PRODUCT MONOGRAPH

PrNOVO-VALPROIC

(Valproic Acid)

250 mg Capsules, USP Standard
500 mg Enteric Coated Capsules, Teva Standard

Antiepileptic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

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[Pr]NOVO-VALPROIC
(Valproic Acid)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Non-medicinal Ingredients
oral	capsule / 250 mg	Corn oil, ethyl vanillin, FD&C Yellow #6, gelatin, glycerin, purified water and titanium dioxane.
	capsule / 500 mg	Aquacoat ECD-30, Aquateric (Type CD-910), Carnauba wax, ethyl vanillin, FD&C Yellow #6, gelatin, glycerin, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate, propylene glycol, purified water, titanium dioxane and triacetin.

INDICATIONS AND CLINICAL USE

NOVO-VALPROIC (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 **(CONTRAINDICATIONS)** and **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity)** for statement regarding serious or fatal hepatic dysfunction.

Geriatrics (≥ 65 years of age):

The safety and efficacy of NOVO-VALPROIC in elderly patients with epilepsy and mania 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 valproic acid in this population. For a brief discussion, see **[WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics ≥ 65 years of age)], (DOSAGE AND ADMINISTRATION)** and **(ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).**

Pediatrics < 18 years of age):

When NOVO-VALPROIC 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 **[WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics < 18 years of age)].**

CONTRAINDICATIONS

- NOVO-VALPROIC (valproic acid) should not be administered to patients with hepatic disease or significant hepatic dysfunction.

- NOVO-VALPROIC is contraindicated in patients with known hypersensitivity to the drug.

- NOVO-VALPROIC is contraindicated in patients with known urea cycle disorders. See **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders).**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Hepatotoxicity:** Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidences usually occurred during the first 6 months of treatment with valproic acid. Caution should be observed when administering valproic acid 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 **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatoxocity).**

- **Teratogenicity:** Valproic acid can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of the medication in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. See **(WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).**

- **Pancreatitis:** Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproic acid. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. See **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis).**

General

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 **(DRUG INTERACTIONS, Drug-Drug Interactions, Table 1).**

Patients with Special Diseases and Conditions

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.

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 **TOXICOLOGY, Mutagenicity and Carcinogenicity).**

Endocrine and Metabolism

Urea Cycle Disorders

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

1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;

2) those with signs and symptoms of UCD, for example, cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen (BUN), protein avoidance;

3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males);

4) those with other signs or symptoms of UCD. Patients receiving valproic acid who develop symptoms of unexplained hyperammonemic encephalopathy should receive prompt treatment (including discontinuation of valproic acid) and be evaluated for underlying urea cycle disorders. See **(CONTRAINDICATIONS)** and **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and Hyperammonemia and Encephalophathy Associated with Concomitant Topiramate Use).**

Hyperammonemia

Hyperammonemia has been reported in association with valproic acid 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 **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothermia).** If serum ammonia is increased, NOVO-VALPROIC should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders. See **(CONTRAINDICATIONS)** and **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders and Hyperammonemia and Encephalophathy Associated with Concomitant Topiramate Use).**

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

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia. See **(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 monotherapy is associated with hyperammonemia.

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons. See (CONTRAINDICATIONS) and (WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders and Hyperammonemia).

Hypothermia

Hypothermia, defined as an unintentional drop in core body temperature to < 35°C (95°F), has been reported in association with valproic acid both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproic acid after starting topiramate treatment or after increasing the daily dose of topiramate. See **(DRUG INTERACTIONS, Drug-Drug Interactions, Table 1).** 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 valproic acid in patients who develop hypothermia. See **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia).**

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 NOVO-VALPROIC (valproic acid) 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 valproic acid dosage or withdrawal of therapy. See also **(WARNINGS AND PRECAUTIONS, Hematologic, Dose-related Adverse Reactions: Thrombocytopenia).**

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

In addition, the findings from a crossover clinical trial conducted with divalproex sodium extended-release tablets, in 44 epilepsy patients, indicate that the frequency of treatment-emergent mild thrombocytopenia (platelet count between 100 to l50 x 10^9/L) was significantly higher after 12 weeks of treatment with divalproex sodium extended-release tablets than after 12 weeks of treatment with divalproex sodium (7 versus 3 low counts, respectively).

