PRODUCT MONOGRAPH

[Pr] phl-DIVALPROEX

(Divalproex Sodium USP)

Enteric-Coated Tablets (125 mg, 250 mg, 500 mg)

Antiepileptic

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(Divalproex sodium, USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	enteric-coated tablets / 125 mg, 250 mg, 500 mg	Carnauba wax, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, maltodextrin, microcrystalline cellulose, polyethylene glycol, polyvinyl acetate phthalate, povidone, pregelatinized starch, purified stearic acid, sodium alginate, sodium bicarbonate, talc, titanium dioxide, triethyl citrate. In addition, individual tablets contain: 125 mg: D&C Red No.27, FD & C Blue No.2, FD & C Yellow No.6, and FD&C Yellow No.10 250 mg: FD & C Blue No.2, FD & C Yellow No.6 500 mg: D & C Red No.30, FD & C Blue No.1, FD & C Red No.40.

INDICATIONS AND CLINICAL USE

phl-DIVALPROEX (divalproex sodium) enteric-coated tablets are indicated for:

Epilepsy

- 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.

Acute Mania

- the treatment of the manic episodes associated with bipolar disorder (DSM-III-R).

The safety and effectiveness of divalproex sodium for long-term use in mania, that is for more than 3 weeks, has not been evaluated in controlled trials.

phl-DIVALPROEX is not indicated for use as a mood stabilizer in patients under 18 years of age.

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 divalproex sodium 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 divalproex sodium in this population. For a brief discussion, see [**WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics (≥ 65 years of age)**], (**DOSAGE AND ADMINISTRATION**, **Dosing in Elderly Patients)** and (**ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Pediatrics (< 18 years of age):
When divalproex sodium 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)**]. The safety and effectiveness divalproex sodium for the treatment of acute mania has not been studied in individuals below the age of 18 years.

CONTRAINDICATIONS

- phl-DIVALPROEX (divalproex sodium) enteric-coated tablets should not be administered to patients with hepatic disease or significant hepatic dysfunction.

- phl-DIVALPROEX is contraindicated in patients with known hypersensitivity to the drug. For a complete listing, see the (**DOSAGE FORMS, COMPOSITION AND PACKAGING)** section of the Product Monograph.

- phl-DIVALPROEX 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 divalproex sodium. These incidences usually occurred during the first 6 months of treatment with divalproex sodium. Caution should be observed when administering divalproex sodium 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 Hepatotoxicity**).

- **Teratogenicity:** divalproex sodium 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 divalproex sodium. 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 2**).

Patients with Special Diseases and Conditions
There are in vitro studies that suggest valproate stimulates the replication of the Human Immunodeficiency Virus and Cytomegalovirus (HIV and CMV) 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
Divalproex sodium enteric-coated tablet is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of divalproex sodium in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to initiation of divalproex sodium evaluation for urea cycle disorders (UCD) should be considered in the following patients:

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

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

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

- those with other signs or symptoms of UCD. Patients receiving divalproex sodium who develop symptoms of unexplained hyperammonemic encephalopathy should receive prompt treatment (including discontinuation of divalproex sodium 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 divalproex sodium 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 who present with hypothermia. See (**WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, **Hypothermia**). If serum ammonia is increased, divalproex sodium 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 Encephalopathy 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 divalproex sodium should be considered.

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use

Concomitant administration of topiramate and divalproex sodium 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 divalproex sodium 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 divalproex sodium therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with divalproex sodium after starting topiramate treatment or after increasing the daily dose of topiramate. See (**WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, **Hyperammonemia**, **Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use** and **DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Table 2**). 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 divalproex sodium in patients who develop hypothermia. See (**WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, **Hyperammonemia** and **Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use**).

Hematologic

Thrombocytopenia

Because of reports of thrombocytopenia, 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 divalproex sodium 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 the 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 (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 ER (divalproex sodium extended-release tablets), in 44 epilepsy patients, indicate that the frequency of treatment-emergent mild thrombocytopenia (platelet count between 100 to150 $\times 10^9$/L) was significantly higher after 12 weeks of treatment with divalproex sodium ER 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 divalproex sodium and its derivatives. These incidences usually occurred during the first 6 months of treatment with divalproex sodium Caution should be observed when administering divalproex sodium 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 divalproex sodium as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only divalproex sodium. 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 divalproex sodium alone.

