



## Divalproex Sodium Delayed-release Tablets, USP

**Rx 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 ANTICONSULVANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DIVALPROEX SODIUM DELAYED-RELEASE TABLETS ARE 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 DIVALPROEX SODIUM DELAYED-RELEASE 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 ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G., MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS.

**PANCREATITIS:**

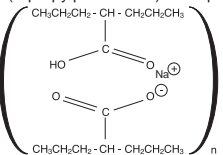
PANCREATITIS INFORMATION LEAFLET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.

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



Divalproex sodium, USP occurs as a white powder with a characteristic odor. Each divalproex sodium delayed-release tablet, intended for oral administration contains divalproex sodium equivalent to 125 mg or 250 mg or 500 mg of valproic acid. In addition each tablet also contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, methylcellulose, methacrylic acid copolymer dispersion, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, starch, talc and triethyl citrate.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

Divalproex sodium is bioequivalent 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**

Equivalent oral doses of divalproex sodium delayed-release tablets products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

However, it is possible that differences among the various valproate products in  $T_{max}$  and  $C_{min}$  could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the tablet (increase in  $T_{max}$  from 4 to 8 hours) than on the absorption of the sprinkle capsules (increase in  $T_{max}$  from 3.3 to 4.8 hours). While the absorption rate from the G.I. tract and 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 employing dosing regimens from once-a-day to four-times-a-day in patients with epilepsy maintain a constant rate of plasma valproate ion concentrations that is 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 inconsequential from a practical clinical standpoint. Whether or not rate of absorption influences the efficacy of valproate as an anticonvulsant or antimigraine agent is unknown.

Co-administration of oral valproate products with food and substitution among the various divalproex sodium and valproic acid formulations should cause no clinical problems in the management of patients with epilepsy (see **DOSEAGE AND ADMINISTRATION**). 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.

**Distribution**

**Protein Binding:**

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mg/mL to 18.5% at 130 mg/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  $\beta$ -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.

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 m<sup>2</sup> and 11 L/1.73 m<sup>2</sup>, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m<sup>2</sup> and 92 L/1.73 m<sup>2</sup>. 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. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

**Special Populations**

**Effect of Age:**

**Neonates -** Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronidation 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 children under 10 days ranged from 10 to 67 hours compared to a range of 7 to 13 hours in children greater than 2 months.

**Children - Pediatric patients (i.e., 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, clearance 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%. Accordingly, the initial dosage should be reduced in the elderly (see **DOSEAGE 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 m<sup>2</sup>, 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-third of patients with mild to moderate liver disease. In elderly patients with mild to moderate liver disease, plasma protein binding, 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 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 mg/mL to 18.5% at 130 mg/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 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

**Mania:**

In placebo-controlled clinical trials of acute mania, patients were dosed to clinical response with trough plasma concentrations between 10 and 125 mcg/mL (see **DOSEAGE AND ADMINISTRATION**).

**Clinical Trials**

**Mania**

The effectiveness of divalproex sodium delayed-release tablets for the treatment of acute mania was demonstrated in two 3-week, placebo controlled, parallel group studies.

(1) Study 1: The first study enrolled adult patients who met DSM-III-R criteria for Bipolar Disorder and who were hospitalized for acute mania. In addition, they had a history of failing to respond to or not tolerating previous lithium carbonate treatment. Divalproex sodium delayed-release tablets were initiated at a dose of 250 mg tid and adjusted to achieve serum valproate concentrations in a range of 50-100 mcg/mL by day 7. Mean divalproex sodium delayed-release tablets doses for completers in this study were 1118, 1525, and 2402 mg/day at days 7, 14, and 21, respectively. Patients were assessed on the Young Mania Rating Scale (YMRS, score ranges from 0-50), an augmented Brief Psychiatric Rating Scale (BPRS-A), and the Global Assessment Scale (GAS). Baseline scores and change from baseline in the week 3 endpoint (last-observation-carry-forward) analysis were as follows:

Group	Study 1 YMRS Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Wk 3 <sup>3</sup>	
Placebo	28.8	+0.2	9.7
	28.5	-9.5	
Divalproex sodium delayed-release tablets	28.5	+1.8	18.8
	28.5	-17.0	

Group	BPRS-A Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Wk 3 <sup>3</sup>	
Placebo	76.2	+1.8	6.1
	76.4	-17.0	
Divalproex sodium delayed-release tablets	76.4	-17.0	18.8
	76.4	-17.0	

Group	GAS Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Wk 3 <sup>3</sup>	
Placebo	31.8	0.0	18.1
	30.3	+18.1	
Divalproex sodium delayed-release tablets	31.8	0.0	18.1
	30.3	+18.1	