Hepatic/Biliary/Pancreatic

Serious or Fatal Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. These incidences usually have occurred during the first 6 months of treatment with valproic acid. Caution should be observed when administering valproic acid 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 valproic acid as monotherapy. Similarly, patients aged 3 to 10 years were at some what greater risk if they received multiple anticonvulsants than those who received only valproic acid. 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 valproic acid alone.

If NOVO-VALPROIC 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 **[WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (< 18 years of age)].**

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 valproic acid.

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, valproic acid 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 **(CONTRAINDICATIONS).**

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproic acid. Some of the cases have been described as hemorrhagic with 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 valproic acid. 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, valproic acid should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Neurologic

Driving and Hazardous Occupations
Valproic acid 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.

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.

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.

Sensitivity/Resistance

Multi-organ Hypersensitivity Reaction

Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of valproic acid 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, valproic acid 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.

Sexual Function/Reproduction

Fertility

The effect of valproic acid on the development of the testis and on sperm production and fertility in humans is unknown. See **(TOXICOLOGY, Reproduction and Teratology, Fertility)** for results in animal studies.

Skin

Serious Skin Reactions

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

Special Populations

Pregnant Women

According to published and unpublished reports in the medical literature, valproic acid may produce teratogenic effects, such as neural tube defects (e.g., spina bifida) in the offspring of human females receiving the drug during pregnancy. There are data that suggest an increased incidence of congenital malformations associated with the use of valproic acid during pregnancy when compared with some other AEDs. Therefore, valproic acid should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.

Multiple reports in the clinical literature indicate an association between the use of AEDs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women, this incidence may be increased two- to three-fold. The increase is largely due to specific defects such as congenital malformations of the heart, cleft lip and/or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving antiepileptic medications deliver normal infants.

Neural Tube Defects

The data described below were gained almost exclusively from women who received valproic acid to treat epilepsy. The incidence of neural tube defects in the fetus is increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid-exposed women having children with spina bifida is approximately 1 to 2%.

Congenital Anomalies

Other congenital anomalies (e.g., craniofacial defects, cardiovascular malformations and anomalies involving various body systems), compatible and incompatible with life, have been reported. Sufficient data to determine the incidence of these congenital anomalies are not available.

The higher incidence of congenital anomalies in AED-treated women with seizure disorders cannot be regarded as a cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself, may be more important than the drug therapy in contributing to congenital anomalies.

Developmental Delay, Autism and/or Autism Spectrum Disorders

There have been post-marketing reports of developmental delay, autism and/or autism spectrum disorder in the offspring of women exposed to valproic acid during pregnancy. Cognitive testing at year 2 or 3 in a 6-year, prospective study of long-term cognitive development in 309 children

(born to 303 mothers) exposed in utero to antiepileptic drug monotherapy showed that children exposed to valproic acid had significantly lower IQs (92; 95% confidence interval, 88 to 97) than did children exposed to other antiepileptic drugs (carbamazepine, 98; lamotrigine, 101; phenytoin, 99), whereas IQ scores did not differ significantly among children exposed to the other 3 antiepileptic drugs. There was a significant correlation between the dose of valproic acid during pregnancy and the child's IQ.

Patients taking valproic acid may develop clotting abnormalities. A patient who had low fibrinogen when taking multiple anticonvulsants, including valproic acid, gave birth to an infant with afibrinogenemia who subsequently died of hemorrhage. If valproic acid is used in pregnancy, the clotting parameters should be monitored carefully.

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

AEDs should not be abruptly discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

In summary, current best practice guidelines should be considered in order to provide the optimal counsel to patients regarding the teratogenic risks associated with valproic acid.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation is indicated.

If valproic acid is used 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.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproic acid.

Teratogenicity in Animals

Animal studies have demonstrated valproic acid induced teratogenicity, see **(TOXICOLOGY, Reproduction and Teratology),** 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).

Nursing Women

Valproic acid is secreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving valproic acid. It is not known what effect this may have on a nursing infant.

Pediatrics (< 18 years of age)

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 **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity).** When valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks.

