

(No. 3826 and, 7126)
NEW

DEPAKOTE[®] ER
DIVALPROEX SODIUM
EXTENDED-RELEASE TABLETS
R_x Only

BOX WARNING:

HEPATOTOXICITY:

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. 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. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

TERATOGENICITY:

VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA). ACCORDINGLY, THE USE OF DEPAKOTE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G., MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS.

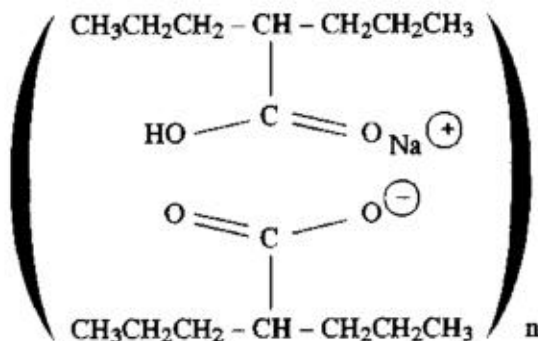
AN INFORMATION SHEET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.

PANCREATITIS:

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See **WARNINGS** and **PRECAUTIONS**.)

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. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



Divalproex sodium occurs as a white powder with a characteristic odor.

DEPAKOTE ER 250 and 500 mg tablets are for oral administration. DEPAKOTE ER tablets contain divalproex sodium in a once-a-day extended-release formulation equivalent to 250 and 500 mg of valproic acid.

Inactive Ingredients

DEPAKOTE ER 250 and 500 mg Tablets: FD&C Blue No. 1, hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, polyethylene glycol, potassium sorbate, propylene glycol, silicon dioxide, titanium dioxide, and triacetin.

In addition, 500 mg tablets contain iron oxide and polydextrose.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Pharmacokinetics

Absorption/Bioavailability

The absolute bioavailability of DEPAKOTE ER TABLETS administered as a single dose after a meal was approximately 90% relative to intravenous infusion.

When given in equal total daily doses, the bioavailability of DEPAKOTE ER is less than that of DEPAKOTE (divalproex sodium delayed-release tablets). In five multiple-dose studies in healthy subjects (N=82) and in subjects with epilepsy (N=86), when administered under fasting and nonfasting conditions, DEPAKOTE ER given once daily produced an average bioavailability of 89% relative to an equal total daily dose of DEPAKOTE given BID, TID, or QID. The median time to maximum plasma valproate concentrations (C_{max}) after DEPAKOTE ER administration ranged from 4 to 17 hours. After multiple once-daily dosing of DEPAKOTE ER, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular DEPAKOTE given BID, TID, or QID.

Conversion from DEPAKOTE to DEPAKOTE ER:

When DEPAKOTE ER is given in doses 8 to 20% higher than the total daily dose of DEPAKOTE, the two formulations are bioequivalent. In two randomized, crossover studies, multiple daily doses of DEPAKOTE were compared to 8 to 20% higher once-daily doses of DEPAKOTE ER. In these two studies, DEPAKOTE ER and DEPAKOTE regimens were equivalent with respect to area under the curve (AUC; a measure of the extent of bioavailability). Additionally, valproate C_{max} was lower, and C_{min} was either higher or not different, for DEPAKOTE ER relative to DEPAKOTE regimens (see following table).

Bioavailability of DEPAKOTE ER Tablets Relative to DEPAKOTE When DEPAKOTE ER Dose is 8 to 20% Higher

Study Population	Regimens DEPAKOTE ER vs. DEPAKOTE	Relative Bioavailability		
		AUC ₂₄	C _{max}	C _{min}
Healthy Volunteers (N=35)	1000 & 1500 mg DEPAKOTE ER vs. 875 & 1250 mg DEPAKOTE	1.059	0.882	1.173
Patients with epilepsy on concomitant enzyme- inducing antiepilepsy drugs (N=64)	1000 to 5000 mg DEPAKOTE ER vs. 875 to 4250 mg DEPAKOTE	1.008	0.899	1.022

Concomitant antiepilepsy drugs (topiramate, phenobarbital, carbamazepine, phenytoin, and lamotrigine were evaluated) that induce the cytochrome P450 isozyme system did not significantly alter valproate bioavailability when converting between DEPAKOTE and DEPAKOTE ER.