If divalproex sodium is to be used for the control of seizures 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 risks. See [**WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (< 18 years of age)].**

Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as, malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Patients and parents should be instructed to report such symptoms. Because of the nonspecific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking divalproex sodium.

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, divalproex sodium 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 hepatic effects (particularly elevated liver enzymes) 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 divalproex sodium. 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 divalproex sodium. 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, divalproex sodium should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Neurologic

Driving and Hazardous Occupations
Divalproex sodium 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 indication 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 divalproex sodium therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, 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, divalproex sodium 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 divalproex sodium on testicular development 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 divalproex sodium. Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and divalproex sodium administration (see Lamotrigine Product Monograph for details on lamotrigine dosing with concomitant divalproex sodium administration).

Special Populations

Pregnant Women:
According to published and unpublished reports in the medical literature, divalproex sodium 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 divalproex sodium during pregnancy when compared with some other AEDs. Therefore, divalproex sodium 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 2- to 3-fold. The increase is largely due to specific defects such as congenital malformations of the heart, cleft lip and/or palate, craniofacial abnormalities 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 divalproex sodium to treat epilepsy. The incidence of neural tube defects in the fetus is increased in mothers receiving divalproex sodium during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of divalproex sodium 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 Disorder

There have been post-marketing reports of developmental delay, autism and/or autism spectrum disorder in the offspring of women exposed to divalproex sodium 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 divalproex sodium may develop clotting abnormalities. A patient who had low fibrinogen when taking multiple anticonvulsants, including divalproex sodium gave birth to an

infant with afibrinogenemia who subsequently died of hemorrhage. If divalproex sodium 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 divalproex sodium.

Epileptic women of childbearing 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.

Risk-benefit must be carefully considered when treating or counselling women of childbearing age for bipolar disorder.

If divalproex sodium 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 divalproex sodium.

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:
Divalproex sodium is excreted 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 divalproex sodium. 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 divalproex sodium 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.

The safety and effectiveness of divalproex sodium for the treatment of acute mania has not been studied in individuals below the age of 18 years.

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 divalproex sodium 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 divalproex sodium in this population.

A study of elderly patients revealed valproate-related somnolence and discontinuation of divalproex sodium 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), divalproex sodium 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 divalproex sodium 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 divalproex sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy 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 2**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Epilepsy
The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since divalproex sodium enteric-coated tablets 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 divalproex sodium alone or to the combination of drugs.

Adverse events that have been reported with divalproex sodium 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, constipation and parotid gland swelling have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients. In some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened gastrointestinal transit times, there have been postmarketing reports of divalproex sodium ER extended-release tablets in the stool. There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving divalproex sodium. See (**WARNINGS AND PRECAUTIONS**,

	Hepatic/Biliary/Pancreatic, **Pancreatitis**).
General Disorders and Administration Site Conditions:	Edema of 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 Disorders:	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 (elevated plasma glycine concentration) has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic 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 divalproex sodium. Some studies have indicated that supplemental calcium and vitamin D may be of benefit to patients who are on chronic divalproex sodium therapy.
Nervous System Disorders:	A lupus erythematosus-like syndrome has been reported rarely. Sedative effects have been noted in patients receiving divalproex sodium alone but occur most often in patients on combination therapy. Sedation usually disappears upon reduction of other

	antiepileptic 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 divalproex sodium 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 divalproex sodium.
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 divalproex sodium.
	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 (SJS), 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 divalproex sodium 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 divalproex sodium. See (**DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Table 2**).
	Cutaneous vasculitis has also been reported.

Divalproex sodium versus divalproex sodium extended release
A 24 week cross-over study compared the safety and efficacy of divalproex sodium extended-release tablets administered once daily to that of equal doses of divalproex sodium enteric coated tablets (administered twice daily or three times daily) in the treatment of adolescent and adult epileptic patients with generalized seizures (n=44). Two adverse events occurred in significantly more patients on divalproex sodium extended-release tablets than on divalproex sodium tablets asthenia (15.9% versus 6.8% respectively) and treatment-emergent mild thrombocytopenia (16.2% versus 6.8%, respectively).

