# PRODUCT MONOGRAPH

for

**EPIVAL®**
(Divalproex Sodium Enteric-Coated Tablets)
125, 250, 500 mg

**EPIVAL® ER**
(Divalproex Sodium Extended Release Tablets)
500 mg

**EPIJECT® I.V.**
(valproic acid injection,
present as the sodium salt)

100 mg/mL Fliptop Vials

*Anticonvulsant*

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## THERAPEUTIC CLASSIFICATION

Anticonvulsant

## ACTIONS AND CLINICAL PHARMACOLOGY

EPIVAL® (divalproex sodium) has anticonvulsant properties, and is chemically related to valproic acid. EPIVAL® 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.

### PHARMACOKINETICS

***EPIVAL® (divalproex sodium) Enteric-Coated Tablets***

**Absorption/Bioavailability**

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.

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.

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., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). (See **PRECAUTIONS, Drug Interactions** for more detailed information on the pharmacokinetic interactions of valproate with other drugs).

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.

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (ranging from 7 to 25% of total concentration).

The absolute bioavailability of divalproex sodium extended-release (ER) tablets, administered as a single dose after a meal, was approximately 90% relative to intravenous infusion.

**Metabolism/Clearance**

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.

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% 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 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

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 antiepileptic drugs (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.

**Therapeutic Blood Levels**

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 mcg/mL and 125 mcg/mL. Protein binding of valproate is saturable ranging from 90% at 50 mcg/mL to 82% at 125 mcg/mL.

**Special Populations**

Neonates/ Infants

Within the first two 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.

Elderly

The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. (See **DOSAGE AND ADMINISTRATION**).

Effect of 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).

Effect of Race

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

**Hepatic Dysfunction**

See **CONTRAINDICATIONS,** and **WARNINGS** for statements regarding hepatic dysfunction and associated fatalities.

***EPIVAL® ER (divalproex sodium) Extended-Release Tablets***

After single-dose administration, the absolute bioavailability of EPIVAL® ER tablets averaged 92%, with the maximum plasma concentrations of valproate occurring on average 16 hours after dosing.

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

When administered as EPIVAL® ER, steady state valproate AUC was similar under fasting and non-fasting conditions. Neither co-administration of oral valproate products with food, nor substitution among the various EPIVAL® formulations are expected to cause clinical problems in the management of patients with epilepsy. (See **DOSAGE AND ADMINISTRATION**).

In healthy subjects, EPIVAL® ER administered once daily produced steady-state plasma concentrations equivalent with respect to AUC to those of EPIVAL® tablets administered twice daily, with a lower degree of fluctuation.

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

In patients with epilepsy also receiving antiepilepsy drugs that are known to induce hepatic microsomal enzymes (i.e., carbamazepine, phenobarbital, or phenytoin), steady-state plasma concentrations of valproate (Figure 1) obtained from once-a-day or twice-a-day dosing regimens of EPIVAL® ER were comparable to those from the same daily dose of q6h divalproex sodium enteric-coated tablets (1000 to 3000 mg/day).

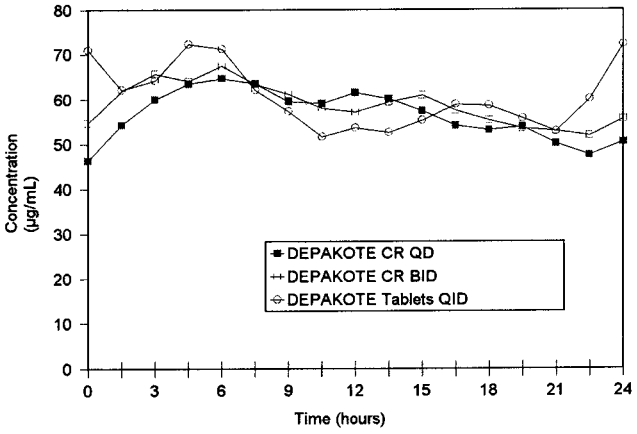



**Figure 1:** Steady-State Valproate Plasma Concentration Versus Time for Two regimens of EPIVAL® ER, and one of EPIVAL®, all in Patients Also Taking Drugs That Induce Hepatic Enzymes.

***EPIJECT® I.V. (valproic acid injection, present as the sodium salt)***

EPIJECT® I.V. exists as the valproate ion in the blood.

EPIJECT® I.V. has not been studied in children under two years of age. No unique safety concerns were identified in either the 24 patients of 2 to 17 years of age or the 19 patients over 65 years of age who received EPIJECT® I.V. in clinical trials.

Mean terminal half-life for valproate monotherapy after a 60-minute intravenous infusion of 1000 mg was 16 ± 3.0 hours.

Equivalent doses of intravenous (I.V.) valproate and oral valproate products are expected to result in equivalent $C_{max}$, $C_{min}$, and total systemic exposure to the valproate ion. However, the rate of valproate ion absorption may vary with the formulation used. These differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

Administration of divalproex sodium (EPIVAL®) tablets and I.V. valproate (given as a 60-minute infusion), 250 mg every 6 hours for four days to healthy male volunteers resulted in equivalent AUC, $C_{max}$, $C_{min}$ at steady state, as well as after the first dose. The $T_{max}$ after I.V. valproate sodium occurs at the end of the 60-minute infusion, while the $T_{max}$ after oral dosing with valproate sodium occurs at approximately four hours. Because the kinetics of unbound valproate are linear, bioequivalence between valproate sodium and divalproex sodium up to the maximum recommended dose of 60 mg/kg/day can be assumed. The AUC and $C_{max}$ resulting from administration of I.V. valproate 500 mg as a single 60-minute infusion and a single 500 mg dose of valproic acid syrup to 17 healthy male volunteers were also equivalent.