Distribution

Protein Binding:

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 µg/mL to 18.5% at 130 µg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide) (see **PRECAUTIONS, Drug Interactions** for more detailed information on the pharmacokinetic interactions of valproate with other drugs).

CNS Distribution:

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism

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 β-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.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m² and 11 L/1.73 m², respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m² and 92 L/1.73 m². Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly.

Special Populations

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 years). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly (see **DOSAGE AND ADMINISTRATION**).

Effect of Gender:

There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m², respectively).

Effect of Race:

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

Effect of Disease:

Liver Disease - (see **BOXED WARNING, CONTRAINDICATIONS, and WARNINGS**).

Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease - A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

Plasma Levels and Clinical Effect

The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 µg/mL to 18.5% at 130 µg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy:

The therapeutic range in epilepsy is commonly considered to be 50 to 100 µg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Clinical Trials

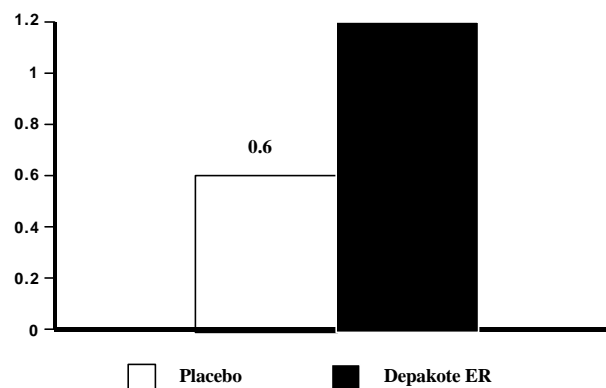
Migraine

The results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial demonstrated the effectiveness of DEPAKOTE ER in the prophylactic treatment of migraine headache. This trial recruited patients with a history of migraine headaches with or without aura occurring on average twice or more a month for the preceding three months. Patients with cluster or chronic daily headaches were excluded. Women of childbearing potential were allowed in the trial if they were deemed to be practicing an effective method of contraception.

Patients who experienced 2 migraine headaches in the 4-week baseline period were randomized in a 1:1 ratio to DEPAKOTE ER or placebo and treated for 12 weeks. Patients initiated treatment on 500 mg once daily for one week, and were then increased to 1000 mg once daily with an option to permanently decrease the dose back to 500 mg once daily during the second week of treatment if intolerance occurred. Ninety-eight of 114 DEPAKOTE ER-treated patients (86%) and 100 of 110 placebo-treated patients (91%) treated at least two weeks maintained the 1000 mg once daily dose for the duration of their treatment periods. Treatment outcome was assessed on the basis of reduction in 4-week migraine headache rate in the treatment period compared to the baseline period.

Patients (50 male, 187 female) ranging in age from 16 to 69 were treated with DEPAKOTE ER (N=122) or placebo (N=115). Four patients were below the age of 18 and 3 were above the age of 65. Two hundred and two patients (101 in each treatment group) completed the treatment period. The mean reduction in 4-week migraine headache rate was 1.2 from a baseline mean of 4.4 in the DEPAKOTE ER group, versus 0.6 from a baseline mean of 4.2 in the placebo group. The treatment difference was statistically significant (see Figure 1).

Figure 1
Mean Reduction In 4-Week
Migraine Headache Rates
1.2*



* p=0.006

Epilepsy

The efficacy of DEPAKOTE in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials using DEPAKOTE (divalproex sodium delayed-release tablets).