Bipolar Disorder
The incidence of adverse events has been ascertained based on data from two short-term (21 day) placebo-controlled clinical trials of divalproex sodium in the treatment of acute mania, and from 2 long- term (up to 3 years) retrospective open trials.

Most Commonly Observed

During the short-term placebo-controlled trials, the six most commonly reported adverse events in patients (n = 89) exposed to divalproex sodium were nausea (22%), headache (21%), somnolence (19%), pain (15%), vomiting (12%), and dizziness (12%).

In the long-term retrospective trials (634 patients exposed to divalproex sodium), the six most commonly reported adverse events were somnolence (31%), tremor (29%), headache (24%), asthenia (23%), diarrhea (22%), and nausea (20%).

Associated With Discontinuation of Treatment
In the placebo-controlled trials, adverse events which resulted in divalproex sodium discontinuation in at least one percent of patients were nausea (4%), abdominal pain (3%), somnolence (2%), and rash (2%).

In the long-term retrospective trials, adverse events which resulted in divalproex sodium discontinuation in at least one percent of patients were alopecia (2.4%), somnolence (1.9%), nausea (1.7%), and tremor (1.4%). The time to onset of these events was generally within the first two months of initial exposure to divalproex sodium. A notable exception was alopecia, which was first experienced after 3 to 6 months of exposure by 8 of the 15 patients who discontinued divalproex sodium in response to the event.

Controlled Trials

Table 1 summarizes those treatment-emergent adverse events reported for patients in the placebo-controlled trials when the incidence rate in the divalproex sodium group was at least 5%. (Maximum treatment duration was 21 days; maximum dose in 83% of patients was between 1,000 to 2,500 mg per day).

System Organ Class/Event	Divalproex sodium N = 89 (%)	placebo N = 97 (%)
Gastrointestinal Disorders		
Nausea	22.5	15.5
Vomiting	12.4*	3.1
Diarrhea	10.1	13.4
Abdominal Pain	9	8.2
Dyspepsia	9	8.2
Constipation	7.9	8.2
General Disorders and Administration Site Conditions		
Pain	14.6	15.5
Asthenia	10.1	7.2
Injury, Poisoning and Procedural Complications		
Accidental Injury	11.2	5.2
Musculoskeletal and Connective Tissue Disorders		
Back Pain	5.6	6.2
Nervous System Disorders		
Headache	21.3	30.9
Somnolence	19.1	12.4
Dizziness	12.4	4.1
Tremor	5.6	6.2
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngitis	6.7	9.3
Skin and Subcutaneous Tissue Disorders		
Rash	5.6	3.1

* Statistically significant at $P < 0.05$ level.

The following adverse events not listed above were reported by at least 1%, but less than 5%, of the 89 patients from the two placebo-controlled clinical trials of divalproex sodium tablets.

Cardiac Disorders:	Palpitations, tachycardia.
Congenital, Familial and Genetic Disorders:	Vascular anomaly.
Ear and Labyrinth Disorders:	Deafness, ear disorder, ear pain, tinnitus, vertigo.
Eye Disorders:	Abnormal vision, amblyopia, conjunctivitis, diplopia, dry eyes, eye pain.
Gastrointestinal Disorders:	Fecal incontinence, flatulence, gastroenteritis, glossitis.
General Disorders and Administration Site Conditions:	Abnormal gait, chest pain, chills, chills and fever, cyst, edema, fever, furunculosis, periodontal abscess, peripheral edema.
Infections and Infestations:	Infection, rhinitis.
Metabolism and Nutrition Disorders:	Anorexia.
Musculoskeletal and Connective Tissue Disorders:	Arthralgia, arthrosis, leg cramps, neck pain, neck rigidity twitching
Nervous System Disorders	Ataxia, dysarthria, hypertonia, hypokinesia, paresthesia, reflexes increased, tardive dyskinesia.
Psychiatric Disorders:	Abnormal dreams, agitation, catatonic reaction, confusion, depression, hallucinations, insomnia, thinking abnormalities.
Renal and Urinary Disorders:	Dysurea, urinary incontinence.
Reproductive System and Breast Disorders:	Dysmenorrhea.
Respiratory, Thoracic and Mediastinal Disorders:	Dyspnea.
Skin and Subcutaneous Tissue Disorders:	Alopecia, discoid lupus erythematosus, dry skin, maculopapular rash, seborrhea.
Vascular Disorders:	Ecchymosis, hypertension, hypotension, postural hypotension, vasodilation.