Patients maintained on valproic acid doses between 750 mg and 4250 mg daily (average daily dose was 1961 mg given in divided doses every six hours) as oral divalproex sodium alone (n=24) or with another stabilized antiepileptic drug [carbamazepine (n=15), phenytoin (n=11), or phenobarbital (n=1)], showed comparable plasma levels for valproic acid when switching from oral divalproex sodium to I.V. valproate (60-minute infusion).

**CLINICAL TRIALS**

A 24 week cross-over study compared the safety and efficacy of a controlled-release formulation of divalproex sodium (EPIVAL® ER) administered once daily, to equal doses of an enteric-coated formulation of divalproex sodium (EPIVAL®) administered b.i.d. or t.i.d., 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 EPIVAL®, 41/43 patients, or 95.3%, were seizure-free while the seizure control rate on EPIVAL® ER 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 EPIVAL®.

## INDICATIONS AND CLINICAL USE

### Epilepsy

EPIVAL® (divalproex sodium) enteric-coated tablets and EPIVAL® ER (divalproex sodium) extended-release tablets are indicated for use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal, and are useful in primary generalized seizures with tonic-clonic manifestations. Divalproex sodium may also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

EPIJECT® I.V. (valproic acid injection, present as the sodium salt) is indicated as an intravenous alternative in patients already stabilized on oral valproate products, and for whom oral administration is temporarily not feasible.

There is insufficient information on safety in patients requiring daily doses of I.V. valproate greater than 2000 mg, or more than 48 hours of I.V. dosing.

EPIJECT® I.V. has not been studied in children under two years of age.

### Acute Mania

EPIVAL® (divalproex sodium) enteric-coated tablets are indicated in the treatment of the manic episodes associated with bipolar disorder (DSM-III-R). EPIVAL® ER (divalproex sodium) extended-release tablets have not been studied in the treatment of manic episodes associated with bipolar disorder (DSM-III-R)

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

EPIVAL® is not indicated for use as a mood stabilizer in patients under 18 years of age.

See **CONTRAINDICATIONS**, and **WARNINGS** for statement regarding serious or fatal hepatic dysfunction.

## CONTRAINDICATIONS

EPIVAL® (divalproex sodium) ENTERIC-COATED TABLETS, EPIVAL® ER (divalproex sodium) EXTENDED-RELEASE TABLETS AND EPIJECT® I.V. (valproic acid injection, present as the sodium salt) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

They are also contraindicated in patients with known hypersensitivity to the drug(s).

Divalproex sodium is contraindicated in patients with known urea cycle disorders (See **WARNINGS**).

## WARNINGS

### Serious skin reactions

The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration (See Lamotrigine Product Monograph for details on lamotrigine dosing with concomitant valproate administration).

### Serious or Fatal Hepatoxocity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. These incidences usually occurred during the first six months of treatment with valproic acid. Caution should be observed when administering EPIVAL® products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received

only valproate. Above the age of two 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 valproate alone.

If EPIVAL® products are to be used for the control of seizures in children two 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 **PRECAUTIONS**, Use in Pediatrics)

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 EPIVAL® products.

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. Caution should be observed when administering divalproex sodium products to patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

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 **PRECAUTIONS**).

**Pancreatitis**

**Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 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, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.**

**Urea Cycle Disorders (UCD)**

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

1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;
2) those with signs and symptoms of UCD, for example, cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, protein avoidance;
3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males);
4) those with other signs or symptoms of UCD. Patients receiving valproate therapy who develop symptoms of unexplained hyperammonemic encephalopathy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (See **CONTRAINDICATIONS and PRECAUTIONS, General**).

**Somnolence in the elderly**

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

**Use in Pregnancy**

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

Multiple reports in the clinical literature indicate an association between the use of anti-epileptic drugs 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, e.g. congenital malformations of the heart, cleft lip and/or palate, craniofacial abnormalities and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

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

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 antiepileptic drug-treated women with seizure disorders cannot be regarded as a cause and effect relationship. There are intrinsic methodologic 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.

There have been reports of developmental delay in the offspring of women who have received valproic acid during pregnancy.

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

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

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

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

Epileptic women of 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 anti-epileptic 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 EPIVAL®, EPIVAL® ER, or EPIJECT® I.V. is used during pregnancy, or if the patient becomes pregnant while taking either of these 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 valproate.

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

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

An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a $mg/m^2$ basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a $mg/m^2$ basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 mcg/mL (2.8 times the upper limit of the human therapeutic range for epilepsy).

**Use in Nursing Mothers**

Valproic acid 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 EPIVAL®, EPIVAL® ER, or EPIJECT® I.V. It is not known what effect this may have on a nursing infant.