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

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

Geriatrics (≥ 65 years of age)

Alterations in the kinetics of unbound valproate in the elderly indicate that the initial dosage should be reduced in this population. See **(DOSAGE AND ADMINISTRATION)** and **(ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).**

The safety and efficacy of valproic acid 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 valproic acid in this population.

A study of elderly patients revealed valproate-related somnolence and discontinuation of valproic acid for this adverse event. See **(WARNINGS AND PRECAUTIONS, Special Populations, 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 **(DOSAGE AND ADMINISTRATION).**

Somnolence in the elderly

In a group of elderly patients (mean age 83 years old, n = 172), valproic acid 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 valproic acid should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. See **(DOSAGE AND ADMINISTRATION).**

Monitoring and Laboratory Tests

Since valproic acid may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy and whenever enzyme-inducing drugs are introduced or withdrawn. See (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 **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic), (WARNINGS AND PRECAUTIONS, Endocrine and**

Metabolism, Hyperammonemia), (WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia) and **(DRUG INTERACTIONS, Drug-Drug Interactions, Table 1).**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since 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 valproic acid alone or to the combination of drugs.

Adverse events that have been reported with valproic acid 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 frank hemorrhage. See (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 has been reported.
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 and constipation have also been reported. There have been reports of acute pancreatitis, including rare fatal cases, occurring in association with valproic acid therapy. See **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis).** Parotid gland swelling has also been reported in patients receiving valproic acid.
General Disorders and Administration Site Conditions:	Edema of the extremities, fever and hypothermia has been reported.

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 **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity).**
Immune System Disorder:	Allergic reaction, anaphylaxis has been reported.
Infections and Infestations:	Pneumonia and otitis media have been reported.
Investigations:	Abnormal thyroid function tests have been reported. See **(DRUG INTERACTIONS, Drug-Laboratory Interactions).**
Metabolism and Nutrition Disorders:	Hyperammonemia, see **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia)**, hyponatremia and inappropriate antidiuretic hormone (ADH) secretion. There have been rare reports of Fanconi syndrome 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.
Musculoskeletal and Connective Tissue Disorders:	Weakness and bone pain have been reported. Reports have been received of decreased bone mass, potentially leading to osteoporosis and osteopenia, during long-term therapy with some anticonvulsant medications, including valproic acid. Some studies have indicated that supplemental calcium and vitamin D may be of benefit to patients who are on chronic valproic acid therapy. A lupus erythematosus-like syndrome has been reported rarely.
Nervous System Disorders:	Sedative effects have been noted in patients receiving valproic acid 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 and parkinsonism have been noted. Rare cases of coma have been reported in patients receiving valproic acid 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. Reversible cerebral atrophy and dementia have been reported in association with valproic acid.
Psychiatric Disorders:	Emotional upset, depression, psychosis, aggression, hyperactivity, hostility and behavioural deterioration have been reported.
Renal and Urinary Disorders	Enuresis 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 valproic acid. 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 has been reported.
Skin and Subcutaneous Tissue Disorders:	Transient increases in hair loss 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 valproic acid 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 valproic acid. See **(DRUG INTERACTIONS, Drug-Drug Interactions, Table 1).** Cutaneous vasculitis has also been reported.

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 valproic acid.

DRUG INTERACTIONS

Serious Drug Interactions

- Rare cases of coma have been reported in patients receiving valproic acid alone or in conjunction with phenobarbital. See **(Drug-Drug Interactions, Table 1).**
- Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and valproic acid administration. See **(Drug-Drug Interactions, Table 1).**

Overview

Valproic acid 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, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on valproic acid 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 P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

The concomitant administration of valproic acid 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 valproic acid may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy and whenever enzyme-inducing drugs are introduced or withdrawn.

Drug-Drug Interactions

Table 1 provides information about the potential influence of several commonly prescribed medications on valproic acid pharmacokinetics as well as the potential influence of valproic acid 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. Please note that drugs may be listed under specific name, family or pharmacologic class. Reading the entire section is recommended.