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 divalproex sodium.

DRUG INTERACTIONS

Serious Drug Interactions

- Rare cases of coma have been reported in patients receiving divalproex sodium alone or in conjunction with phenobarbital. See (**Drug-Drug Interactions**, **Table 2**).
- Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and divalproex sodium administration. See (**Drug-Drug Interactions**, **Table 2**).

Overview

Divalproex sodium 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 divalproex sodium 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 divalproex sodium clearance because cytochrome P_{450} microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

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

Drug-Drug Interactions

Table 2 provides information about the potential influence of several commonly prescribed medications on valproate pharmacokinetics as well as the potential influence of valproate 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 2- Summary of Drug-Drug Interaction Studies Including Important Interaction, Non-clinically Important Interactions and No Observed Interactions

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

Benzodiazepines			divalproex sodium 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 divalproex sodium 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 carbamazepine decreased 17% while that of carbamazepine-10,11-epoxide increased by 45% upon co-administration of divalproex sodium 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 paitents 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 divalproex sodium (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 divalproex sodium by altering its metabolism. In patients receiving divalproex sodium, serum valproic acid levels should be monitored when treatment with cimetidine is instituted, increased, decreased, or discontinued. The divalproex sodium dose should be adjusted accordingly.
Clonazepam	T	No PK interaction	The concomitant use of divalproex sodium 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 divalproex sodium was co-administered with clozapine.

Diazepam	CT	↑ diazepam	Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of divalproex sodium (1,500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n = 6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.
Ethosuximide	CT	↑ ethosuximide	Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with divalproex sodium (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 divalproex sodium 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 divalproex sodium to patients with epilepsy (n = 10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to divalproex sodium 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 divalproex sodium dosage may be necessary when felbamate therapy is initiated. Lower doses of divalproex sodium 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 divalproex sodium (200 mg twice daily) revealed no significant changes in valproate trough plasma levels.

Lamotrigine	CT	↑ lamotrigine ↓ valproate	The effects of divalproex sodium on lamotrigine were investigated in 6 healthy male subjects. Each subject received a single oral dose of lamotrigine alone and with divalproex sodium 200 mg every 8 hours for 6 doses starting 1 hour before the lamotrigine dose was given. divalproex sodium 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 divalproex sodium co-administration (a 165% increase). In a study involving 16 epileptic patients, divalproex sodium 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 divalproex sodium 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 divalproex sodium 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 divalproex sodium administration.
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 Cmax of valproate. Tmax was also reduced. Although these changes were statistically significant, they are not likely to have clinical importance. Co-administration of divalproex sodium (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 divalproex sodium (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. divalproex sodium is not a significant enzyme inducer and would not be expected to decrease concentrations of steroid hormones. However, clinical data about the interaction of divalproex sodium with oral contraceptives are minimal. Administration of a single-dose of ethinyloestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on divalproex sodium (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 divalproex sodium (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.
Phenytoin	CT	↑ phenytoin	Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of PIVAL® (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 divalproex sodium 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 divalproex sodium as phenobarbital.

Rifampin	CT	↓ valproate	A study involving the administration of a single dose of divalproex sodium (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. divalproex sodium 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 divalproex sodium 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 divalproex sodium. The clinical relevance of this displacement is unknown.
Topiramate	CT	Effect unknown	Hyperammonemia Concomitant administration of divalproex sodium 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 divalproex sodium 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).**
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 divalproex sodium is instituted in patients taking anticoagulants. Caution is recommended when divalproex sodium 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 divalproex sodium (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 divalproex sodium 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

Divalproex sodium 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 divalproex sodium; 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

Epilepsy

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 divalproex sodium is titrated upward, blood concentrations of phenobarbital, carbamazepine 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 divalproex sodium 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

Epilepsy

phl-DIVALPROEX (divalproex sodium) enteric-coated tablets are 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 is 250 mg and over, it should be given in a divided regimen (**Table 3**).

