage should be reduced in this population (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

The safety and efficacy of DEPAKENE® in elderly patients with epilepsy has not been evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience with DEPAKENE® in this population.

A study of elderly patients revealed valproate-related somnolence and discontinuation of DEPAKENE® for this adverse event (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Geriatrics, Somnolence in the Elderly). The starting dose should be reduced in elderly patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see 4 DOSAGE AND ADMINISTRATION).

- **Somnolence in the elderly**

  In a group of elderly patients (mean age 83 years old, n = 172), DEPAKENE® doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. Compared to placebo a significantly higher number of valproate-treated patients had somnolence, and although not statistically significant, a higher number of valproate-treated patients experienced dehydration. Discontinuations for somnolence were also significantly higher in valproate-treated patients compared to placebo. In approximately one-half of the patients with somnolence, there was also associated reduced nutritional intake and weight loss. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid intake, dehydration, somnolence, urinary tract infection and other adverse events. Dose reductions or discontinuation of DEPAKENE® should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since DEPAKENE® (valproic acid) has usually been used with other antiepileptics, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to DEPAKENE® alone or to the combination of drugs.

Adverse events that have been reported with DEPAKENE® from epilepsy trials, spontaneous reports, and other sources are listed below by system organ class.

Blood and Lymphatic System Disorders:	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 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia). Relative lymphocytosis, macrocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia, including macrocytic with or without folate deficiency, aplastic anemia, pancytopenia, bone marrow suppression, agranulocytosis and acute intermittent porphyria have been reported.
Cardiac Disorders:	Bradycardia
Ear and Labyrinth Disorders:	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.

Gastrointestinal Disorders:	Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, constipation and gingival disorder (mainly gingival hyperplasia) have also been reported. There have been reports of acute pancreatitis, including rare fatal cases, occurring in association with DEPAKENE® therapy (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis). Parotid gland swelling has also been reported in patients receiving DEPAKENE®.
General Disorders and Administration Site Conditions:	Edema of the extremities, fever and hypothermia
Hepatobiliary Disorders:	Minor elevations of transaminases [e.g., serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT)] and lactate dehydrogenase (LDH) are frequent and appear to be dose-related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity).
Immune System Disorder:	Allergic reaction, anaphylaxis
Infections and Infestations:	Pneumonia and otitis media
Investigations:	Abnormal thyroid function tests (including both hyperthyroidism and hypothyroidism) (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Thyroid Gland Abnormalities and 9 DRUG INTERACTIONS, 9.7 Drug-Laboratory Test Interactions).
Metabolism and Nutrition Disorders:	Hyperammonemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia), hyponatremia, biotin deficiency/biotinidase deficiency and inappropriate antidiuretic hormone (ADH) secretion. There have been rare reports of Fanconi syndrome (proximal renal tubular dysfunction) occurring primarily in children. Decreased carnitine concentrations have been reported although the clinical relevance is undetermined. Hyperglycinemia has been reported and associated with a fatal outcome in patient with pre-existing nonketotic hyperglycinemia. Anorexia with some weight loss and increased appetite with some weight gain have also been reported. Obesity has been reported in post-marketing experience.

Musculoskeletal and Connective Tissue Disorders:	Weakness, rhabdomyolysis and bone pain have been reported (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal/Rhabdomyolysis). Reports have been received of decreased bone mass, potentially leading to osteoporosis and osteopenia, during long-term therapy with some anticonvulsant medications, including DEPAKENE®. Some studies have indicated that supplemental calcium and vitamin D may be of benefit to patients who are on chronic DEPAKENE® therapy. A lupus erythematosus-like syndrome has been reported rarely.
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps):	Myelodysplastic syndrome in both adults and children (all children were on valproate monotherapy). In some cases in adults and/or children, myelodysplastic syndrome was reversible upon valproate discontinuation.
Nervous System Disorders:	Sedative effects have been noted in patients receiving DEPAKENE® alone but occur most often in patients on combination therapy. Sedation usually disappears upon reduction of other anti-epileptic medication. Hallucination, ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor (may be dose-related), confusion, dysarthria, dizziness, 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 been reported in patients receiving DEPAKENE® alone or in conjunction with phenobarbital. Encephalopathy, with or without fever or hyperammonemia, has been reported without evidence of hepatic dysfunction or inappropriate valproate plasma levels. Most patients recovered, with noted improvement of symptoms, upon discontinuation of the drug. There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy associated with the use of valproate products. In some cases the patients recovered with permanent sequelae (see 7 WARNINGS AND PRECAUTIONS, Neurologic, 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 (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women). Congenital malformations and developmental disorders have also been reported. Aggravated convulsions (increase in number of seizures or appearance of new seizure type or worsening of seizures) have been reported in patients with epilepsy treated with valproate monotherapy.