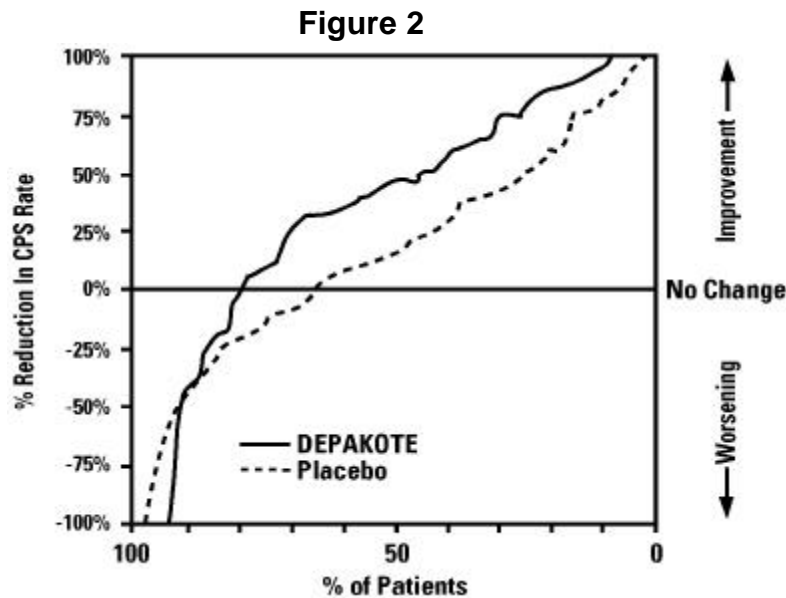
In one, multiclinic, placebo controlled study employing an add-on design, (adjunctive therapy) using DEPAKOTE, 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either DEPAKOTE or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

**Adjunctive Therapy Study
 Median Incidence of CPS per 8 Weeks**

Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
DEPAKOTE	75	16.0	8.9*
Placebo	69	14.5	11.5

*Reduction from baseline statistically significantly greater for DEPAKOTE than placebo at $p \leq 0.05$ level.

Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for DEPAKOTE than for placebo. For example, 45% of patients treated with DEPAKOTE had a $\geq 50\%$ reduction in complex partial seizure rate compared to 23% of patients treated with placebo.



The second study assessed the capacity of DEPAKOTE to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to DEPAKOTE. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to DEPAKOTE monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 µg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

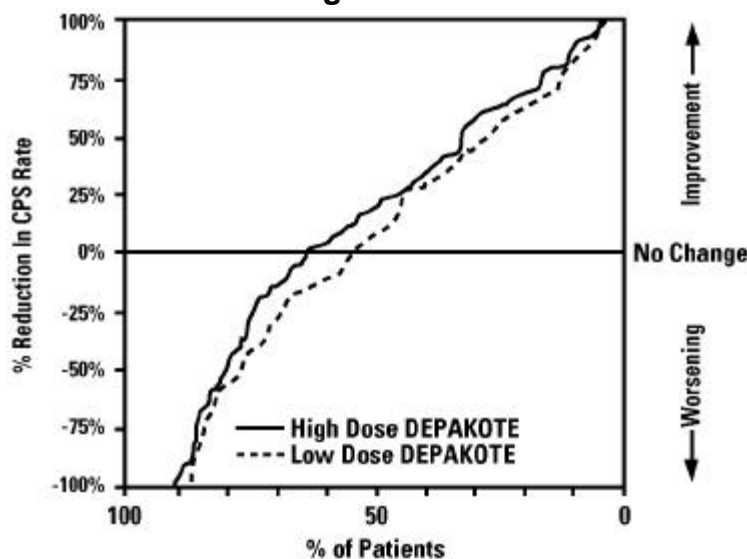
**Monotherapy Study
 Median Incidence of CPS per 8 Weeks**

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose DEPAKOTE	131	13.2	10.7 *
Low dose DEPAKOTE	134	14.2	13.8

* Reduction from baseline statistically significantly greater for high dose than low dose at p ≤0.05 level.

Figure 3 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose DEPAKOTE than for low dose DEPAKOTE. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose DEPAKOTE monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose DEPAKOTE.