Table 3. Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Dosage (mg) equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10 to 24.9	22 to 54.9	250	125	0	125
25 to 39.9	55 to 87.9	500	250	0	250
40 to 59.9	88 to 131.9	750	250	250	250
60 to 74.9	132 to 164.9	1,000	250	250	500
75 to 89.9	165 to 197.9	1,250	500	250	500

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 phl-DIVALPROEX

phl-DIVALPROEX enteric-coated tablets dissociate to the valproate ion in the gastrointestinal tract. phl-DIVALPROEX 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 divalproex sodium tablets is equivalent to that of valproic acid capsules.

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

Acute Mania

phl-DIVALPROEX is not indicated for the treatment of the symptoms of mania in patients under 18 years of age.

The recommended initial dose is 250 mg three times a day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations.

In placebo-controlled trials, 84% of patients received and tolerated maximum daily doses of between 1,000 to 2,500 mg/day. The maximum recommended dosage is 60 mg/kg/day.

The relationship of plasma concentration to clinical response has not been established for divalproex sodium. In controlled clinical studies, 79% of patients achieved and tolerated serum valproate concentrations between 50 mcg/mL and 125 mcg/mL.

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

phl-DIVALPROEX 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 the initial low level. The tablets should be swallowed without chewing. Co-administration of phl-DIVALPROEX with food should cause no clinical problems in the management of patients with epilepsy.

OVERDOSAGE

Overdosage with divalproex sodium 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 divalproex sodium 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. 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 divalproex sodium overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of divalproex sodium, it should be used with caution in patients with epilepsy.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Divalproex sodium has anticonvulsant properties, and is chemically related to valproic acid. divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. Although its 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). 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 concentration 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 ADMINISTRATION**). In placebo-controlled clinical studies in acute mania, 79% of patients were dosed to a plasma concentration between 50 and 125 mcg/mL. Protein binding of valproate is saturable ranging from 90% at 50 mcg/mL to 82% at 125 mcg/mL.

Pharmacokinetics

Table 4 Summary of the Pharmacokinetic Parameters of divalproex sodium in Healthy, Fasting Subjects

			Mean (SD) Pharmacokinetic Parameters					
Single Dose	**Dosage**	**N**	**C_{max} (mg/L)**	**T_{max} (h)**	**$t_{½}$ (h)**	**AUC_4 (mg•h/L)**	**CL (1/h)**	**V_d (L)**
divalproex sodium	2 x 500 mg once daily	28	93.9 (11.7)	4.0 (1.2)	15.2 (15.3)	1818 (345)	--	--

Absorption:

Peak serum levels of valproic acid occur in 3 to 4 hours. 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 doses 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 drugs capable of hepatic 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., mL/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 tablets between 15 °C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

phl-DIVALPROEX particle coated tablets :

125 mg: Each red coloured tablets contains 125 mg divalproex sodium, and the following non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, D&C Red No.27, FD & C Blue No.2, FD & C Yellow No.10, FD&C Yellow No.6, hydroxypropyl methylcellulose, magnesium stearate, maltodextrin, microcrystalline cellulose, polyethylene glycol, polyvinyl acetate phthalate, povidone, pregelatinized starch, purified stearic acid, sodium alginate, sodium bicarbonate, talc, titanium dioxide, triethyl citrate.
Available in bottles of 100 and 500 tablets.

250 mg: Each peach tablet contains 250 mg divalproex sodium and the following non-medicianl ingredients: carnauba wax, colloidal silicon dioxide, FD & C Blue No.2, FD & C Yellow No. 6, hydroxypropyl methylcellulose, magnesium stearate, maltodextrin, microcrystalline cellulose, polyethylene glycol, polyvinyl acetate phthalate, povidone,

pregelatinized starch, purified stearic acid, sodium alginate, sodium bicarbonate, talc, titanium dioxide, triethyl citrate,
Available in bottles of 100 and 500 tablets.