Psychiatric Disorders:	Emotional upset, depression, psychosis, aggression, psychomotor hyperactivity, hostility, agitation, disturbance in attention, abnormal behaviour, learning disorder and behavioural deterioration. (see 7 WARNINGS AND PRECAUTIONS, Psychiatric).
Renal and Urinary Disorders:	Enuresis, urinary incontinence, acute renal failure, tubulointerstitial nephritis and urinary tract infection.
Reproductive System and Breast Disorders:	There have been reports of irregular menses, secondary amenorrhea, breast enlargement and galactorrhea in patients receiving DEPAKENE®. Hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased). There have been post-marketing reports of aspermia, azoospermia, decreased sperm count, decreased spermatozoa motility, abnormal spermatozoa morphology and ultimately infertility in male patients who received sodium valproate products (effects may be improved by dose reduction or discontinuation). There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.
Respiratory, Thoracic and Mediastinal Disorders:	Increased cough, pleural effusion
Skin and Subcutaneous Tissue Disorders:	Transient and/or dose related alopecia (hair loss), hair disorders (such as hair texture abnormal, hair colour changes, hair growth abnormal), have been observed. Skin rash, photosensitivity, generalized pruritus, erythema multiforme, Stevens-Johnson syndrome, and petechiae have rarely been noted. Rare cases of Toxic Epidermal Necrolysis (TEN) have been reported including a fatal case of a 6 month old infant taking DEPAKENE® and several other concomitant medications. An additional case of Toxic Epidermal Necrolysis 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 DEPAKENE® (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3). Cutaneous vasculitis has also been reported. Nail and nail bed disorders have also been reported in post-marketing experience.

8.5 Post-Market Adverse Reactions

Adverse Events in Elderly Patients:

In elderly patients (above 65 years of age), there were more frequent reports of accidental injury, infection, pain, and to a lesser degree, somnolence and tremor, when compared to patients 18 to 65 years of age. Somnolence and tremor tended to be associated with the discontinuation of DEPAKENE®.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Rare cases of coma have been reported in patients receiving DEPAKENE® alone or in conjunction with phenobarbital (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3).
- Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and DEPAKENE® administration (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 3).

9.2 Drug Interactions Overview

DEPAKENE® has been found to be a weak inhibitor of some P_{450} isozymes, epoxide hydrase, and glucuronyl transferases.

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronyl transferases (such as ritonavir; see **Table 3** below), may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on DEPAKENE® 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 P_{450} isozymes, such as antidepressants, may be expected to have little effect on valproate clearance because cytochrome P_{450} microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

The concomitant administration of DEPAKENE® with drugs that exhibit extensive protein binding (e.g., acetylsalicylic acid, carbamazepine, dicumarol, warfarin, tolbutamide, and phenytoin) may result in alteration of serum drug levels.

Since DEPAKENE® 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 and whenever enzyme-inducing drugs are introduced or withdrawn.

9.3 Drug-Behavioural Interactions

Refer to 7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery for details.

9.4 Drug-Drug Interactions

Table 3 provides information about the potential influence of several commonly prescribed medications on DEPAKENE® pharmacokinetics as well as the potential influence of DEPAKENE® on the pharmacokinetics and pharmacodynamics of several commonly prescribed medications. The list is not exhaustive nor could it be, since new interactions are continuously being reported. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated). Please note that drugs may be listed under specific name, family or pharmacologic class. Reading the entire section is recommended.