**Fertility**

The effect of valproate on testicular development and on sperm production and fertility in humans is unknown. (See **TOXICOLOGY**: **Fertility**; for results in animal studies)

**Dose-related Adverse Reactions: Thrombocytopenia**

The frequency of adverse effects thrombocytopenia (see **PRECAUTIONS**) 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 effects.

In addition, the findings from a crossover clinical trial conducted with EPIVAL® ER extended-release tablets, in 44 epilepsy patients, indicate that the frequency of treatment-emergent mild thrombocytopenia (platelet count between 100-150 x $10^9$/L) was significantly higher after 12 weeks of treatment with EPIVAL® ER than after 12 weeks of treatment with EPIVAL® (7 vs 3 low counts, respectively).

**Acute Head Injuries**

A study was conducted to evaluate the effect of I.V. valproate in the prevention of post-traumatic seizures in patients with acute head injuries. Patients were randomly assigned to receive either I.V. valproate given for one week (followed by oral valproate products for either one or six months per random treatment assignment) or I.V. phenytoin given for one week (followed by placebo). In this study, the incidence of death was found to be higher in the two groups assigned to valproate treatment compared to the rate in those assigned to the I.V. phenytoin treatment group (13% vs 8.5%, respectively). Many of these patients were critically ill with multiple and/or severe injuries, and evaluation of the causes of death did not suggest any specific drug-related causation.

Further, in the absence of a concurrent placebo control during the initial week of intravenous therapy, it is impossible to determine if the mortality rate in the patients treated with valproate was greater or less than that expected in a similar group not treated with valproate, or whether the rate seen in the I.V. phenytoin treated patients was lower than would be expected. Nonetheless, until further information is available, I.V. valproate sodium is not recommended in patients with acute head trauma for the prophylaxis of post-traumatic seizures.

**Carcinogenicity**

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**).

## PRECAUTIONS

### General

Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered as a possible cause and serum ammonia level should be measured. If serum ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (See **CONTRAINDICATIONS and WARNINGS**- **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 valproate therapy should be considered.

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 valproic acid: the clinical significance of these is unknown.

Suicidal ideation may be a manifestation of preexisting psychiatric disorders, and close supervision of high risk patients should accompany initial drug therapy.

Patients with Special Diseases and Conditions

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

### 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 instituting therapy and at periodic intervals. It is recommended that patients receiving either EPIVAL® (divalproex sodium) enteric-coated tablets, or EPIVAL® ER (divalproex sodium) extended-release tablets, 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 EPIVAL® or EPIVAL® ER dosage or withdrawal of therapy pending investigation. (See also **WARNINGS**, **Dose-related Adverse Reactions: Thrombocytopenia**).

**Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use**

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

It is not known if topiramate monotherapy is associated with hyperammonemia.

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

**Multi-organ Hypersensitivity Reaction**

Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritis, 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, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

**Hepatic Dysfunction**

See **CONTRAINDICATIONS** and **WARNINGS**.

**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.

**Use in Pediatric Patients**

Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (See **WARNINGS**). When EPIVAL® 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.

EPIVAL® ER has not been studied in pediatric patients.

EPIJECT® I.V. has not been studied in children under the age of two years. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations. The variability in free fraction limits the clinical usefulness of monitoring total serum valproic concentrations. Interpretation of valproic acid 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.

**Use in the Elderly**

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, Elderly).

The safety and efficacy of EPIVAL® in elderly patients with epilepsy and mania has not been systematically 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 EPIVAL® in this population.

A study of elderly patients revealed valproate-related somnolence and discontinuation of valproate therapy for this adverse event (See **WARNINGS- 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**).

**Use in Pregnancy**

See **WARNINGS**.

**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., aspirin). Accordingly, measurements of plasma levels of valproate may be misleading in these patients, as actual drug exposure may be higher than measured values. See **PRECAUTIONS, General, Thrombocytopenia**, and **Drug Interactions.**

## Driving and Hazardous Occupations

Divalproex sodium may produce 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.

## Drug Interactions

### 1. Effects of Co-administered Drugs on Valproate

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 valproate 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, e.g. antidepressants, may be expected to have little effect on valproate clearance because cytochrome $P_{450}$ microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

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

Since valproate 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.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported. Please note that drugs may be listed under specific name, family or pharmacologic class. Reading the entire section is recommended.

**1.1 Drugs for which a potentially important interaction has been observed:**

Aspirin

A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. Caution should be observed when valproate is administered with drugs affecting coagulation, (e.g., aspirin and warfarin) (See also **Effects of Valproate on Other Drugs** and **ADVERSE REACTIONS**).

Carbamazepine/carbamazepine-10,11-Epoxide

Concomitant use of carbamazepine with valproic acid may result in decreased serum concentrations and half-life of valproate due to increased metabolism induced by hepatic microsomal enzyme activity. Monitoring of serum concentrations is recommended when either medication is added to or withdrawn from an existing regimen (See also **Effects of Valproate on Other Drugs**).

Cimetidine

Cimetidine may decrease the clearance and increase the half-life of valproic acid by altering its metabolism. In patients receiving valproic acid, serum valproic acid levels should be monitored when treatment with cimetidine is instituted, increased, decreased, or discontinued. The valproic acid dose should be adjusted accordingly.