500 mg: Each pink tablet contains 500 mg divalproex sodium and the following non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, D & C Red No.30, FD & C Blue No.1, FD & C Red No.40, hydroxypropyl methylcellulose, magnesium stearate, maltodextrin, microcrystalline cellulose, polyethylene glycol, polyvinyl acetate phthalate, povidone, pregelatinized starch, purified stearic acid, sodium alginate, sodium bicarbonate, talc, titanium dioxide, triethyl citrate.
Available in bottles of 100 and 500 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Divalproex Sodium USP

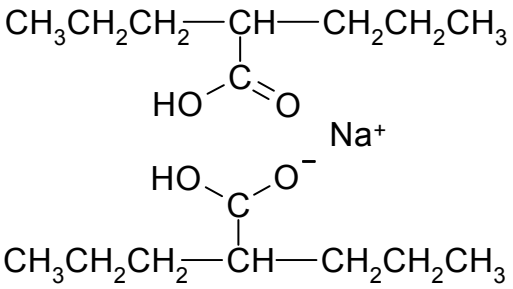
USAN Names: INN: Valproate Semisodium
BAN: Semisodium Valproate

Chemical Name: Sodium hydrogen bis (2-propylpentanoate) or Sodium hydrogen bis (2- propylvalerate)

Molecular Weight: Undefined (polymeric in nature)

Molecular Formula: $(C_{16}H_{31}NaO_4)_n$

Structural Formula:



Description:

Divalproex sodium, is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. It is a white powder with a characteristic odor, freely soluble in many organic solvents and in aqueous alkali solutions.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single dose, randomized, two-period, two-sequences, crossover comparative bioavailability studies were carried out to compare the pharmacokinetic parameters of phl-DIVALPROEX 125 mg tablets (Pharmel Inc.) versus EPIVAL® 125 mg tablets (Abbott Laboratories Ltd.) in 28 healthy male subjects under fasting state. The results from 28 healthy male subjects who completed the study are presented in the following table:

Fasting state **Valproic Acid** **(1 x 125 mg Divalproex Sodium)** **From measured data** **Geometric Mean** **Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval (95%)**
AUC_T (ng•h/mL)	214338 220287 (26.05)	214226 219975 (25.09)	100	97 - 103
AUC_I (ng•h/mL)	233581 242852 (32.90)	233553 242368 (31.46)	100	97 - 103
C_{max} (ng/mL)	13432 13573 (15.40)	13586 13962 (12.86)	99	95 - 103
T_{max}‖ (h)	1.94 (35.13)	2.38 (37.38)		
$T_{1/2el}$‖ (h)	15.87 (23.08)	15.54 (23.32)		

* phl-DIVALPROEX, Pharmel Inc., Canada
† EPIVAL®, Abbott Laboratories Ltd, Canada.
‖ Expressed as the arithmetic mean (CV%) only.

A single dose, randomized, two-period, two-sequences, crossover comparative bioavailability studies were carried out to compare the pharmacokinetic parameters of phl-DIVALPROEX 125 mg tablets (Pharmel Inc.) versus EPIVAL® 125 mg tablets (Abbott Laboratories Ltd.) in 28 healthy male subjects under fasting state. The results from 26 healthy male subjects who completed the study are presented in the following table:

Fed state **Valproic Acid** **(1 x 125 mg Divalproex Sodium)** **(1 x 125 mg)** **From measured data** **Geometric Mean** **Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval (95%)**
AUC_T (ng•h/mL)	197383 294121 (27.24)	196999 203582 (26.92)	100	97 to 103
AUC_I (ng•h/mL)	216229 225679 (31.96)	217058 226443 (31.74)	100	97 to 103
C_{max} (ng/mL)	12789 12840 (9.07)	12973 13099 (13.99)	99	94 to 103
T_{max}‖ (h)	4.31 (35.66)	4.81 (28.05)	--	
$T_{1/2el}$‖ (h)	15.25 (22.84)	14.83 (26.85)	--	

* phl-DIVALPROEX, Pharmel Inc., Canada
† EPIVAL®, Abbott Laboratories Ltd, Canada.
‖ Expressed as the arithmetic mean (CV%) only.

Study results

A 24 week cross-over study compared the safety and efficacy of a controlled-release formulation of divalproex sodium administered once daily, to equal doses of an enteric-coated formulation of divalproex sodium administered twice daily or three times daily, in the treatment of adolescent and adult epileptic patients with generalized seizures. The seizure control rate did not differ significantly between the two treatments. On enteric-coated divalproex sodium, 41/43 patients, or 95.3%, were seizure-free while the seizure control rate on controlled-release divalproex sodium was 40/43 or 93.0%. This does not appear to be clinically different from the estimated general seizure control rate during the year before the start of the study when 40/44 (90.9%) patients reported being seizure-free on enteric-coated divalproex sodium.