Table 3 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetaminophen	CT	↔ acetaminophen	DEPAKENE® had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.
Acetazolamide			Concomitant administration of valproate and acetazolamide has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).
Acetylsalicylic Acid	CT	↑ valproate	A study involving the co-administration of acetylsalicylic acid at antipyretic doses (11 to 16 mg/kg) with DEPAKENE® to pediatric patients (n = 6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of acetylsalicylic acid compared to DEPAKENE® alone. The beta-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 DEPAKENE® alone to 8.3% in the presence of acetylsalicylic acid. Caution should be observed when DEPAKENE® is administered with drugs affecting coagulation, [e.g., acetylsalicylic acid and warfarin] (see 8 ADVERSE REACTIONS).
Alcohol	T	No pharmacokinetic (PK) interaction	DEPAKENE® may potentiate the CNS depressant action of alcohol.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Amitriptyline / Nortriptyline	CT	In general: ↓ amitriptyline ↓ nortriptyline Rarely: ↑ amitriptyline ↑ nortriptyline	Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received DEPAKENE® (500 mg twice daily) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare post-marketing reports of concurrent use of DEPAKENE® and amitriptyline resulting in an increased amitriptyline and nortriptyline levels have been received. Concurrent use of DEPAKENE® and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking DEPAKENE® concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of DEPAKENE®.
Antacids	CT	↔ valproate	A study involving the co-administration of DEPAKENE® 500 mg with commonly administered antacids (Maalox®, Trisogel, and Titralac™ - 160 milliequivalent doses) did not reveal any effect on the extent of absorption of DEPAKENE®.
Other - Antipsychotics, Monoamine Oxidase Inhibitors (MAOIs) and Tricyclic Antidepressants			In addition to enhancing CNS depression when used concurrently with DEPAKENE®, antipsychotics, tricyclic antidepressants and MAOIs may lower the seizure threshold. Dosage adjustments may be necessary to control seizures.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Antiretroviral agents - Ritonavir - Lopinavir - Zidovudine - Lamivudine	C	↓ valproate	Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when co-administered with valproate. Reduction of therapeutic effect of valproate was observed in a patient with bipolar disorder with the initiation of HIV treatment with lopinavir/ritonavir, zidovudine, and lamivudine.
	CT	↑ zidovudine	In 6 patients who were seropositive for HIV, the clearance of zidovudine (100 mg every 8 hours) was decreased by 38% after administration of valproate (250 or 500 mg every 8 hours); the half-life of zidovudine was unaffected.
Benzodiazepines			DEPAKENE® may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations. (see Table 3. Diazepam and Lorazepam).
Carbamazepine / carbamazepine-10,11-epoxide	CT	↓ CBZ ↑ CBZ-E	Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of DEPAKENE® and CBZ to epileptic patients.
		↓ valproate	Concomitant use of CBZ with DEPAKENE® may result in decreased serum concentrations and half-life of valproate due to increased metabolism induced by hepatic microsomal enzyme activity. Monitoring of serum concentrations is recommended when either medication is added to or withdrawn from an existing regimen. Changes in the serum concentration of the CBZ-E metabolite of CBZ, however, will not be detected by routine serum CBZ assay.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Carbapenem Antibiotics		↓ valproate	Carbapenem antibiotics (ertapenem, imipenem, meropenem, doripenem) can reduce serum valproic acid concentrations to sub-therapeutic levels. This can result in loss of seizure control in epileptic patients or loss of efficacy in non-epileptics. In some cases of co-administration in epileptic patients breakthrough seizures have occurred. Increasing valproic acid dose may not be sufficient to overcome this interaction. If co-administration is essential, serum valproic acid concentrations should be monitored daily. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates (see 7 WARNINGS AND PRECAUTIONS, General, Interaction with Carbapenem Antibiotics).
Chlorpromazine	CT	↑ valproate	A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving DEPAKENE® (200 mg twice daily) revealed a 15% increase in trough plasma levels of valproate. This increase is not considered clinically important.
Cholestyramine		↓ valproate	Cholestyramine may lead to a decrease in plasma levels of valproate when co-administered.
Cimetidine	T	↑ valproate	Cimetidine may decrease the clearance and increase the half-life of DEPAKENE® by altering its metabolism. In patients receiving DEPAKENE®, serum valproic acid levels should be monitored when treatment with cimetidine is instituted, increased, decreased, or discontinued. The DEPAKENE® dose should be adjusted accordingly.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Clonazepam	T	No PK interaction	The concomitant use of DEPAKENE® and clonazepam may induce absence status in patients with a history of absence type seizures.
Clozapine	CT	No interaction	In psychotic patients (n = 11), no interaction was observed when DEPAKENE® was co-administered with clozapine.
Diazepam	CT	↑ diazepam	Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of DEPAKENE® (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.
Estrogen-containing products	C CT T	↓ valproate	Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially increased seizure frequency. Prescribers should monitor valproate plasma levels and clinical response (seizure control), when adding, or discontinuing estrogen-containing products. Valproate does not affect the metabolism/clearance of hormonal contraceptives.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Ethosuximide	CT	↑ ethosuximide	Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with DEPAKENE® (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 DEPAKENE® and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.
Felbamate	CT	↑ valproate	A study involving the co-administration of 1,200 mg/day of felbamate with DEPAKENE® to patients with epilepsy (n = 10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to DEPAKENE® alone. Increasing the felbamate dose to 2,400 mg/day increased the mean valproate peak concentration to 133 mcg/mL (another 16% increase). A decrease in DEPAKENE® dosage may be necessary when felbamate therapy is initiated. Lower doses of DEPAKENE® may be necessary when used concomitantly with felbamate.
Haloperidol	CT	↔ valproate	A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving DEPAKENE® (200 mg twice daily) revealed no significant changes in valproate trough plasma levels.
Lamotrigine	CT	↑ lamotrigine ↓ valproate	The effects of DEPAKENE® on lamotrigine were investigated in 6 healthy male subjects. Each subject received a single oral dose of lamotrigine alone and with DEPAKENE® 200 mg every 8 hours for 6 doses starting 1 hour before the lamotrigine dose was given. DEPAKENE® administration reduced