Felbamate

A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated. Lower doses of valproate may be necessary when used concomitantly with felbamate.

Meropenem

Subtherapeutic valproic acid levels have been reported when meropenem was co-administered.

Rifampin

A study involving the administration of a single dose of valproate (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. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Selective Serotonin Re-Uptake Inhibitors (SSRI's)

Some evidence suggests that SSRI's inhibit the metabolism of valproate, resulting in higher than expected levels of valproate.

Antipsychotics, MAO Inhibitors and Tricyclic Antidepressants

In addition to enhancing central nervous system (CNS) depression when used concurrently with valproic acid, antipsychotics, tricyclic antidepressants and MAO inhibitors may lower the seizure threshold. Dosage adjustments may be necessary to control seizures.

**1.2 Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:**

Antacids

A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine

A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg b.i.d.) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol

A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg b.i.d.) revealed no significant changes in valproate trough plasma levels.

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 EPIVAL®. The presence of lithium, however, resulted in an 11% to 12% increase in the AUC and $C_{max}$ of valproate. $T_{max}$ was also reduced. Although these changes were statistically significant, they are not likely to have clinical importance. (See also **Effects of Valproate on Other Drugs**).

## 2. Effects of Valproate on Other Drugs

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

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

Since valproate 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.

The following two sections (e.g., sections 2.1 and 2.2) provide information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The information in these two sections 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. It is recommended that the two sections be read.

### 2.1 Drugs for Which a Potentially Important Interaction has been Observed

Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration (See Lamotrigine sub-section below for additional information on concomitant lamotrigine and valproate administration).

Alcohol

Valproate potentiate the CNS depressant action of alcohol.

Amitriptyline/Nortriptyline

Administration of a single oral dose of amitriptyline 50 mg to 15 normal volunteers (10 males and five females) who received valproate (500 mg b.i.d.) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline.

Rare post-marketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline and nortriptyline levels have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Aspirin

Caution is recommended when valproate is administered with drugs affecting coagulation. (See **ADVERSE REACTIONS** and **PRECAUTIONS**- **Effects of Co-administered Drugs on Valproate**).

Benzodiazepines

Valproic acid may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations (See also **Diazepam** and **Lorazepam**).

Carbamazepine/carbamazepine-10,11-Epoxide

Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients. 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 metabolite of carbamazepine, however, will not be detected by routine serum carbamazepine assay. (See also **Effects of Co-administered Drugs on Valproate**).

Clonazepam

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide

Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine

The effects of sodium valproate on lamotrigine were investigated in six healthy male subjects. Each subject received a single oral dose of lamotrigine every 8 hours for six doses; half the doses were given alone and half with valproic acid 200 mg (administered 1 hour before the lamotrigine dose) Valproic acid administration reduced the total clearance of lamotrigine by 21% and increased the plasma elimination half-life from 37.4 hours to 48.3 hours ($p < 0.005$). Renal clearance of lamotrigine was unchanged. In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase).

In a study involving 16 epileptic patients, valproic acid doubled the elimination half-life of lamotrigine. In an open-labelled study, patients receiving enzyme inducing antiepileptic drugs (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 sodium valproate plus an enzyme inducing antiepileptic agent. The latter value is similar to the lamotrigine half-life during monotherapy indicating that valproic acid may counteract the effect of the enzyme inducer. If valproic acid is discontinued in a patient receiving lamotrigine and an enzyme inducing antiepileptic serum lamotrigine concentrations may decrease. Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered.

Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration.

Phenobarbital

Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg b.i.d. for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in 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

Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) 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 valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Primidone

Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction with valproate as phenobarbital.

Tolbutamide

From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Topiramate

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see **CONTRAINDICATIONS** and **WARNINGS**, **Urea Cycle Disorders (UCD)** and **PRECAUTIONS**, **General** and **Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use**).

Warfarin

In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown, however, coagulation tests should be monitored if valproate therapy is instituted in patients taking anticoagulants.

Caution is recommended when valproate is administered with drugs affecting coagulation. (See **ADVERSE REACTIONS**).

Zidovudine

In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

## 2.2 Drugs for Which Either No Interaction or a Likely Clinically Unimportant Interaction has been Observed

Acetaminophen

Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine

In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium

Co-administration of valproate (500 mg b.i.d.) and lithium carbonate (300 mg t.i.d.) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium. (See also

**Effects of Co-administered Drugs on Valproate**).

Lorazepam

Concomitant administration of valproate (500 mg b.i.d.) and lorazepam (1 mg b.i.d.) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids

Evidence suggests that there is an association between the use of certain antiepileptic drugs capable of enzyme induction and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing drugs effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. Valproic acid is not a significant enzyme inducer and would not be expected to decrease concentrations of steroid hormones. However, clinical data about the interaction of valproic acid with oral contraceptives are minimal.

Administration of a single-dose of ethinyloestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on valproate (200 mg b.i.d.) therapy for 2 months did not reveal any pharmacokinetic interaction.