Figure 3



INDICATIONS AND USAGE

Migraine

DEPAKOTE ER is indicated for prophylaxis of migraine headaches in adults. There is no evidence that DEPAKOTE ER is useful in the acute treatment of migraine headaches. Because valproic acid may be a hazard to the fetus, DEPAKOTE ER should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patient and weighed against the potential benefits of treatment (see **WARNINGS - Usage In Pregnancy, PRECAUTIONS - Information for Patients**).

Epilepsy

DEPAKOTE ER is indicated as monotherapy and adjunctive therapy in the treatment of adult patients with complex partial seizures that occur either in isolation or in association with other types of seizures. DEPAKOTE ER is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adult patients, and adjunctively in adult patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present. SEE **WARNINGS** FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DIVALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.

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

WARNINGS

Hepatotoxicity

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

fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering DEPAKOTE 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 with the aforementioned conditions. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups. The use of DEPAKOTE ER in children is not recommended (see PRECAUTIONS – Pediatric Use).

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.

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 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 (see **BOXED WARNING**).

Urea Cycle Disorders (UCD)

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

Somnolence in the Elderly

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see **DOSAGE AND ADMINISTRATION**).

Thrombocytopenia

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia [see **PRECAUTIONS**]) may be dose-related. In a clinical trial of DEPAKOTE (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 $\geq 110 \mu\text{g/mL}$ (females) or $\geq 135 \mu\text{g/mL}$ (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage In Pregnancy

ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THE DATA DESCRIBED BELOW WERE GAINED ALMOST EXCLUSIVELY FROM WOMEN WHO RECEIVED VALPROATE TO TREAT EPILEPSY. THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPSY DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.

OTHER CONGENITAL ANOMALIES (EG, 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 IS 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 DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

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 VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. 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 approximately 230 $\mu\text{g/mL}$ (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 $\mu\text{g/mL}$ or greater (3.4 times the upper limit of the human therapeutic range for epilepsy or greater). Behavioral 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 $\mu\text{g/mL}$ (2.8 times the upper limit of the human therapeutic range for epilepsy).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepileptic drugs should not be discontinued abruptly 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. 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.

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.

PRECAUTIONS

Hepatic Dysfunction

See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS**.

Pancreatitis

See **BOXED WARNING** and **WARNINGS**.

Hyperammonemia

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 and an ammonia level should be measured. If 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**).

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

General

Because of reports of thrombocytopenia (see **WARNINGS**), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of DEPAKOTE 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 $\geq 110 \mu\text{g/mL}$ (females) or $\geq 135 \mu\text{g/mL}$ (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since DEPAKOTE 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 where clinically appropriate (see **PRECAUTIONS - Drug Interactions**).

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

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

Information for Patients

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

Patients should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see **PRECAUTIONS – Hyperammonemia**) and be told to inform the prescriber if any of these symptoms occur.

Since DEPAKOTE products may produce CNS depression, especially when combined with another CNS depressant (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Since DEPAKOTE has been associated with certain types of birth defects, female patients of child-bearing age considering the use of DEPAKOTE ER for the prevention of migraine should be advised to read the **Patient Information Leaflet**, which appears as the last section of the labeling.

Drug Interactions

Effects of Co-Administered Drugs on Valproate Clearance

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed:

Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β -oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Whether or not the interaction observed in this study applies to adults is unknown, but caution should be observed if valproate and aspirin are to be co-administered.

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 µg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 µg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin - A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 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.

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 Titalac - 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 BID) 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 BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine - Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrolase, and glucuronyltransferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed:

Amitriptyline/Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/carbamazepine-10,11-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.

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 - 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). The dose of lamotrigine should be reduced when co-administered with valproate.

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

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

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.

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.

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 DEPAKOTE therapy is instituted in patients taking anticoagulants.

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.

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 BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

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

Oral Contraceptive Steroids - Administration of a single-dose of ethinylloestradiol (50 µg)/levonorgestrel (250 µg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m² basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. 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 an increase in SCE frequency is not known.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m² basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m² basis). Segment I fertility studies in rats have shown oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m² basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy

Pregnancy Category D: see **WARNINGS**.