Proper/Common name	Source of Evidence	Effect	Clinical comment
			the total clearance of lamotrigine by 21% and increased the plasma elimination half-life from 37.4 hours to 48.3 hours ($p < 0.005$). Renal clearance of lamotrigine was unchanged. In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with DEPAKENE® co-administration (a 165% increase). In a study involving 16 epileptic patients, DEPAKENE® doubled the elimination half-life of lamotrigine. In an open-labelled study, patients receiving enzyme inducing AEDs (e.g., carbamazepine, phenytoin, phenobarbital, or primidone) demonstrated a mean lamotrigine plasma elimination half-life of 14 hours while the elimination half-life was 30 hours in patients taking DEPAKENE® plus an enzyme inducing antiepileptic agent. The latter value is similar to the lamotrigine half-life during monotherapy indicating that valproic acid may counteract the effect of the enzyme inducer. If DEPAKENE® is discontinued in a patient receiving lamotrigine and an enzyme inducing antiepileptic serum, lamotrigine concentrations may decrease. Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered. Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and DEPAKENE® administration.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Lithium	CT	↔ lithium	In a double-blind placebo-controlled multiple dose crossover study in 16 healthy male volunteers, pharmacokinetic parameters of lithium were not altered by the presence or absence of valproate. The presence of lithium, however, resulted in an 11 to 12% increase in the AUC and C_{max} of valproate. T_{max} was also reduced. Although these changes were statistically significant, they are not likely to have clinical importance. Co-administration of DEPAKENE® (500 mg twice daily) and lithium carbonate (300 mg three times daily) to normal male volunteers (n = 16) had no effect on the steady-state kinetics of lithium.
Lorazepam	CT	↑ lorazepam	Concomitant administration of DEPAKENE® (500 mg twice daily) and lorazepam (1 mg twice daily) in normal male volunteers (n = 9) was accompanied by a 17% decrease in the plasma clearance of lorazepam. This decrease is not considered clinically important.
Nimodipine	CT	↑ nimodipine	Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50%.
Olanzapine	CT	↓ olanzapine	Valproic acid may decrease the olanzapine plasma concentration. Administration of a single 5 mg dose of olanzapine to 10 healthy, non-epileptic volunteers with Depakote ER® (divalproex sodium extended-release tablets) 1000 mg QD did not affect olanzapine Cmax and elimination half-life. However, olanzapine AUC was 35% lower in the presence of Depakote ER® (divalproex sodium extended-release tablets). The clinical significance of these observations is unknown.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Oral contraceptive Steroids	CT	No PK interaction	Evidence suggests that there is an association between the use of certain AEDs capable of enzyme induction and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing drugs effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. DEPAKENE® is not a significant enzyme inducer and would not be expected to decrease concentrations of steroid hormones. However, clinical data about the interaction of DEPAKENE® with oral contraceptives are minimal. Administration of a single-dose of ethinyloestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on DEPAKENE® (200 mg twice daily) therapy for 2 months did not reveal any pharmacokinetic interaction.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Phenobarbital	CT	↑ phenobarbital	Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of DEPAKENE® (250 mg twice daily 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 the presence of valproate.
	C	↓ valproate	Phenobarbital increases the metabolism of valproic acid and hence, increases valproic acid metabolite levels. Therefore patients treated with this drug should be carefully monitored for signs and symptoms of hyperammonemia. 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.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Phenytoin	CT	↑ phenytoin	Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of DEPAKENE® (400 mg three times daily) 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. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.
	C	↓ valproate	Phenytoin increases the metabolism of valproic acid and hence, increases valproic acid metabolite levels. Therefore patients treated with this drug 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 DEPAKENE® and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.
Primidone	T	↑ phenobarbital	Primidone is metabolized into a barbiturate (phenobarbital), and therefore, may also be involved in a similar or identical interaction with DEPAKENE® as phenobarbital.
Propofol		↑ propofol	Valproic acid may inhibit the metabolism of propofol, thus increasing propofol exposure. Reductions in propofol dose of 26 – 35% have been observed when co-administered with valproic acid. The normal dose of propofol may be excessive for patients receiving oral valproic acid treatment and may induce complications or delay recovery from anesthesia in electroconvulsive therapy (ECT).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Quetiapine			Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.
Rifampin	CT	↓ valproate	A study involving the administration of a single dose of DEPAKENE® (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. DEPAKENE® dosage adjustment may be necessary when it is co-administered with rifampin.
Rufinamide		↑ rufinamide	Valproic acid may lead to an increase in plasma levels of rufinamide in a dose-dependent manner. This increase is dependent on concentration of valproic acid. Caution should be exercised, particularly in children, as this effect is larger in the pediatric population.
Selective Serotonin Re-Uptake Inhibitors (SSRIs)	C	↑ valproate	Some evidence suggests that SSRIs inhibit the metabolism of DEPAKENE®, resulting in higher than expected levels of valproate.
Tolbutamide	T	↑ 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 DEPAKENE®. The clinical relevance of this displacement is unknown.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Topiramate	CT	Effect unknown	Hyperammonemia Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy (see also 2 CONTRAINDICATIONS, patients with known urea cycle disorders and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). Hypothermia Concomitant administration of topiramate with DEPAKENE® 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 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothermia).
Warfarin	T	Effect unknown	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 DEPAKENE® is instituted in patients taking anticoagulants. Caution is recommended when DEPAKENE® is administered with drugs affecting coagulation (see 8 ADVERSE REACTIONS).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Co-administration of DEPAKENE® with food should cause no clinical problems in the management of patients with epilepsy (see 4 DOSAGE AND ADMINISTRATION, 4.4 Administration).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

DEPAKENE® is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with DEPAKENE®; the clinical significance of these is unknown (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Thyroid Gland Abnormalities).

10 CLINICAL PHARMACOLOGY

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

10.1 Mechanism of Action

DEPAKENE® (valproic acid) has anticonvulsant properties. Although its mechanism of action has not yet been established, it has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

10.2 Pharmacodynamics

A good correlation has not been established between daily dose, serum level and therapeutic effect of DEPAKENE®. In epilepsy, the therapeutic plasma concentrations range is believed to be from 50 to 100 mcg/mL (350 to 700 micromole/L) of total valproate. Occasional patients may be controlled with serum levels lower or higher than this range (see 4 DOSAGE AND ADMINISTATION).

10.3 Pharmacokinetics

Absorption:

Valproic acid is rapidly absorbed after oral administration. Peak serum levels occur approximately 1 to 4 hours after a single oral dose. A slight delay in absorption occurs when the drug is administered with meals but this does not affect the total absorption.

Distribution:

Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and variable changes in valproic acid clearance and elimination.

- **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, in hyperlipidemic patients, and in the presence of other drugs (e.g., acetylsalicylic acid). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). See 9 DRUG INTERACTIONS 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 (ranging from 7 to 25% of total concentration).

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 (beta)-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.

Due to the saturable plasma protein binding, 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. The kinetics of unbound drug are linear.

Elimination:

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, respectively. These estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproic acid clearance, monitoring of valproate and concomitant drug concentrations should be intensified whenever enzyme-inducing drugs are introduced or withdrawn.

Elimination of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine.