Table 1. Summary of Drug-Drug Interaction Studies Including Important Interactions, Non-clinically Important Interaction and No observed Interactions

Concomitant Drug	Ref	Effect	Clinical comment
Acetaminophen	CT	↔ acetaminophen	Valproic acid had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.
Acetylsalicylic Acid	CT	↑ valproate	A study involving the co-administration of acetylsalicylic acid at antipyretic doses (11 to 16 mg/kg) with valproic acid 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 valproic acid 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 valproic acid alone to 8.3% in the presence of acetylsalicylic acid. Caution should be observed when valproic acid is administered with drugs affecting coagulation, (e.g., acetylsalicylic acid and warfarin). See **(ADVERSE REACTIONS).**
Alcohol	T	No pharmacokinetic (PK) interaction	Valproic acid may potentiate the CNS depressant action of alcohol.
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 valproic acid (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 valproic acid and amitriptyline resulting in an increased nortriptyline amitriptyline and nortriptyline levels have been received. Concurrent use of valproic acid and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproic acid concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproic acid.
Antacids	CT	↔ valproate	A study involving the co-administration of valproic acid 500 mg with commonly administered antacids (Maalox®, Trisogel, and Titralac™ - 160 milliequivalent doses) did not reveal any effect on the extent of absorption of valproic acid.
Other – Antipsychotics, Monoamine Oxidase Inhibitors (MAOIs) and Tricyclic Antidepressants			In addition to enhancing CNS depression when used concurrently with valproic acid, antipsychotics, tricyclic antidepressants and MAOIs may lower the seizure threshold. Dosage adjustments may be necessary to control seizures.

Concomitant Drug	Ref	Effect	Clinical comment
Benzodiazepines			Valproic acid may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations. See **(Table 1. Diazepam and Lorazepam).**
Carbamazepine / carbamazepine-10,11-epoxide	CT	↓ CBZ ↑ CBZ-E ↓ valproate	Concomitant use of carbamazepine (CBZ) with valproic acid 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 10,11-epoxide (CBZ-E) metabolite of carbamazepine, however, will not be detected by routine serum carbamazepine assay. Serum levels of carbarnazepine decreased 17% while that of carbamazepine-10,l 1-epoxide increased by 45% upon co-administration of valproic acid and CBZ to epileptic patients.
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 (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 valproic acid (200 mg twice daily) revealed a 15% increase in trough plasma levels of valproate. This increase is not considered clinically important.
Cimetidine	T	↑ valproate	Cimetidine may decrease the clearance and increase the half-life of valproic acid by altering its metabolism. In patients receiving valproic acid, serum valproic acid levels should be monitored when treatment with cimetidine is instituted, increased, decreased, or discontinued. The valproic acid dose should be adjusted accordingly.
Clonazepam	T	No PK interaction	The concomitant use of valproic acid 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 valproic acid was co-administered with clozapine.
Diazepam	CT	↔ valproate	Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproic acid (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.

Concomitant Drug	Ref	Effect	Clinical comment
Ethosuximide	CT	↑ Ethosuximide	Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproic acid (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 valproic acid 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 valproic acid to patients with epilepsy (n = 10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to valproic acid 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 valproic acid dosage may be necessary when felbamate therapy is initiated. Lower doses of valproic acid 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 valproic acid (200 mg twice daily) revealed no significant changes in valproate trough plasma levels.
Lamotrigine	CT	↑ lamotrigine ↓ valproate	The effects of valproic acid on lamotrigine were investigated in 6 healthy male subjects. Each subject received a single oral dose of lamotrigine alone and with valproic acid 200 mg every 8 hours for 6 doses starting 1 hour before the lamotrigine dose was given. valproic acid administration reduced 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 valproic acid co-administration (a 165% increase). In a study involving 16 epileptic patients, valproic acid 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 valproic acid 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 valproic acid 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 valproic acid administration.

Concomitant Drug	Ref	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 valproic acid (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 valproic acid (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.
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. Valproic acid is not a significant enzyme inducer and would not be expected to decrease concentrations of steroid hormones. However, clinical data about the interaction of valproic acid with oral contraceptives are minimal. Administration of a single-dose of ethinyloestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on valproic acid 200 mg twice daily) therapy for 2 months did not reveal any pharmacokinetic interaction.
Phenobarbital	CT	↑ phenobarbital	Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproic acid (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. 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.