Group	MSS Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Day 21 <sup>3</sup>	
Placebo	18.9	-2.5	6.1
	18.5	-6.2	
Divalproex sodium delayed-release tablets	18.9	-6.2	3.7
	18.5	-6.2	

Group	BIS Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Day 21 <sup>3</sup>	
Placebo	16.4	-1.4	2.4
	15.7	-3.2	
Divalproex sodium delayed-release tablets	16.4	-1.4	1.8
	15.7	-3.2	

<sup>1</sup> Mean score at baseline

<sup>2</sup> Change from baseline to week 3 (LOCF)

<sup>3</sup> Difference in change from baseline to week 3 endpoint (LOCF) between divalproex sodium delayed-release tablets and placebo

Divalproex sodium delayed-release tablets were statistically significantly superior to placebo on all three measures of outcome. (2) Study 2: The second study enrolled adult patients who met Research Diagnostic Criteria for manic disorder and who were hospitalized for acute mania. Divalproex sodium delayed-release tablets were initiated at a dose of 250 mg tid and adjusted within a dose range of 750-2500 mg/day to achieve serum valproate concentrations in a range of 40-150 mcg/mL. Mean divalproex sodium delayed-release tablets doses for completers in this study were 1116, 1683, and 2006 mg/day at days 7, 14, and 21, respectively. Study 2 also included a lithium group for which lithium doses for completers were 1312, 1869, and 1984 mg/day at days 7, 14, and 21, respectively. Patients were assessed on the Manic Rating Scale (MRS; score ranges from 11 to 63), and the primary outcome measures were the total MRS score, and scores for two subscales of the MRS, i.e., the Manic Symptom Scale (MSS) and the Behavior and Ideation Scale (BIS). Baseline scores and change from baseline in the week 3 endpoint (last-observation-carry-forward) analysis were as follows:

Group	Study 2 MRS Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Wk 3 <sup>3</sup>	
Placebo	28.8	+0.2	9.7
	28.5	-9.5	
Divalproex sodium delayed-release tablets	28.5	+1.8	18.8
	28.5	-17.0	

Group	BPRS-A Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Wk 3 <sup>3</sup>	
Placebo	76.2	+1.8	6.1
	76.4	-17.0	
Divalproex sodium delayed-release tablets	76.4	-17.0	18.8
	76.4	-17.0	

Group	GAS Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Wk 3 <sup>3</sup>	
Placebo	31.8	0.0	18.1
	30.3	+18.1	
Divalproex sodium delayed-release tablets	31.8	0.0	18.1
	30.3	+18.1	

Group	MSS Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Day 21 <sup>3</sup>	
Placebo	18.9	-2.5	6.1
	18.5	-6.2	
Divalproex sodium delayed-release tablets	18.9	-6.2	3.7
	18.5	-6.2	

Group	BIS Total Score		Difference <sup>1</sup>
	Baseline <sup>2</sup>	BL to Day 21 <sup>3</sup>	
Placebo	16.4	-1.4	2.4
	15.7	-3.2	
Divalproex sodium delayed-release tablets	16.4	-1.4	1.8
	15.7	-3.2	

<sup>1</sup> Mean score at baseline



<sup>1</sup> Change from baseline to day 21 (LOCF)

<sup>2</sup> Difference in change from baseline to day 21 endpoint (LOCF) between divalproex sodium delayed-release tablets and placebo and lithium and placebo

Divalproex sodium delayed-release tablets were statistically significantly superior to placebo on all three measures of outcome. An exploratory analysis for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or gender.

A comparison of the percentage of patients showing  $\geq 30\%$  reduction in the symptom score from baseline in each treatment group, separated by study, is shown in Figure 1.

**Migraine**

The results of two multicenter, randomized, double-blind, placebo-controlled clinical trials established the effectiveness of divalproex sodium delayed-release tablets in the prophylactic treatment of migraine headache. Both studies employed essentially identical designs and recruited patients with a history of migraine with or without aura (of at least 6 months in duration) who were experiencing at least 2 migraine headaches a month during the 3 months prior to enrollment. Patients with cluster headaches were excluded. Women of childbearing potential were excluded entirely from one study, but were permitted in the other if they were deemed to be practicing an effective method of contraception.

In each study following a 4-week single-blind placebo baseline period, patients were randomized, under double blind conditions, to divalproex sodium delayed-release tablets or placebo for a 12-week treatment phase, comprised of a 4-week dose titration period followed by an 8-week maintenance period. Treatment outcome was assessed on the basis of 4-week migraine headache rates during the treatment phase.