The serum half-life (t½) of valproic acid is typically in the range of 6 to 16 hours. Half-lives in the lower part of the above range are usually found in patients taking other AEDs capable of enzyme induction.

Special Populations and Conditions:

- **Neonates/Infants:** Within the first 2 months of life, infants have a markedly decreased ability to eliminate valproate compared to children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in neonates under 10 days ranged from 10 to 67 hours, compared to a range of 7 to 13 hours in children greater than 2 months.
- **Pediatrics:** Patients between 3 months and 10 years have 50% higher clearances expressed on weight (i.e., L/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

- **Geriatrics:** 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 years). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44% (see 4 DOSAGE AND ADMINISTRATION).
- **Sex:** There are no differences in unbound clearance (adjusted for body surface area) between males and females (4.8 ± 0.17 and 4.7 ± 0.07 L/hr per 1.73 m^2, respectively).
- **Genetic Polymorphism:** No data available on genetic polymorphism.
- **Ethnic Origin:** The effects of race on the kinetics of valproate have not been studied.
- **Hepatic Insufficiency:** See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity for statements regarding hepatic dysfunction and associated fatalities.
- **Renal Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Renal, Renal Impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store DEPAKENE® (valproic acid) oral solution between 15 and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

No Special Handling Instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

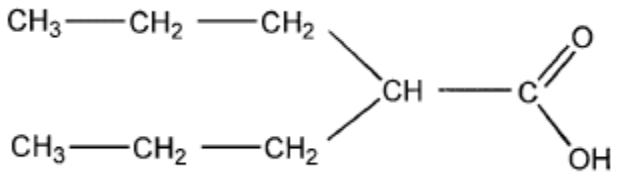
Drug Substance:

Proper name: valproic acid

Chemical name: 2-propylpentanoic acid or dipropylacetic acid

Molecular formula and molecular mass: $C_8H_{16}O_2$ 144.21

Structural formula:



Physicochemical properties: Valproic acid is a clear colorless to faint brown viscous liquid having a characteristic odor. The bulk drug substance displays solubility characteristics consistent with aliphatic carboxylic acids having limited solubility in water. The compound is freely soluble in dilute base and slightly soluble in dilute aqueous

mineral acids.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Safety Pharmacology:

Valproic acid has been shown to be effective against several types of chemically and electrically induced convulsions in a variety of animal species. These included maximal electroshock, low frequency electroshock, CO_2 withdrawal, pentylene tetrazole, cobalt, bemegride, bicuculline and 1-glutamate. Many forms of photic and auditory induced seizures are also effectively blocked by valproic acid.

In animal studies, valproic acid at doses of 175 mg/kg or less had no effect on locomotor activity and conditioned responses to positive reinforcement.

Doses greater than 175 mg/kg inhibited spontaneous and conditioned behaviour in mice and rats and interfered with coordination of hind limbs in rats. Suppression of spontaneous and evoked brain potentials was also demonstrated at these higher dose levels.

Valproic acid at doses of 175 mg/kg or less had little or no effect on the autonomic nervous system, cardiovascular system, respiration, body temperature, inflammatory responses, smooth muscle contraction or renal activity. Intravenous doses of 22, 43 and 86 mg/kg in animals caused very transient decreases followed by compensatory increases in blood pressure.

Sodium valproate injectable caused decreased activity, ataxia, dyspnea, prostration and death in rats and mice acutely exposed to dosages exceeding 200 mg/kg.

General Toxicology:

The initial animal testing was done with sodium valproate, whereas most of the recent research has been with valproic acid. The conversion factor is such that 100 mg of the sodium salt is equivalent to 87 mg of the acid. References to dosage are in terms of valproic acid activity.

- **Acute Toxicity**

  Acute toxicity has been determined in several animal species using oral, intravenous, intraperitoneal and subcutaneous routes. The oral median lethal dose in adult rats and dogs was about 1 to 2 g/kg. Toxicity was similar for both sexes; however, it tended to be greater in newborn and 14-day old rats and in young adult rats. The signs of toxicity were those of central nervous system depression. Specific organ damage was limited to cellular debris in reticuloendothelial tissue and slight fatty degeneration of the liver.

  Large oral doses (more than 500 mg/kg) produced irritation of the gastrointestinal tract of rats.

In adult male mice, the oral medial lethal dose of divalproex sodium was 1.66 g/kg (equal to approximately 1.54 g/kg valproic acid).

Pulverized divalproex sodium enteric-coated tablets (equivalent to 250 mg valproic acid), suspended in 0.2% methylcellulose, were administered orally to mice and rats of both sexes (10/sex/species/group) in dosages ranging from 1.74 to 4.07 g/kg. The oral median lethal dose (LD_{50}) ranged from 2.06 to 2.71 g/kg. No consistent sex-related or species-related differences were observed.

Signs of central nervous system depression, such as decreased activity, ataxia, and sleep, were observed. At necropsy, discolouration and/or thickening of the glandular mucosa were observed in only 2 female rats treated with 2.71 g/kg that died acutely.

When mature rats and dogs were administered up to 240 mg/kg/day or 120 mg/kg/day, respectively, for at least four consecutive weeks, no significant toxicologic effects were reported. However, significant reductions in testicular weights and total white cell counts in rats given 240 mg/kg/day were considered as evidence of subtle toxicity from sodium valproate injectable. Therefore, 90 mg/kg/day in rats and 120 mg/kg/day in dogs were considered the highest non-toxic doses.