## ADVERSE REACTIONS

### ORAL ADMINISTRATION

### Epilepsy

Since divalproex sodium has usually been used with other anti-epileptic drugs, in the treatment of epilepsy, 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 valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since divalproex sodium has usually been used with other anti-epilepsy drugs, in the treatment of epilepsy, 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.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain 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 extended-release tablets in the stool.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but occur most often in patients on combination therapy. Sedation usually disappears upon reduction of other 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 valproic acid alone or in conjunction with phenobarbital. Encephalopathy, with or without fever or hyperammonemia, has been reported without evidence of hepatic dysfunction or inappropriate valproate plasma levels. Most patients recovered, with noted improvement of symptoms, upon discontinuation of the drug.

Reversible cerebral atrophy and dementia have been reported in association with valproate therapy.

Dermatologic: 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 six month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions.

Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (See **PRECAUTIONS - Drug Interactions**).

Endocrine: There have been reports of irregular menses and secondary amenorrhea, breast enlargement, galactorrhea and parotid gland swelling in patients receiving valproic acid. Abnormal thyroid function tests have been reported (See **PRECAUTIONS**; **General**). There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility and behavioural deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: 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 **PRECAUTIONS**; **General**). 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.

Hepatic: Minor elevations of transaminases (e.g. SGOT and SGPT) and 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**).

Metabolic: Hyperammonemia (See **PRECAUTIONS**), hyponatremia and inappropriate ADH secretion. There have been rare reports of Fanconi syndrome occurring primarily in children. Hyperglycinemia (elevated plasma glycine concentration) has been reported and associated with a fatal outcome in a patient with preexisting non-ketotic hyperglycinemia. Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Genitourinary: Enuresis and urinary tract infection.

Pancreatic: There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving valproate therapy (See **WARNINGS**).

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

Other: Allergic reaction, anaphylaxis has been reported. Edema of the extremities has been reported. A lupus erythematosus-like syndrome has been reported rarely. Bone pain, increased cough, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia have also been reported.

EPIVAL® versus EPIVAL® ER

A 24 week cross-over study compared the safety and efficacy of EPIVAL® ER (administered once daily) to that of equal doses of EPIVAL® (administered b.i.d. or t.i.d.) in the treatment of adolescent and adult epileptic patients with generalized seizures (n = 44), two adverse events occurred in significantly more patients on EPIVAL® ER than on EPIVAL: asthenia (15.9% vs 6.8% respectively) and treatment-emergent mild thrombocytopenia (16.2% vs 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 two 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 valproate 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 valproate 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 valproate. A notable exception was alopecia, which was first experienced after 3 to 6 months of exposure by 8 of the 15 patients who discontinued valproate 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 1000 mg to 2500 mg per day).

**Table 1**
**Treatment-Emergent Adverse Event Incidence (≥ 5%) in Short-Term Placebo-Controlled Trials (Oral Administration)**

| Body System/Event | Percentage of Patients | |
|---|---|---|
| | **divalproex sodium** (N=89) | **placebo** (N=97) |
| **Body as a Whole** | | |
| Headache | 21.3 | 30.9 |
| Pain | 14.6 | 15.5 |
| Accidental injury | 11.2 | 5.2 |
| Asthenia | 10.1 | 7.2 |
| Abdominal Pain | 9 | 8.2 |
| Back Pain | 5.6 | 6.2 |
| **Digestive System** | | |
| Nausea | 22.5 | 15.5 |
| Vomiting | 12.4* | 3.1 |
| Diarrhea | 10.1 | 13.4 |
| Dyspepsia | 9 | 8.2 |
| Constipation | 7.9 | 8.2 |
| **Nervous System** | | |
| Somnolence | 19.1 | 12.4 |
| Dizziness | 12.4 | 4.1 |
| Tremor | 5.6 | 6.2 |
| **Respiratory System** | | |
| Pharyngitis | 6.7 | 9.3 |
| **Skin and Appendages** | | |
| 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 EPIVAL® tablets

Body as a Whole: chest pain, chills, chills and fever, cyst, fever, infection, neck pain, neck rigidity;

Cardiovascular System: hypertension, hypotension, palpitations, postural hypotension, tachycardia, vascular anomaly, vasodilation;

Digestive System: anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess;

Hemic and Lymphatic System: ecchymosis;

Metabolic and Nutritional Disorders: edema, peripheral edema;

Musculoskeletal System: athralgia, arthrosis, leg cramps, twitching;

| | |
|---|---|
| Nervous System: | abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo; |
| Respiratory System | dyspenea, rhinitis |
| Skin and Appendages: | alopecia, discoid lupus erythematosis, dry skin, furunculosis, maculopapular rash, seborrhea; |
| Special Senses: | abnormal vision, amblyopia, conjunctivitis, deafness, dry eyes, ear disorder, ear pain, eye pain, tinnitus; |
| Urogenital System: | dysmennorrhea, dysuria, urinary incontinence. |

**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 valproate.

**INTRAVENOUS ADMINISTRATION**

The adverse events that can result from use of EPIJECT® I.V. include all of those associated with oral forms of valproate. The following describes experience specifically with EPIJECT® I.V.

EPIJECT® I.V. has been generally well tolerated in clinical trials involving 111 healthy adult male volunteers and 352 patients with epilepsy, given at doses of 125 to 6000 mg (total daily dose). A total of 2% of patients discontinued treatment with EPIJECT® I.V. due to adverse events. The most common adverse events leading to discontinuation were 2 cases each of nausea/vomiting and elevated amylase. Other adverse events leading to discontinuation were hallucinations, pneumonia, headache, injection site reaction, and abnormal gait.