In the first study, a total of 107 patients (24 M, 83 F), ranging in age from 26 to 73 were randomized 2:1, divalproex sodium delayed-release tablets to placebo. Ninety patients completed the 8-week maintenance period. Drug dose titration, using 250 mg tablets, was individualized at the investigator's discretion. Adjustments were guided by actual/sham trough total serum valproate levels in order to maintain the study blind. In patients on divalproex sodium delayed-release tablets doses ranged from 500 to 2500 mg a day. Doses over 500 mg were given in three divided doses (TID). The mean dose during the treatment phase was 1087 mg/day resulting in a mean trough total valproate level of 72.5 mcg/mL, with a range of 31 to 133 mcg/mL.

The mean 4-week migraine headache rate during the treatment phase was 5.7 in the placebo group compared to 3.5 in the divalproex sodium delayed-release tablets group (see Figure 2). These rates were significantly different.

In the second study, a total of 176 patients (19 males and 157 females), ranging in age from 17 to 76 years, were randomized equally to one of three divalproex sodium delayed-release tablets dose groups (500, 1000, or 1500 mg/day) or placebo. The treatments were given in two divided doses (BID). One hundred thirty-seven patients completed the 8-week maintenance period. Efficacy was to be determined by a comparison of the 4-week migraine headache rate in the combined 1000/1500 mg/day group and placebo group.

The initial dose was 250 mg daily. The regimen was advanced by 250 mg every 4 days (8 days for 500 mg/day group), until the randomized dose was achieved. The mean trough total valproate levels during the treatment phase were 39.6, 62.5, and 72.5 mcg/mL in the 500, 1000, and 1500 mg/day groups, respectively. The mean 4-week migraine headache rates during the treatment phase, adjusted for differences in baseline rates, were 4.5 in the placebo group, compared to 3.3, 3.0, and 3.3 in the divalproex sodium delayed-release tablets, 500, 1000, and 1500 mg/day groups, respectively, based on intent-to-treat results (see Figure 2). Migraine headache rates in the combined divalproex sodium delayed-release tablets, 1000/1500 mg group were significantly lower than in the placebo group.

<sup>1</sup> Mean dose of divalproex sodium delayed-release tablets were 1087 mg/day.

<sup>2</sup> Dose of divalproex sodium delayed-release tablets were 500 or 1000 mg/day.

**Epilepsy**

The efficacy of divalproex sodium delayed-release tablets 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.

In one, multicentric, placebo controlled study employing an add-on design (adjunctive therapy), 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 antiepileptic drug (AED), either divalproex sodium delayed-release tablets 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
Divalproex sodium delayed-release tablets	69	16.0	8.9 <sup>1</sup>
	Placebo	75	14.5

<sup>1</sup> Reduction from baseline statistically significant greater for divalproex sodium delayed-release tablets than placebo at p  $\leq$  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 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 high dose divalproex sodium delayed-release tablets than for placebo. For example, 45% of patients treated with divalproex sodium delayed-release tablets 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 divalproex sodium delayed-release tablets to reduce the incidence of CPS when administered as the sole AED. This 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 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 divalproex sodium delayed-release tablets. 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 24 weeks. In each of the patients randomized, however, completed the study. In patients converted to divalproex sodium delayed-release tablets monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 mcg/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.

Treatment	Monotherapy Study Median Incidence of CPS per 8 Weeks		
	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose divalproex sodium delayed-release tablets	131	13.2	10.7 <sup>1</sup>
Low dose divalproex sodium delayed-release tablets	134	14.2	13.8

<sup>1</sup> Reduction from baseline statistically significant greater for high dose than low dose at p  $\leq$  0.05 level.

Figure 4 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 divalproex sodium delayed-release tablets than for low dose divalproex sodium delayed-release tablets. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose divalproex sodium delayed-release tablets monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose of divalproex sodium delayed-release tablets.

**INDICATIONS AND USAGE**

**Mania**

Divalproex sodium delayed-release tablets, USP are indicated for the treatment of the manic or manic depressive associated with bipolar disorder. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility.

The efficacy of divalproex sodium delayed-release tablets, USP was established in 3-week trials with patients meeting DSM-III-R criteria for bipolar disorder who were hospitalized for acute mania (see **Clinical Trials under CLINICAL PHARMACOLOGY**).

The safety and effectiveness of divalproex sodium delayed-release tablets, USP for long-term use in mania, i.e., more than 3 weeks, has not been systematically evaluated in controlled clinical trials. Therefore, healthcare providers who elect to use divalproex sodium delayed-release tablets, USP for extended periods should continually reevaluate the long-term usefulness of the drug for the individual patient.