The acute intravenous toxicity of sodium valproate injectable formulation containing the equivalent of 100 mg valproic acid/mL was evaluated in both sexes of mice and rats. Groups of mice and rats (five/sex/species/group) were treated at dosages ranging from 0.5 to 9.0 mL/kg (50 to 900 mg valproate/kg). No overt signs of toxicity were present in rats and mice given 0.5 mL/kg (50 mg valproate/kg). LD_{50} values for the test solution in mice and rats (data combined for both sexes) were 7.3 and 7.0 mL/mg (730 and 700 mg valproate/kg), respectively.

- **Subacute and Chronic Toxicity**

Subacute and chronic toxicity studies consisted of 1, 3, 6 and 18 months studies in rats and 3, 6 and 12 months studies in dogs. Pathologic changes included suppression of the hematopoietic system, depletion of lymphocytes from lymphoid tissues and the loss of germinal epithelial cells from seminiferous tubules. Reduced spermatogenesis and testicular atrophy occurred in dogs at doses greater than 90 mg/kg/day and in rats at doses greater than 350 mg/kg/day. In rats, the first indication of toxicity at 350 mg/kg/day was decreased food consumption and growth.

Carcinogenicity:

Two hundred rats were given valproic acid in the diet for 107 weeks. Mean doses consumed in the treatment period were: 81 mg/kg/day (males) and 85 mg/kg/day (females), in the low dose group; 161 mg/kg/day (males) and 172 mg/kg/day (females) in the high dose group (approximately 10 to 50% of the maximum human daily dose on a mg/m^2 basis). Control animals received corn oil in the diet. The chief finding in the study was an increased incidence of skin fibrosarcomas in treated males of the high-dose group. There were 2 such neoplasms in the low dose group, 5 in the high dose group and none in control males. Fibrosarcomas in rats are relatively infrequent, usually occurring in less than 3% of animals.

Valproic acid was also administered in the diet to female mice for nearly 19 months at doses of 81 and 163 mg/kg/day and to male mice for nearly 23 months at doses of 80 and 159 mg/kg/day. A significant dose related trend occurred in male mice in the incidence of bronchoalveolar adenomas, and when the data were adjusted for the times of death, the incidence in the high dose group was significantly increased.

Depending on the method of statistical analysis, the incidence of hepatocellular carcinomas and/or adenomas also showed significant or almost significant increases for the corresponding observations. The results of these two studies indicate that valproic acid is a weak carcinogen or promoter in rats and mice. The significance of these findings for humans is unknown at present.

Subcutaneous fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to those in registries of historical controls.

Genotoxicity:

Valproate was not mutagenic in bacteria (Ames test), or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay), and did not induce DNA repair activity in primary culture of rat hepatocytes. After oral administration, valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice.

In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand-breaks, chromosomal aberrations or micronuclei) have been reported in rodents. However, the clinical significance 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 epileptic children exposed to valproate as compared to healthy children or epileptic children not exposed to valproate. However, contradictory results were reported in another study conducted in a mixed population of adults and children who showed similar SCE frequencies in treated or untreated epileptic patients. The clinical significance of an increase in SCE frequency is not known.

Reproductive and Developmental Toxicology:

- **Development**

  Studies in rats have shown placental transfer of the drug. Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits. Doses greater than 65 mg/kg/day given to rats, mice and rabbits produced an increased incidence of skeletal abnormalities of the ribs, vertebrae and palate. Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

  Doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring.

  In rats, there was a dose related delay in onset of parturition. Post-natal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period. Embryolethality or major developmental abnormalities occurred in rats and rabbits at doses of 350 mg/kg/day.

Survival among pups born to the high dose females was very poor but was improved when pups were transferred to control dams shortly after birth.

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 from dams dosed with valproate at 300 mg/kg (i.p.) or 500 mg/kg (s.c.) valproate on GD 10 or 10.5, respectively. The relevance of these findings for humans is unknown.

- **Fertility**

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of valproic acid of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown that oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m^2 basis) for 60 days have no effect on fertility. The effect of valproate on testicular development in humans is unknown.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDEPAKENE®

valproic acid oral solution

Read this carefully before you start taking **DEPAKENE®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DEPAKENE®**.

Serious Warnings and Precautions

- **Liver Failure:** cases of fatal liver failure have occurred in patients receiving DEPAKENE®. If liver failure occurs, it usually happens during the first 6 months of treatment. You are more at risk for liver failure if you:
    - take other drugs used to treat seizures
    - are a child (especially a child under 2 years of age taking multiple drugs to treat seizures)
    - have a history of liver disease
    - were born with a metabolic disorder
    - have seizures with an intellectual disability
    - have brain disease
- **Birth Defects:** DEPAKENE® can cause birth defects in your child if you take it during pregnancy. These birth defects can seriously affect your child and include:
    - *spina-bifida* (a condition where the bones of the spine are not properly developed);
    - problems with the development of the bones of the face and skull;
    - problems with the development of organs, arms and legs;
    - hearing problems or deafness;
    - problems with early childhood development such as slow to walk and talk, lower IQ or problems with brain development;
    - autism or autism spectrum disorders;
    - Attention Deficit Hyperactivity Disorder (ADHD)

  These can begin early in the pregnancy, even before you know that you are pregnant. DEPAKENE® should not be used in female children, in women of childbearing potential or in pregnant women unless your doctor decides that you should. If you are taking DEPAKENE® and are of childbearing potential, you should use an effective method of birth control. If you become pregnant, or think you may be pregnant while taking DEPAKENE®, tell your doctor **right away**.
- **Mitochondrial Disorders:** if you or your child have a mitochondrial disorder such as Alpers Huttenlocher Syndrome, do not take DEPAKENE®. If your child is under 2 years of age and you

think they may have a mitochondrial disorder, they should not be given DEPAKENE® unless all other medications have failed.