Adverse events reported by at least 0.5% of all those exposed to EPIJECT® I.V. during clinical trials are summarized in Table 2.

**Table 2**

**Adverse Events Reported During Studies of EPIJECT® I.V.**

| Body System/Event | N = 463 |
|---|---|
| **Body as a Whole** | |
| Chest Pain | 1.7% |
| Headache | 4.3% |
| Injection Site Inflammation | 0.6% |
| Injection Site Pain | 2.6% |
| Injection Site Reaction | 2.4% |
| Pain (unspecified) | 1.3% |
| **Cardiovascular** | |
| Vasodilation | 0.9% |
| **Dermatologic** | |
| Sweating | 0.9% |
| **Digestive System** | |
| Abdominal Pain | 1.1% |
| Diarrhea | 0.9% |
| Nausea | 3.2% |
| Vomiting | 1.3% |
| **Nervous System** | |
| Dizziness | 5.2% |
| Euphoria | 0.9% |
| Hypesthesia | 0.6% |
| Nervousness | 0.9% |
| Paresthesia | 0.9% |
| Somnolence | 1.7% |
| Tremor | 0.6% |
| **Respiratory** | |
| Pharyngitis | 0.6% |
| **Special Senses** | |
| Taste Perversion | 1.9% |

## Adverse Events in Pediatric and Elderly Patients

No unique safety concerns were identified in either of the 24 patients 2 to 17 years of age or the 19 patients over 65 years of age who received EPIJECT® I.V. in clinical trials.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however, patients have recovered from valproate levels as high as 2120 mcg/mL.

In a reported case of overdosage with valproic acid after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An 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 valproic acid overdosage. Because naloxone could theoretically also reverse the anti-epileptic effects of valproate, it should be used with caution in patients with epilepsy.

## DOSAGE AND ADMINISTRATION

### ORAL ADMINISTRATION

#### Epilepsy

EPIVAL® (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 (See 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 |
| 10-24.9 | 22-54.9 | 250 | 125 | 0 | 125 |
| 25-39.9 | 55-87.9 | 500 | 250 | 0 | 250 |
| 40-59.9 | 88-131.9 | 750 | 250 | 250 | 250 |
| 60-74.9 | 132-164.9 | 1000 | 250 | 250 | 500 |
| 75-89.9 | 165-197.9 | 1250 | 500 | 250 | 500 |

**Conversion from EPIVAL® to EPIVAL® ER**

EPIVAL® ER (divaproex sodium) 500 mg extended-release tablets are intended for once-a-day oral administration. To maintain the extended-release properties of the product, EPIVAL® ER tablets should be swallowed whole and should not be crushed or chewed. Patients should be informed to take EPIVAL® ER every day as prescribed, at a consistent time of day.

EPIVAL® (divaproex sodium) enteric coated tablets should be used to titrate the patient to the optimal daily dose. When switching from EPIVAL® to EPIVAL® ER, the dose of EPIVAL® ER used should be the nearest equivalent to, without exceeding, the current daily dose of EPIVAL. If the current dose of EPIVAL® does not equal a single (or combination of ) EPIVAL® ER tablet strength(s), then the dose administered should be rounded down to the nearest number/combination of whole tablets available. As with other valproate products, EPIVAL® ER should be individualized, and dose adjustment may be necessary. In selected patients, a twice-a-day regimen may be preferred; in this case, if the dose cannot be divided equally, the larger dose should be given in the evening (e.g., for 1500 mg/day, give 500 mg in the morning and 1000 mg in the evening). If a patient requires closer titration than that available with the 500 mg EPIVAL® ER tablets, such incremental dose increases may be achieved with the addition of the appropriate EPIVAL® enteric coated tablet(s).

**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 **PRECAUTIONS**).

Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered (See **PRECAUTIONS**; under **Drug Interactions**).

As the dosage of divalproex sodium is titrated upward, blood concentrations of phenobarbital, carbamazepine and/or phenytoin may be affected (See **PRECAUTIONS**; under **Drug interactions**).

Antiepileptic drugs 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.

**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 valproate 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**).

**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 **PRECAUTIONS**). Therefore, the benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse effects.

**G.I. Irritation**

Patients who experience G.I. 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 oral valproate products with food should cause no clinical problems in the management of patients with epilepsy

**Conversion from DEPAKENE® to EPIVAL®:**

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

The bioavailability of both types of divalproex sodium tablets (EPIVAL® and EPIVAL® ER) is equivalent to that of DEPAKENE® (valproic acid) capsules.

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

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 1000 mg/day to 2500 mg/day. The maximum recommended dosage is 60 mg/kg/day.

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

When changing therapy involving drugs known to induce hepatic microsomal enzymes (e.g., carbamazepine) or other drugs with valproate interactions (See **PRECAUTIONS**; **Drug Interactions**), it is advisable to monitor serum valproate concentrations.