Nursing Mothers

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when divalproex sodium is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Depakote ER for the prophylaxis of migraine headaches and for the treatment of epilepsy (see **INDICATIONS AND USAGE** for specific seizure types) in pediatric patients has not been established.

Experience has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see **BOXED WARNING**). Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m² basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m² basis.

Geriatric Use

Safety and effectiveness of DEPAKOTE ER in the prophylaxis of migraine patients over 65 have not been established.

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness using DEPAKOTE (divalproex sodium delayed-release tablets). In a case review study of 583 patients using various valproate products, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see **WARNINGS—Somnolence in the Elderly**). The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Migraine

Based on the results of one multicenter, randomized, double-blind, placebo-controlled clinical trial, DEPAKOTE ER was well tolerated in the prophylactic treatment of migraine headache. Of the 122 patients exposed to DEPAKOTE ER in the placebo-controlled study, 8% discontinued for adverse events, compared to 9% for the 115 placebo patients.

Based on two placebo-controlled clinical trials and their long term extension, DEPAKOTE (divalproex sodium delayed-release tablets) was generally well tolerated with most adverse events rated as mild to moderate in severity. Of the 202 patients exposed to DEPAKOTE in the

placebo-controlled trials, 17% discontinued for intolerance. This is compared to a rate of 5% for the 81 placebo patients. Including the long term extension study, the adverse events reported as the primary reason for discontinuation by $\geq 1\%$ of 248 DEPAKOTE-treated patients were alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

Table 1 includes those adverse events reported for patients in the placebo-controlled trial where the incidence rate in the DEPAKOTE ER-treated group was greater than 5% and was greater than that for placebo patients.

Table 1
Adverse Events Reported by >5% of DEPAKOTE ER-Treated Patients During the Migraine Placebo-Controlled Trial with a Greater Incidence than Patients Taking Placebo¹

Body System Event	Depakote ER (N=122)	Placebo (N=115)
Gastrointestinal System		
Nausea	15%	9%
Dyspepsia	7%	4%
Diarrhea	7%	3%
Vomiting	7%	2%
Abdominal Pain	7%	5%
Nervous System		
Somnolence	7%	2%
Other		
Infection	15%	14%

¹The following adverse events occurred in greater than 5% of DEPAKOTE ER-treated patients and at a greater incidence for placebo than for DEPAKOTE ER: asthenia and flu syndrome.

The following additional adverse events were reported by greater than 1% but not more than 5% of DEPAKOTE ER-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trial for migraine prophylaxis:

Body as a Whole: Accidental injury, viral infection.

Digestive System: Increased appetite, tooth disorder.

Metabolic and Nutritional Disorders: Edema, weight gain.

Nervous System: Abnormal gait, dizziness, hypertonia, insomnia, nervousness, tremor, vertigo.

Respiratory System: Pharyngitis, rhinitis.

Skin and Appendages: Rash.

Special Senses: Tinnitus.

Table 2 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in the DEPAKOTE-treated group was greater than 5% and was greater than that for placebo patients.

Table 2
Adverse Events Reported by >5% of DEPAKOTE-Treated Patients
During Migraine Placebo-Controlled Trials with a Greater Incidence than Patients Taking Placebo¹

Body System Event	Depakote (N=202)	Placebo (N=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal Pain	9%	4%
Increased Appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%
Tremor	9%	0%
Other		
Weight Gain	8%	2%
Back Pain	8%	6%
Alopecia	7%	1%

¹The following adverse events occurred in greater than 5% of DEPAKOTE -treated patients and at a greater incidence for placebo than for DEPAKOTE: flu syndrome and pharyngitis.