- **Pancreatitis** (inflammation of the pancreas): cases of life-threatening pancreatitis have occurred in both children and adults taking DEPAKENE®. Some instances happen shortly after the first use of DEPAKENE®, while others after several years of use. Talk to your healthcare professional right away if you start to have any symptoms of pancreatitis.
- (See the **Serious side effects and what to do about them** table below for symptoms of liver failure and pancreatitis).

What is DEPAKENE® used for?

- DEPAKENE® is used in adults and children to control epilepsy (a disorder of the brain that causes seizures. Please follow your doctor's instructions carefully.

How does DEPAKENE® work?

DEPAKENE® is thought to work by increasing the amount of an amino acid in the brain called "gamma-aminobutyric acid" (GABA). By changing the amount of GABA in the brain, DEPAKENE® is able to help control epilepsy.

What are the ingredients in DEPAKENE®?

Medicinal ingredients: valproic acid

Non-medicinal ingredients: artificial cherry flavor, FD&C Red No. 40, glycerin, methylparaben*, propylparaben*, purified water, sorbitol, sucrose, vanillin, and hydrochloric acid and sodium hydroxide for pH adjustment.

* methylparaben and propylparaben may cause an immediate or delayed allergic reaction.

DEPAKENE® comes in the following dosage forms:

Oral solution; 250 mg of valproic acid for every 5 mL.

Do not use DEPAKENE® if:

- you are allergic to valproic acid or to any other ingredient in DEPAKENE®
- you are pregnant, think you are pregnant or are planning to become pregnant, unless you and your doctor have decided you should
- you are a woman of childbearing potential, unless you meet all conditions of the **Pregnancy Prevention Program**, your doctor will talk to you about this
- you have liver disease or severe liver problems
- you have a mitochondrial disorder such as Alpers-Huttenlocher Syndrome. Children under 2 years of age who may have a mitochondrial disorder should not take DEPAKENE®
- you have or have a family history of a urea cycle disorder (a condition that affects how your body removes waste)
- you have porphyria (a condition that affects the nervous system and skin)
- you or any of your close relatives have a history of severe hepatitis, especially when caused by medicines

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DEPAKENE®. Talk about any health conditions or problems you may have, including if you:

- have or have a history of liver disease or liver problems;
- are breastfeeding or planning to breastfeed. You must discuss with your doctor whether to breastfeed or take DEPAKENE®, you cannot do both. Do not breastfeed for one month after stopping DEPAKENE®;
- have kidney disease or kidney problems;
- have diabetes;
- have any of the following rare conditions, DEPAKENE® contains sucrose:
  - fructose intolerance
  - glucose-galactose malabsorption
  - sucrose-isomaltase insufficiency
- have Human Immunodeficiency Virus (HIV) or Cytomegalovirus (CMV);
- have a history of muscular disorders (including carnitine palmitoyl transferase type II deficiency);
- have other medical conditions including a history of unexplained coma, intellectual disability or any type of brain dysfunction;
- drink alcohol on a regular basis;
- are elderly (65 years of age or older).

Other warnings you should know about:

Pregnancy: DEPAKENE® may harm your unborn baby. Your doctor may require you to do a pregnancy test before you start treatment with DEPAKENE® to make sure that you are not pregnant. **You must use effective methods of birth control.** It is recommended that you use a form of birth control that does not depend on you to remember to use or take it, such as an intrauterine device (IUD) or 2 forms of birth control, such as the pill and a condom. You should use birth control:

- for at least one month before starting DEPAKENE®;
- while you are taking DEPAKENE®;
- for at least one month after stopping DEPAKENE®.

Talk to your doctor about the best form of birth control for you. Some hormonal birth controls that contain estrogen may affect how well DEPAKENE® works.

Before prescribing DEPAKENE®, your doctor should have explained to you what might happen to your baby if you become pregnant while taking DEPAKENE® (see the **Serious warnings and precautions** box above). If you are a parent or caring for a female child taking DEPAKENE®, tell the doctor as soon as your child has her first period. If you have any questions about what may happen if you become pregnant, talk to a healthcare professional. If you become pregnant, or think you are pregnant while taking DEPAKENE®, tell your doctor **right away**.

When you are prescribed DEPAKENE®:

- your doctor will give you a patient guide;
- you should receive a patient card every time you get DEPAKENE® from the pharmacy.

Make sure you understand these documents.

Pregnancy Registry: If you become pregnant while taking DEPAKENE®, talk to your doctor about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicines during pregnancy. Information on the registry can also be found at the following website: http://www.aedpregnancyregistry.org/.

Pregnancy Prevention Program: Information on the Pregnancy Prevention Program including educational resources, as well as to report suspected embryo-fetal exposure to valproate, can be found at the following website: www.depakene.ca.

Fertility:

Use in Women: If you are female and taking DEPAKENE® you may no longer get your period. You may also develop cysts (fluid filled sacs) on the ovaries and your testosterone levels may increase.