**INTRAVENOUS ADMINISTRATION**

EPIJECT® I.V. (valproic acid injection, present as the sodium salt) is indicated as an intravenous alternative in patients already stabilized on oral valproate products, and for whom oral administration is temporarily not feasible. The total daily dose of EPIJECT® I.V. should be equivalent to the total daily dose of the oral valproate product. There is insufficient information on safety in patients requiring daily doses of I.V. valproate of more than 2000 mg, or more than 48 hours of I.V. dosing.

EPIJECT® I.V. is for intravenous use only. It should be diluted with a compatible diluent in order to obtain a final concentration of 2 mg/mL (See **PHARMACEUTICAL INFORMATION**; **Compatibility of Diluted Solutions**) and any unused portion of the vial contents should be discarded.

EPIJECT® I.V. should be administered as a 60 minute infusion, given at the same dosage and frequency as the oral products (every 6 hours), but not more than 10 mg/min. Plasma concentration monitoring and dosage adjustments may be necessary.

A maximum of 48 hours of perfusion, at maximum doses of 2000 mg/day (500 mg/dose) and a maximum rate of 10 mg/minute should not be exceeded. There are insufficient data to support larger doses and more rapid rates of administration, as well as more than two days of infusion.

If the total daily dose exceeds 250 mg, it should be given in a divided regimen. However, the equivalence shown between EPIJECT® I.V. and oral valproate products (DEPAKENE®) at steady state was only evaluated in an every 6-hour regimen. Whether, when EPIJECT® I.V. is given less frequently (i.e., twice or three times a day), trough levels fall below those that result from an oral dosage form given via the same regimen, is unknown. For this reason, when EPIJECT® I.V. is given twice or three times a day, close monitoring of trough plasma levels may be needed.

Rapid infusion of EPIJECT® I.V. has been associated with an increase in adverse events. There is limited information on infusion times of less than 60 minutes or rates of infusion > 10 mg/min (See **ADVERSE REACTIONS**).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

## PHARMACEUTICAL INFORMATION

### ORAL FORMULATION

***Drug Substance***

**Proper Name**: Divalproex sodium

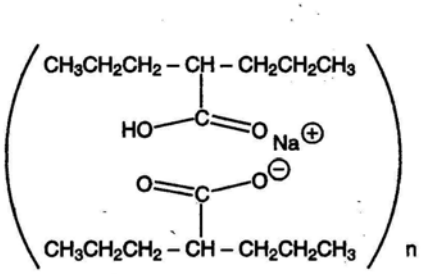
**USAN Names**: INN: Valproate Semisodium
BAN: Semisodium Valproate

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

**Molecular Weight:** $(310.14)_n$

**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.

**Composition**:

**EPIVAL® Enteric-Coated Tablets** contain: Cellulosic polymers, silicon dioxide, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), talc, titanium dioxide, and vanillin.

In addition, individual tablets contain:

125 mg tablets: FD&C Red No.40
250 mg tablets: FD&C Yellow No.6
500 mg tablets: D&C Red No. 30 and FD&C Blue No.2

**EPIVAL® ER Extended-Release Tablets** contain: hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, polydextrose, polyethylene glycol, potassium sorbate, propylene glycol, shellac, silicon dioxide, titanium dioxide, and triacetin.

In addition, individual tablets contain:
500 mg: FD&C Blue No. 1, and iron oxide.

**Stability and Storage Recommendations**:

Store EPIVAL® and EPIVAL® ER tablets between 15° and 25°C (59°- 77°F). Tablets should be protected from light.

**INTRAVENOUS FORMULATION**

***Drug Substance***

**Proper Name**: Sodium Valproate

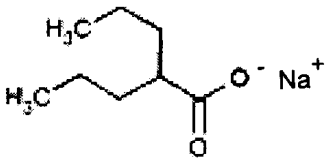
**USAN Names**: Valproate Sodium

**Chemical Name**: Sodium 2-propylpentanoate

**Molecular Weight:** 166.2

**Molecular Formula:** $C_8H_{15}Na\,O_2$

**Structural Formula:**




**Description**:

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

Valproate sodium is the sodium salt of valproic acid designated as sodium 2-propylpentanoate. It occurs as an essentially white and odorless, crystalline, deliquescent powder.

Valproic acid (Abbott-044089) is converted to valproate sodium (Abbott-044090) in the manufacture of the drug product.

**Composition**:

EPIJECT® I.V. (valproic acid injection, present as the sodium salt) is a clear, colorless, nonpyrogenic liquid parenteral dosage form of valproic acid. It is available in 5 mL single-dose vials for intravenous administration only. Each mL contains valproate sodium equivalent to 100 mg valproic acid, edetate disodium 0.40 mg, and Water for Injection to volume. The pH is adjusted to a range of 7.0 to 9.0 with sodium hydroxide and/or hydrochloric acid. No preservatives have been added.

**Stability and Storage Recommendations**:

Store vials between 15° and 25°C. No preservatives have been added. Unused portion of container should be discarded.

**Compatibility of Diluted Solutions**:

EPIJECT® I.V. (valproic acid injection, present as the sodium salt) should be diluted with a compatible diluent in order to obtain a final concentration of 2 mg/mL. EPIJECT® I.V. was found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or polyvinyl chloride (PVC) bags at room temperature (15-30°C):

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP

Note:
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard unused portion.
- Use admixture solutions within 24 hours.