The following additional adverse events not referred to above were reported by greater than 1% but not more than 5% of DEPAKOTE-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trials:

- Body as a Whole: Chest pain.
- Cardiovascular System: Vasodilatation.
- Digestive System: Constipation, dry mouth, flatulence, stomatitis.
- Hemic and Lymphatic System: Ecchymosis.
- Metabolic and Nutritional Disorders: Peripheral edema.
- Musculoskeletal System: Leg cramps.
- Nervous System: Abnormal dreams, confusion, paresthesia, speech disorder, thinking abnormalities.
- Respiratory System: Dyspnea, sinusitis.
- Skin and Appendages: Pruritus.
- Urogenital System: Metrorrhagia.

Epilepsy

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, DEPAKOTE was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the DEPAKOTE-treated patients (6%), compared to 1% of placebo-treated patients.

Table 3 lists treatment-emergent adverse events which were reported by $\geq 5\%$ of DEPAKOTE-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to

determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

Table 3
Adverse Events Reported by ≥ 5% of Patients Treated
with DEPAKOTE During Placebo-Controlled
Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/Event	Depakote (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
Respiratory System		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0

Table 4 lists treatment-emergent adverse events which were reported by ≥5% of patients in the high dose DEPAKOTE group, and for which the incidence was greater than in the low dose group, in a controlled trial of DEPAKOTE monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

Table 4
Adverse Events Reported by ≥ 5% of Patients in the High Dose Group in the Controlled Trial of
DEPAKOTE Monotherapy for Complex Partial Seizures¹

Body System/Event	High Dose (%) (n = 131)	Low Dose (%) (n = 134)
Body as a Whole		
Asthenia	21	10
Digestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal Pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18
Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

¹Headache was the only adverse event that occurred in ≥ 5% of patients in the high dose group and at an equal or greater incidence in the low dose group.

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

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

Cardiovascular System: Tachycardia, hypertension, palpitation.

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

Hemic and Lymphatic System: Petechia.

Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.

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

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

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

Skin and Appendages: Rash, pruritus, dry skin.

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

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

Other Patient Populations

The following adverse events not listed previously were reported by greater than 1% of DEPAKOTE-treated patients and with a greater incidence than placebo in placebo-controlled trials of manic episodes associated with bipolar disorder:

Body as a Whole: Chills, chills and fever, drug level increased, neck rigidity.

Cardiovascular System: Arrhythmia, hypotension, postural hypotension.

Digestive System: Dysphagia, fecal incontinence, gastroenteritis, glossitis, gum hemorrhage, mouth ulceration.

Hemic and Lymphatic System: Anemia, bleeding time increased, leukopenia.

Metabolic and Nutritional Disorders: Hypoproteinemia.

Musculoskeletal System: Arthrosis.

Nervous System: Agitation, catatonic reaction, dysarthria, hallucinations, hypokinesia, psychosis, reflexes increased, sleep disorder, tardive dyskinesia.

Respiratory System: Hiccup.

Skin and Appendages: Discoid lupus erythematosus, erythema nodosum, furunculosis, maculopapular rash, seborrhea, sweating, vesiculobullous rash.

Special Senses: Conjunctivitis, dry eyes, eye disorder, eye pain, photophobia, taste perversion.

Urogenital System: Cystitis, menstrual disorder.

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

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. In some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of DEPAKOTE ER tablets in the stool.

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with

hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders (see **WARNINGS – Urea Cycle Disorders** and **PRECAUTIONS**).

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 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.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: 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 and Drug Interactions**). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, and acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see **WARNINGS**).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see **PRECAUTIONS**).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic: Acute pancreatitis including fatalities (see **WARNINGS**).

Metabolic: Hyperammonemia (see **PRECAUTIONS**), hyponatremia, and inappropriate ADH secretion.

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

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

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis and urinary tract infection.

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: Anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, and fever.

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 µg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive

measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdose. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

DOSAGE AND ADMINISTRATION

DEPAKOTE ER is an extended-release product intended for once-a-day oral administration. DEPAKOTE ER tablets should be swallowed whole and should not be crushed or chewed.