Use in Men: DEPAKENE® may affect male fertility during treatment. DEPAKENE® can make you less fertile or infertile. This **may or may not** be reversible if your dose is decreased or if you stop taking DEPAKENE®.

If you have interest in starting a family, talk to your doctor. Do not stop taking DEPAKENE® unless your doctor has told you to do so.

Monitoring and Blood Tests: Your doctor should do blood tests before starting treatment with DEPAKENE® and while you are taking it. These tests will monitor:

- platelet (a type of blood cell) count and your blood's ability to clot
- liver function
- the amount of valproate (the active ingredient in DEPAKENE®) in the body
- the amount of any other medications you are taking in your body

Your doctor will monitor your response to DEPAKENE® on a regular basis. If you start to have more seizures or your seizures get worse, tell your doctor immediately.

Suicidal Thoughts and Behaviour Changes: If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital right away. DEPAKENE® may also cause behavioural changes in you or you child such as aggression, agitation, change in attention span and learning disorders.

Driving and Using Machines: DEPAKENE® may cause you to become drowsy or light-headed. Avoid driving, using machinery, or doing dangerous activities until you know how DEPAKENE® affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DEPAKENE®:

- **phenobarbital and lamotrigine, which are anticonvulsants (drugs used to treat seizures). These might cause serious life-threatening effects when mixed with DEPAKENE®;**
- other anticonvulsants such as carbamazepine, primidone, topiramate, felbamate, phenytoin, ethosuximide, rufinamide;
- anticoagulants (drugs used to thin blood) such as acetylsalicylic acid, warfarin, dicumarol;
- benzodiazepines such as diazepam, lorazepam, clonazepam;

- some medicines used to treat infections such as rifampin;
- some medicines used to treat diabetes such as tolbutamide;
- some HIV-antiviral medicines such as zidovudine, ritonavir, lopinavir, lamivudine;
- antibiotics in the carbapenem class such as doripenem, ertapenem, imipenem, meropenem;
- some medicines used to treat heartburn and peptic ulcers such as cimetidine;
- medicines used to treat depression such as Selective Serotonin Re-Uptake Inhibitors (SSRIs), Monoamine Oxidase Inhibitors (MAOIs), Tricyclic antidepressants such as amitriptyline, nortriptyline;
- acetazolamide, a drug used to treat glaucoma and epilepsy;
- cholestyramine, a drug used to lower cholesterol;
- propofol, a drug used to relax you before and after surgery;
- nimodipine, a drug used to prevent brain damage;
- antipsychotics (drugs used to manage psychosis) such as olanzapine, chlorpromazine, quetiapine;
- estrogen-containing products (including contraceptives that contain estrogen);
- alcohol.

How to take DEPAKENE®:

- DEPAKENE® treatment must only be started and supervised by a doctor specialised in the treatment of epilepsy.
- It is important to keep your appointments for medical checkups.
- Take DEPAKENE® exactly as your doctor prescribes, do not change your dose unless your doctor tells you to.
- Do not stop taking DEPAKENE® suddenly as this can increase the number of seizures you have and their severity, including status epilepticus.
- DEPAKENE® can be taken with or without food.

Usual dose:

Your doctor will decide the dose of DEPAKENE® for you. The dose is based on your weight, your seizures and the other medicines you or your child take. Your doctor will slowly increase the dosage until your or your child's condition is well controlled, without side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much DEPAKENE®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you or your child misses a dose, do not try to make up for it by doubling the next dose. Take or give the next regularly scheduled dose and try not to miss any more doses.

What are possible side effects from using DEPAKENE®?

These are not all the possible side effects you or your child may have when taking DEPAKENE®. If you or your child experience any side effects not listed here, tell your healthcare professional.

- headache
- nausea or vomiting
- indigestion
- diarrhea
- tremors (involuntary shaking)
- feeling tired
- feeling weak or dizzy
- hair loss or hair growth on the face, chest or back
- increased appetite that may lead to weight gain

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			X
Hallucinations (seeing or hearing things that are not there)	X		
Urinary incontinence (involuntary loss of urine)		X	
UNCOMMON			
Aggravated convulsions (an increase in the number of seizures you have or having new types of seizures)			X
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death. If you have a history of depression, your depression may become		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
worse			
Hyperammonemia (high ammonia levels in the blood): tiredness, vomiting, abnormal walking, extreme irritability, combative/bizarre behaviour, not wanting to eat meat or high protein products			X
Hypothermia (low body temperature): shivering, slurred speech or mumbling, slow, shallow breathing, weak pulse, very low energy, confusion or memory loss		X	
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma)		X	
Liver injury: yellowing of the skin or eyes, itchy skin, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite			X
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			X
Serious skin reactions when taken with lamotrigine: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty,			X

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
urinating less often, less urine			
Thoughts of suicide or hurting yourself			X
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		X	
RARE			
Brain atrophy (loss of brain cells): memory loss, seizures, loss of motor skills, difficulty speaking, reading or understanding.		X	
Coagulation abnormalities (problems with how your blood clots): abnormal bleeding, bruising easily, won't stop bleeding when you are injured, sudden nosebleeds, fatigue, headache		X	
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine			X

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store DEPAKENE® oral solution between 15 and 30°C.

Keep out of reach and sight of children.

If you want more information about DEPAKENE®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.mylan.ca, or by calling 1-844-596-9526.

This leaflet was prepared by BGP Pharma ULC.

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