Concomitant Drug	Ref	Effect	Clinical comment
Phenytoin	CT	↑ phenytoin	Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproic acid (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%. In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproic acid 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 valproic acid as phenobarbital.
Rifampin	CT	↓ valproate	A study involving the administration of a single dose of valproic acid (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. valproic acid dosage adjustment may be necessary when it is co-administered with rifampin.
Selective Serotonin Re-Uptake Inhibitors (SSRIs)	C	↑ valproate	Some evidence suggests that SSRIs inhibit the metabolism of valproic acid, 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 valproic acid. The clinical relevance of this displacement is unknown.
Topiramate	CT	Effect unknown	Hyperammonemia Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy. See **(CONTRAINDICATIONS)** and **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders, Hyperammonemia and Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use).** Hypothermia Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. Blood ammonia levels should be measured in patients with reported onset of hypothermia. See **(WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothermia).**

Concomitant Drug	Ref	Effect	Clinical comment
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 valproic acid is instituted in patients taking anticoagulants. Caution is recommended when valproic acid is administered with drugs affecting coagulation. See **(ADVERSE REACTIONS).**
Zidovudine	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.
Legend: C = Case Study; CT = Clinical Trial; T = Theoretical			

Drug-Food Interactions

Co-administration of valproic acid with food should cause no clinical problems in the management of patients with epilepsy.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Valproic acid 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 valproic acid; the clinical significance of these is unknown.

Drug-Lifestyle Interactions

Refer to **(WARNINGS AND PRECAUTIONS, Neurologic, Driving and Hazardous Occupations)** for details.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

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

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 **(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 valproic acid 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 **[WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (≥ 65 years of age)].**

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 **(WARNINGS AND PRECAUTIONS, Hematologic, Dose-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.

Recommended Dose and Dosage Adjustment

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 maximal recommended dosage is 60 mg/kg/day. When the total daily dose exceeds 250 mg, it should be given in a divided regimen **(Table 2)**. A 500 mg enteric-coated capsule may be substituted for two 250 mg capsules.

Table 2. Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Number of 250 mg Capsules or 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 **(WARNINGS AND PRECAUTIONS).**

Conversion from valproic acid to divalproex sodium

Divalproex sodium enteric-coated tablets dissociate to the valproate ion in the gastrointestinal tract. Divalproex sodium tablets are uniformly and reliably absorbed, however, because of the enteric coating, absorption is delayed by an hour when compared to valproic acid.

The bioavailability of both types of divalproex sodium tablets and divalproex sodium extended-release tablets is equivalent to that of valproic acid capsules.

In patients previously receiving valproic acid therapy, divalproex sodium should be initiated at the same daily dosing schedule. After the patient is stabilized on divalproex sodium, a dosing schedule of two or three times a day may be elected in selected patients. Changes in dosage administration of divalproex sodium 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.

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.

Administration

NOVO-VALPROIC 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. The capsules should be swallowed without chewing to avoid local irritation of the mouth and throat. Co-administration of NOVO-VALPROIC with food should cause no clinical problems in the management of patients with epilepsy.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Overdosage with valproic acid may result in somnolence, heart block, and deep coma. Fatalities have been reported; however, patients have recovered from valproate levels as high as 2,120 mcg/mL.

In a reported case of overdosage with valproic acid 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 valproic acid overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproic acid, it should be used with caution.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

NOVO-VALPROIC (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.

Pharmacodynamics

A good correlation has not been established between daily dose, serum level and therapeutic effect. 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 **(DOSAGE AND ADMINISTATION).**

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 **(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.

Excretion

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate

are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2, 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 ($t_{½}$) 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 **(DOSAGE AND ADMINISTRATION).**

Gender

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).

Race

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

Hepatic Insufficiency

See **(CONTRAINDICATIONS)** and **(WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity)** for statements regarding hepatic dysfunction and associated fatalities.

Renal Insufficiency

See **(WARNINGS AND PRECAUTIONS, Renal, Renal Impairment).**

Genetic Polymorphism

No data available on genetic polymorphism.

STORAGE AND STABILITY

Store between 15°C and 30°C. Unit dose strips should be stored between 15°C and 25°C and protected from high humidity.