## AVAILABILITY OF DOSAGE FORMS

EPIVAL® (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg; peach-coloured tablets of 250 mg; pink-coloured tablets of 500 mg. EPIVAL® 125 mg is supplied in bottles of 100 tablets. Epival 250 mg and 500 mg are supplied in bottles of 100 tablets and 500 tablets.

EPIVAL® ER (divalproex sodium) extended-release tablets are available as gray coloured tablets with the corporate logo, and the Abbo Code HC. Each EPIVAL® ER tablet contains divalproex sodium equivalent to 500 mg of valproic acid. Supplied in bottles of 60, 100, and 500 tablets.

EPIJECT® I.V. (valproic acid injection, present as the sodium salt), equivalent to 100 mg of valproic acid per mL, is available in 10 mL single-dose vials, each containing 5 mL sterile solution, in trays of 5 vials.

## INFORMATION FOR THE PATIENT/GUARDIAN

**Please read the following information carefully prior to starting EPIVAL® or EPIVAL® ER therapy, even if you have taken this drug before**.

### What is EPIVAL® or EPIVAL® ER:

EPIVAL® or EPIVAL® ER, are the brand names for divalproex sodium, and this drug has been prescribed to you to control your epilepsy. Please follow your doctor's recommendations carefully.

### Before taking EPIVAL® or EPIVAL® ER:

Please inform your doctor 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 EPIVAL® or EPIVAL® ER.
- You are allergic to any component of EPIVAL® or EPIVAL® ER tablets.
- You are pregnant or are planning to become pregnant.
- You are breast-feeding (nursing); EPIVAL® and EPIVAL® ER is excreted in breast milk.
- You are taking any other prescription or over the counter medicine.
- You have liver or kidney disease, or other medical conditions.
- You consume alcohol on a regular basis.

### How to take EPIVAL® or EPIVAL® ER:

- It is very important to take EPIVAL® or EPIVAL® ER exactly as instructed by your doctor.
- Your doctor may increase or decrease your medication according to your specific needs. You should carefully follow the instructions that were given to you and not change your dose without consulting with your doctor.
- Do not suddenly stop taking your medicine abruptly because of the risk of increasing their 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. EPIVAL® or EPIVAL® ER may be taken with or without food.
- 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 EPIVAL® or EPIVAL® ER.
- It is important to keep your appointments for medical checkups.

### Precautions while taking EPIVAL® or EPIVAL® ER:

- You should contact your doctor immediately if you do not feel well, develop weakness, extreme fatigue, facial swelling , loss of appetite and vomiting, particularly in the first weeks of therapy. If your child is taking EPIVAL® or EPIVAL® ER, you should report to his/her doctor immediately if the child develops any of the above-mentioned symptoms.

- The symptoms that may be associated with hyperammonemic encephalopathy are increased lethargy (drowsiness), vomiting and episodic extreme irritability in young children and ataxia, (abnormal gait, abnormal walking), combative/bizarre behaviour and refusal to eat meat or high protein products in older children and adults. You should inform the doctor if any of these symptoms occur.
- Abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, you should contact your doctor immediately if you experience any of these.
- Your doctor will monitor your response to EPIVAL® or EPIVAL® ER on a regular basis. However, if your seizures get worse, you should tell your doctor immediately. You should also promptly report the onset of pregnancy.
- Different side effects have been reported by other patients taking EPIVAL®. 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.
- Since EPIVAL® or EPIVAL® ER 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 consult your doctor.
- You should check with your doctor or pharmacist right away if they notice any bothersome or unusual effects while taking EPIVAL® or EPIVAL® ER.
- You should not stop taking your medication unless directed by your doctor. You should always check that you have an adequate supply of EPIVAL® or EPIVAL® ER. You should remember that this medicine was prescribed only for you; you should never be given to anyone else.

**What to do in case of an overdose:**

If you accidentally take an overdose of EPIVAL® or EPIVAL® ER, you should contact your doctor or nearest hospital emergency, even though you may not feel sick.

**How to store EPIVAL® or EPIVAL® ER:**

EPIVAL® or EPIVAL® ER tablets should be stored between 15 and 25°C. Tablets should be protected from light. The bottle should be capped tightly immediately after use. **EPIVAL® or EPIVAL® ER should be kept out of reach of children**.

**What do EPIVAL® Tablets contain:**

**EPIVAL® tablets contain divalproex sodium and the following non medicinal ingredients:** Cellulosic polymers, silicon dioxide, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch) talc, titanium dioxide, and vanillin.

In addition, individual tablets contain:

125 mg tablets: FD&C Red No. 40
250 mg tablets: FD&C Yellow No. 6
500 mg tablets: D&C Red No. 30 and FD&C Blue No. 2

**What do EPIVAL® ER Tablets contain:**

**EPIVAL® ER tablets contain divalproex sodium and the following non medicinal ingredients:** hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, polydextrose, polyethylene glycol, potassium sorbate, propylene glycol, shellac, silicon dioxide, titanium dioxide, and triacetin.

In addition, individual tablets contain:

500 mg: FD&C Blue No. 1, and iron oxide.

## PHARMACOLOGY

### Animals

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 was 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.

**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.

**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.

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