Migraine

The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1000 mg once daily. Although doses other than 1000 mg once daily of DEPAKOTE ER have not been evaluated in patients with migraine, the effective dose range of DEPAKOTE (divalproex sodium delayed-release tablets) in these patients is 500-1000 mg/day. As with other valproate products, doses of DEPAKOTE ER should be individualized and dose adjustment may be necessary. If a patient requires smaller dose adjustments than that available with DEPAKOTE ER, DEPAKOTE should be used instead.

Epilepsy

DEPAKOTE ER is indicated as monotherapy and adjunctive therapy in complex partial seizures in adult patients, and in simple and complex absence seizures in adult patients. As the DEPAKOTE ER dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see **PRECAUTIONS -- Drug Interactions**).

Complex Partial Seizures for adult patients:

Monotherapy (Initial Therapy) : DEPAKOTE ER has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 µg/mL in females and 135 µg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy : Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of DEPAKOTE ER therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy : DEPAKOTE ER may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to DEPAKOTE, no adjustment of carbamazepine or phenytoin dosage was needed (see **CLINICAL STUDIES**). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see **Drug Interactions**), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see **PRECAUTIONS -- Drug Interactions**).

Simple and Complex Absence Seizures for adult patients:

The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50 to 100 µg/mL. Some patients may be controlled with lower or higher serum concentrations (see **CLINICAL PHARMACOLOGY**).

As the DEPAKOTE ER dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see **PRECAUTIONS**).

Antiepilepsy 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.

Conversion from DEPAKOTE to DEPAKOTE ER:

In adult patients with epilepsy previously receiving DEPAKOTE, DEPAKOTE ER should be administered once-daily using a dose 8 to 20% higher than the total daily dose of DEPAKOTE (Table 5). For patients whose DEPAKOTE total daily dose can not be directly converted to DEPAKOTE ER, consideration may be given at the clinician's discretion to increase the patient's DEPAKOTE total daily dose to the next higher dosage before converting to the appropriate total daily dose of DEPAKOTE ER.

Table 5
Dose Conversion

DEPAKOTE	DEPAKOTE ER
Total Daily Dose (mg)	(mg)
500* - 625	750
750* - 875	1000
1000*-1125	1250
1250-1375	1500
1500-1625	1750
1750	2000
1875-2000	2250
2125-2250	2500
2375	2750
2500-2750	3000
2875	3250
3000-3125	3500

* These total daily doses of DEPAKOTE cannot be directly converted to an 8 to 20% higher total daily dose of DEPAKOTE ER because the required dosing strengths of DEPAKOTE ER are not available. Consideration may be given at the clinician's discretion to increase the patient's DEPAKOTE total daily dose to the next higher dosage before converting to the appropriate total daily dose of DEPAKOTE ER.

There is insufficient data to allow a conversion factor recommendation for patients with DEPAKOTE doses above 3125 mg/day.

Plasma valproate C_{\min} concentrations for DEPAKOTE ER on average are equivalent to DEPAKOTE, but may vary across patients after conversion. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 $\mu\text{g/mL}$) (see **Pharmacokinetics-Absorption/Bioavailability**).

General Dosing Advice


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 in these patients. Starting doses in the elderly lower than 250 mg can only be achieved by the use of DEPAKOTE. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see **WARNINGS**).

Dose-Related Adverse Events - The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of $\geq 110 \mu\text{g/mL}$ (females) or $\geq 135 \mu\text{g/mL}$ (males) (see **PRECAUTIONS**). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.


G.I. Irritation - Patients who experience G.I. irritation may benefit from administration of the drug with food or by initiating therapy with a lower dose of DEPAKOTE.

Compliance - Patients should be informed to take DEPAKOTE ER every day as prescribed. If a dose is missed it should be taken as soon as possible, unless it is almost time for the next dose. If a dose is skipped, the patient should not double the next dose.