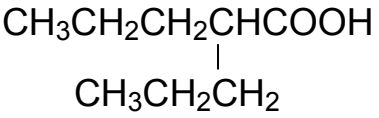
DOSAGE FORMS, COMPOSITION AND PACKAGING

NOVO-VALPROIC (valproic acid) 250 mg is available as an orange coloured, oblong, soft gelatin capsule, 8 minim size, containing 250 mg of valproic acid as a clear, colourless liquid. Available in bottles of 100 and 500 and boxes of 100 as unit dose strips.

NOVO-VALPROIC 500 mg is available as a pale yellow coloured, oblong, soft gelatin enteric coated capsule, 11 minim size, containing 500 mg of valproic acid as a clear, colourless liquid. Available in bottles of 100 and 500.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name:	valproic acid	
Chemical name:	2-propylpentanoic acid	
Molecular formula and molecular mass:	$C_8H_{16}O_2$	144.21g/mol
Structural formula:		
Physicochemical properties:	Valproic acid is a carboxylic acid derivative anticonvulsant which occurs as a colourless to pale yellow, slightly viscous, clear liquid with a characteristic odour. It is slightly soluble in water and freely soluble in 1N sodium hydroxide, methanol, alcohol, acetone, chloroform, benzene, ether and n-heptane; slightly soluble in 0.1N hydrochloric acid. It has a pH of 4.3 and a pKa of 4.6.	

CLINICAL TRIALS

Comparative Bioavailability studies

A comparative two-way, single-dose bioavailability study was performed on NOVO-VALPROIC (valproic acid) 250 mg Capsules and DEPAKENE® (valproic acid) 250 mg Capsules. Two studies, a fasted and a fed state study, were performed on NOVO-VALPROIC 500 mg Capsules and DEPAKENE® 500 mg Capsules. The pharmacokinetic data calculated for valproic acid in the NOVO-VALPROIC and DEPAKENE® Capsule formulations are tabulated as follows:

Pharmacokinetic Indices for Valproic Acid (250 mg):

Geometric Mean Arithmetic Mean (CV)				
	Novo-Valproic	Depakene®**	% Ratio of Geometric	Confidence Interval, 95%
	(2 x 250 mg)	(2 x 250 mg)	Means	%
AUC_T (µg•h/mL)	820.57 826.60 (12)	796.32 807.68 (14)	103	99.65-105.65%
AUC_I (µg•h/mL)	845.56 855.26 (15)	820.57 826.28 (14)	103	99.49-107.68%
Cmax (µg•h/mL)	55.04 (8.00)	51.17 (8.66)	107	100.91-115.59%
T_{max}* (h)	1.39 (0.87)	1.83 (1.21)	-	-
$T_{1/2}$* (h)	14.57 (17.51)	10.62 (2.77)	-	-

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).
**Depakene® 250mg capsules (Abbott Laboratories, Limited, Canada) Purchased in Canada

Pharmacokinetic Indices for Valproic Acid (500 mg) Fasted Study:

Geometric Mean Arithmetic Mean (CV)				
	Novo-Valproic	Depakene®**	% Ratio of Geometric	Confidence Interval, 95%
	(1 x 500 mg)	(1 x 500 mg)	Means	%
AUC_T (µg•h/mL)	871.91 886.67 (20)	836.02 851.50 (21)	104	100.06-108.70%
$AUC_{(0-12h)}$ (µg•h/mL)	400.66 402.35 (10)	387.82 390.34 (12)	103	98.04-108.87%
AUC_I (µg•h/mL)	916.80 933.68 (21)	886.98 904.23 (21)	103	99.45-107.42%
Cmax (µg•h/mL)	51.86 52.02 (7.8)	55.11 55.42 (11)	94	89.76-98.67%
T_{max}* (h)	3.19 (1.10)	2.94 (1.15)	-	-
$T_{1/2}$* (h)	14.75 (3.27)	14.74 (2.71)	-	-

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).
**Depakene® 500mg capsules (Abbott Laboratories, Limited, Canada) Purchased in Canada

Pharmacokinetic Indices for Valproic Acid (500 mg) Fed Study:

Geometric Mean Arithmetic Mean (CV)				
	Novo-Valproic	Depakene®**	% Ratio of Geometric	Confidence Interval, 95%
	(1 x 500 mg)	(1 x 500 mg)	Means	%
AUC_T (µg•h/mL)	894.77 910.0	941.26 953.9	95	90.2-100.2%
$AUC_{(0\text{-}12h)}$ (µg•h/mL)	208.99 217.2	258.22 155.0	81	15.7-143.6%
AUC_I (µg•h/mL)	938.37 955.8	1001.5 1019.5	94	88.6-99.0%
Cmax (µg•h/mL)	47.38 48.51	52.41 53.01	90	80.2-102.0%
T_{max}* (h)	9.75	14.44	-	-
$T_{1/2}$* (h)	14.46	14.95	-	-

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).
**Depakene® 500mg capsules (Abbott Laboratories, Limited, Canada) Purchased in Canada

DETAILED PHARMACOLOGY

Animal

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, $C0_2$ withdrawal, pentylene tetrazole, cobalt, bemegride, bicuculline and l-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.

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 (l0/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 nontoxic 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.

Mutagenicity and Carcinogenicity

Mutagenicity

Valproate was not mutagenic in an in vitro bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an in vivo cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of increase in SCE frequency is not known.

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 in a weak carcinogen or promoter in rats and mice. The significance of these findings for humans is unknown at present.

Reproduction and Teratology

Studies in rats have shown placental transfer of the drug. 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.

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.

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 and on sperm production and fertility in humans is unknown.

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PART III: CONSUMER INFORMATION

[Pr]NOVO-VALPROIC capsules
valproic acid

This leaflet is PART III of a three-part "Product Monograph" published when NOVO-VALPROIC was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about NOVO-VALPROIC. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for;

- NOVO-VALPROIC has been prescribed to you to control your epilepsy. Please follow your doctor's recommendations carefully.

What it does;

NOVO-VALPROIC has anticonvulsant properties. The mechanism of action has not yet been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

When it should not be used;

NOVO-VALPROIC should not be taken by:

- patients with liver disease or significant liver dysfunction
- patients who are allergic to the drug
- patients with known urea cycle disorders (a genetic disorder)

What the medicinal ingredient is:

valproic acid

What the non-medicinal ingredients are:

250mg: Corn oil, ethyl vanillin, FD&C Yellow #6, gelatin, glycerin, purified water and titanium dioxane.

500 mg: Aquacoat ECD-30, Aquateric (Type CD-910), Carnauba wax, ethyl vanillin, FD&C Yellow #6, gelatin, glycerin, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate, propylene glycol, purified water, titanium dioxane and triacetin.

What dosage forms it comes in:

NOVO-VALPROIC is available as a capsule containing 250 mg or 500mg of valproic acid.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Hepatotoxicity:** liver failure resulting in death has occurred in patients receiving valproic acid. These incidents usually occurred during the first 6 months of treatment with valproic acid. Patients taking several anticonvulsant drugs, children, those with a history of liver disease, metabolic disorders, severe seizure disorders accompanied by mental retardation, and those with 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.
- T**eratogenicity:** Valproic acid can produce birth defects to an unborn baby. Accordingly, the use of valproic acid in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus.
- **Pancreatitis:** cases of life threatening pancreas disorder have been reported in both children and adults receiving valproic acid. Some cases have occurred shortly after first use as well as after several years of use. Abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require immediate medical evaluation.

BEFORE you use NOVO-VALPROIC talk to your doctor or pharmacist if:

- you have a history of, or suffer from a liver disease, such as jaundice (yellowing of the skin and eyes);
- you ever had an unusual or allergic reaction to valproic acid (including fever or rash);
- you are allergic to any component of valproic acid capsules or oral solution;
- you are pregnant or are planning to become pregnant;
- you are breast-feeding (nursing); valproic acid passes into breast milk;
- you are taking any other prescription or over the counter medicine;
- you have kidney disease;
- you have other medical conditions including a history of unexplained coma, mental retardation or any type of brain dysfunction;
- you have a psychiatric disorder or have thoughts of suicide;
- you consume alcohol on a regular basis.