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, CO_2 withdrawal, pentylene tetrazole, cobalt, bemegride, bicuculline and 1-glutamate. Many forms of photic and auditory induced seizures are also effectively blocked by valproic acid.

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

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

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

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

Divalproex sodium produced plasma valproic acid concentrations comparable to those of valproic acid when the two compounds were administered orally at equimolar doses to mice, rats and a beagle dog.

TOXICOLOGY

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

Acute Toxicity

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

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

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

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

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

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

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

Subacute and Chronic Toxicity

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

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] phl-DIVALPROEX
Divalproex sodium

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

ABOUT THIS MEDICATION

What the medication is used for:
phl-DIVALPROEX has been prescribed to you to either:

- control your epilepsy
- treat symptoms of mania associated with bipolar disorder, such as aggressiveness, agitation, impulsive behaviour or excessively elevated mood.

phl-DIVALPROEX is not indicated for the treatment of the symptoms of mania in patients under 18 years of age.

Please follow your doctor's recommendations carefully.

What it does:
phl-DIVALPROEX 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:
phl-DIVALPROEX 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:
Divalproex sodium

What the nonmedicinal ingredients are:
carnauba wax, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, maltodextrin, microcrystalline cellulose, polyethylene glycol, polyvinyl acetate phthalate, povidone, pregelatinized starch, purified stearic acid, sodium alginate, sodium bicarbonate, talc, titanium dioxide, triethyl citrate, and the following:
125 mg: D&C Red No.27, FD & C Blue No.2, FD & C Yellow No.6, and FD&C Yellow No.10
250 mg: FD & C Blue No.2, FD & C Yellow No.6
500 mg: D & C Red No.30, FD & C Blue No.1, FD & C Red No.40.

What dosage forms it comes in:
Enteric Coated Tablets: 125 mg, 250 mg, and 500 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Hepatotoxicity:** liver failure resulting in death has occurred in patients receiving phl-DIVALPROEX. These incidents usually occurred during the first 6 months of treatment with phl-DIVALPROEX. 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.

- **Teratogenicity:** phl-DIVALPROEX can produce birth defects to an unborn baby. Accordingly, the use of phl-DIVALPROEX 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 phl-DIVALPROEX 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 phl-DIVALPROEX 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 phl-DIVALPROEX (including fever or rash);
- you are allergic to any component of phl-DIVALPROEX tablets;
- you are pregnant or are planning to become pregnant;
- you are breast-feeding (nursing); phl-DIVALPROEX 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 phl-DIVALPROEX:

- Your doctor will monitor your response to phl-DIVALPROEX on a regular basis. However, if your seizures get worse, you should tell your doctor immediately.
- Since phl-DIVALPROEX 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 phl-DIVALPROEX. 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 divalproex sodium alone or when taken with phenobarbital.
- Serious skin reactions (such as conditions called Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported when divalproex sodium and lamotrigine were taken together.

Drugs that may interact with phl-DIVALPROEX 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 phl-DIVALPROEX.

It is important to keep your appointments for medical checkups.

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

Usual dose:

It is very important to take phl-DIVALPROEX exactly as instructed by your doctor.

The recommended starting dose of phl-DIVALPROEX 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.

phl-DIVALPROEX may be taken with or without food.

phl-DIVALPROEX is not indicated for the treatment of the symptoms of mania in patients under 18 years of age.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

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 phl-DIVALPROEX.

Different side effects have been reported by patients taking phl-DIVALPROEX. 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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
Common	Nausea	✓		
	Vomiting	✓		
	Indigestion	✓		
	Sedation	✓		
	Headache	✓		
	Diarrhea	✓		
Uncommon	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 phl-DIVALPROEX, contact your doctor or pharmacist.

HOW TO STORE IT

phl-DIVALPROEX tablets should be stored between 15°C and 30°C.

phl-DIVALPROEX 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 online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at 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 obtained by contacting Pharmel Inc. at 1-888-550-6060.

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