HOW SUPPLIED

DEPAKOTE ER 250 mg is available as white ovaloid tablets with the corporate logo , and the Abbo-Code (HF). Each DEPAKOTE ER tablet contains divalproex sodium equivalent to 250 mg of valproic acid in the following package sizes:

- Bottles of 60(NDC 0074-3826-60).
- Bottles of 100.....(NDC 0074-3826-13).
- Bottles of 500.....(NDC 0074-3826-53).
- ABBO-PAC unit dose packages of 100.....(NDC 0074-3826-11).

DEPAKOTE ER 500 mg is available as gray ovaloid tablets with the corporate logo , and the Abbo-Code HC. Each DEPAKOTE ER tablet contains divalproex sodium equivalent to 500 mg of valproic acid in the following packaging sizes:

- Bottles of 100.....(NDC 0074-7126-13).
- Bottles of 500.....(NDC 0074-7126-53).
- ABBO-PAC unit dose packages of 100.....(NDC 0074-7126-11).

Recommended storage: Store tablets at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Revised: NEW

Manufactured by:



PRINTED IN U.S.A.

Patient Information Leaflet **Important Information for Women Who Could Become Pregnant** **About the Use of DEPAKOTE[®] ER (divalproex sodium) Tablets for Migraine**

Please read this leaflet carefully before you take DEPAKOTE[®] ER (divalproex sodium) tablets. This leaflet provides a summary of important information about taking DEPAKOTE ER for migraine to women who could become pregnant. DEPAKOTE ER may also be prescribed for uses other than those discussed in this leaflet. If you have any questions or concerns, or want more information about DEPAKOTE ER, contact your doctor or pharmacist.

Information For Women Who Could Become Pregnant

DEPAKOTE ER is used to prevent or reduce the number of migraines you experience. DEPAKOTE ER can be obtained only by prescription from your doctor. The decision to use DEPAKOTE ER for the prevention of migraine is one that you and your doctor should make together, taking into account your individual needs and medical condition.

Before using DEPAKOTE ER, women who can become pregnant should consider the fact that DEPAKOTE has been associated with birth defects, in particular, with spina bifida and other defects related to failure of the spinal canal to close normally. Although the incidence is unknown in migraine patients treated with DEPAKOTE, approximately 1 to 2% of children born to women with epilepsy taking DEPAKOTE in the first 12 weeks of pregnancy had these defects (based on data from the Centers for Disease Control, a U.S. agency based in Atlanta). The incidence in the general population is 0.1 to 0.2%.

Information For Women Who Are Planning To Get Pregnant

- Women taking DEPAKOTE ER for the prevention of migraine who are planning to get pregnant should discuss with their doctor temporarily stopping DEPAKOTE ER, before and during their pregnancy.

Information For Women Who Become Pregnant While Taking DEPAKOTE ER

- If you become pregnant while taking DEPAKOTE ER for the prevention of migraine, you should contact your doctor immediately.

Other Important Information About DEPAKOTE ER Tablets

- DEPAKOTE ER tablets should be taken exactly as it is prescribed by your doctor to get the most benefits from DEPAKOTE ER and reduce the risk of side effects.
- If you have taken more than the prescribed dose of DEPAKOTE ER, contact your hospital emergency room or local poison center immediately.
- This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

Facts About Birth Defects

It is important to know that birth defects may occur even in children of individuals not taking any medications or without any additional risk factors.

Facts About Migraine

About 23 million Americans suffer from migraine headaches. About 75% of migraine sufferers are women. A migraine is described as a throbbing headache that gets worse with activity. Migraine may also include nausea and/or vomiting as well as sensitivity to light and sound. Migraine usually happens about once a month, but some people may have them as often as once or twice a week. Often, the symptoms from a migraine can cause people to miss work or school.

If you have frequent migraines, or if acute treatment is not working for you, your doctor may prescribe a preventative therapy. Preventative (prophylactic) treatment is used to prevent attacks and reduce the frequency and severity of headache events.

This summary provides important information about the use of DEPAKOTE ER for migraine to women who could become pregnant. If you would like more information about the other potential risks and benefits of DEPAKOTE ER, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them. If you have any questions or concerns about taking DEPAKOTE ER, you should discuss them with your doctor.

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