Precautions while taking NOVO-VALPROIC:

- Your doctor will monitor your response to NOVO-VALPROIC on a regular basis. However, if your seizures get worse, you should tell your doctor immediately.
- Since valproic acid may cause poor coordination and/or drowsiness, you should not engage in hazardous activities, such as driving and operating machinery, until you know that you don't become drowsy from the drug.

- You should not stop taking your medication unless directed by your doctor. You should always check that you have an adequate supply of NOVO-VALPROIC, You should remember that this medicine was prescribed only for you; it should never be given to anyone else.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

- Rare cases of coma have been reported in patients receiving valproic acid alone or when taken with phenobarbital.
- Serious skin reactions (such as conditions called Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported when valproic acid and lamotrigine were taken together.

Drugs that may interact with NOVO-VALPROIC include:

- anticonvulsants such as carbamazepine, lamotrigine, primidone, topiramate, felbamate, phenytoin, ethosuximide, phenobarbital;
- anticoagulants 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 medication such as zidovudine;
- any of the group of 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;
- antipsychotics.

PROPER USE OF THIS MEDICATION

Please consult your doctor before taking any other medication, including over-the-counter medicines. Some drugs can produce various side effects when they are used in combination with NOVO-VALPROIC.

It is important to keep your appointments for medical checkups.

The doctor may need to take blood tests to measure the amount of NOVO-VALPROIC in your blood when adjusting your medications.

Usual dose:

It is very important to take NOVO-VALPROIC exactly as instructed by your doctor.

The recommended starting dose of NOVO-VALPROIC will be decided by your doctor based on your weight, your seizures or manic episodes and your concomitant medications. Be sure to tell your doctor all the prescription and over the counter medications that you are currently taking. Your doctor will gradually increase the dosage until your condition is well controlled without experiencing side effects. You should carefully follow the instructions that were given to you and not change your dose without consulting with your doctor.

NOVO-VALPROIC may be taken with or without food.

Overdose:

If you accidentally take an overdose of NOVO-VALPROIC, you should contact your doctor or nearest hospital emergency, or your Regional Poison Control Centre, even though you may not feel sick.

Missed Dose:

Do not abruptly stop taking your medicine because of the risk of increasing your epileptic seizures.

If you miss a dose, you should not try to make up for it by doubling up on your next dose. You should take your next regularly scheduled dose and try not to miss any more doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should check with your doctor or pharmacist right away if you notice any bothersome or unusual effects while taking NOVO-VALPROIC.

Different side effects have been reported by patients taking valproic acid. The most commonly reported adverse reactions are nausea, vomiting and indigestion. You should know that this does not mean that you will experience such effects, because people can react in different ways to the same medicine.

IMPORTANT: PLEASE READ

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist right away		Seek Emergency medical attention
		Only if severe	In all cases	
Common	Nausea	√		
	Vomiting	√		
	Indigestion	√		
	Sedation	√		
	Headache	√		
	Diarrhea	√		
Un-common	Brain dysfunction with high blood ammonia levels (increased lethargy/ drowsiness, vomiting, ataxia [abnormal gait, abnormal walking], episodes of extreme irritability†, combative/bizarre behaviour†† and refusal to eat meat or high protein products††)		√	
	Decreased number of platelets in the blood (may result in easy bruising and bleeding from the skin or other areas)		√	
	Liver disorder (not feeling well, develop weakness, lethargy, facial swelling, loss of appetite, yellowing of the skin or eyes, dark urine, and vomiting)		√	
	Pancreas disorder (abdominal pain, nausea, vomiting, and/or loss of appetite)		√	
	Thoughts of suicide or hurting yourself		√	

† In young children
†† In older children or adults

This is not a complete list of side effects. For any unexpected effects while taking NOVO-VALPROIC, contact your doctor or pharmacist.

HOW TO STORE IT

NOVO-VALPROIC capsules should be stored between 15°C and 30°C. Unit dose strips should be stored between 15°C and 25°C and protected from high humidity.

NOVO-VALPROIC should be kept out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at:**
  www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:

o Fax toll-free to 1-866-678-6789
o Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON KIA OK9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at http://www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited
at: 1-800-268-4127 ext. 5005 (**English**) or
druginfo@tevacanada.com

or 1-877-777-9117 (**French**)

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