**Epilepsy**

Divalproex sodium delayed-release tablets, USP are indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. Divalproex sodium delayed-release tablets, USP are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in 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.

**Migraine**

Divalproex sodium delayed-release tablets, USP are indicated for prophylaxis of migraine headaches. There is no evidence that divalproex sodium delayed-release tablets, USP are useful in the acute treatment of migraine headaches. Because valproic acid may be a hazard to the fetus, divalproex sodium delayed-release tablets, USP 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**).

**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**

**Hepatitis**

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. 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. 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 delayed-release tablets 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. When divalproex sodium delayed-release tablets are 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.**

**Caution 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 246 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 in patients with urea cycle disorders receiving divalproex sodium. The clinical symptoms of hyperammonemic encephalopathy often include altered level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia (see **PRECAUTIONS - Hypothermia**). In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at 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. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured (see **CONTRAINDICATIONS and WARNINGS - Urea Cycle Disorders and PRECAUTIONS - Hyperammonemia**).

**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. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia (see **PRECAUTIONS - Hypothermia**). In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at 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. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured (see **CONTRAINDICATIONS and WARNINGS - Urea Cycle Disorders and PRECAUTIONS - Hyperammonemia**).

and, therefore, require further medical evaluation promptly.

#### Hyperammonemia

Hyperammonemia is a symptom 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.

#### CNS Depression

Since divalproex sodium delayed-release tablets may produce CNS depression, especially when combined with another CNS depressant (e.g., 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.

#### Birth Defects

Since divalproex sodium delayed-release tablets have been associated with certain types of birth defects, female patients of child-bearing age considering the use of divalproex sodium delayed-release tablets should be advised of the risk and of alternative therapeutic option and to read the Patient Information Leaflet, which appears as the last section of the labeling. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., neurosis) is considered. Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS - Pregnancy).

#### Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including divalproex sodium delayed-release tablets, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to the healthcare providers (see WARNINGS).

#### Multi-Organ Hypersensitivity Reaction

Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug-related and should be reported to the physician immediately (see PRECAUTIONS - Multi-Organ Hypersensitivity Reaction).

#### Effects of Co-Administration of 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 these 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 6-oxidation pathway consisting of 2- $\alpha$ -valproic acid, 3-OH-valproic acid, and 3- $\alpha$ -hydroxyvalproic acid decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. 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 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.

Carbamepem Antibiotics - A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbamepem antibiotics (artemether, imipenem, meropenem) and may result in loss of seizure control. The mechanism of this interaction is not well understood. Serum valproic acid concentrations should be monitored frequently after initiating carbamepem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates (see WARNINGS).

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) resulted in a 15% 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 Titrilac - 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 no significant changes in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with chlorpromazine.

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 glucuronosyltransferases. 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:

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

Clozapepam - The concomitant use of valproic acid and clozapepam 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 (500 to 1500 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 50% decrease in the clearance of 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. Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

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 neurologic 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 the 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.

Topiramate - Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see CONTRAINDICATIONS and WARNINGS - Urea Cycle Disorders and PRECAUTIONS - Hyperammonemia and Hyperammonemia) and Encephalopathy Associated with Concomitant Topiramate Use). Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported (see PRECAUTIONS - Hypothermia and Hyperammonemia).

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 divalproex sodium delayed-release tablets 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:

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

Clozapepam - In psychotropic patients (n=11), no interaction was observed when valproate was co-administered with clozapepam.

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 (1mg 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 ethinylestradiol (50 mcg)/levonorgestrel (250 mcg) 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/m<sup>2</sup> 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 induce 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/m<sup>2</sup> 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<sup>2</sup> basis). Segment I fertility studies in rats have shown delays up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m<sup>2</sup> 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.

To provide information regarding the effects of in utero exposure to divalproex sodium delayed-release tablets, healthcare providers are advised to recommend that pregnant patients taking divalproex sodium delayed-release tablets enroll in the NAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

#### 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

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). When divalproex sodium delayed-release tablets are used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

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

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid 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 delayed-release tablets for the treatment of acute mania has not been studied in individuals below the age of 18 years.

The safety and effectiveness of divalproex sodium delayed-release tablets for the prophylaxis of migraines has not been studied in individuals below the age of 16 years.

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/m<sup>2</sup> basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m<sup>2</sup> basis.

#### Geriatric Use

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 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).

There is insufficient information available to discern the safety and effectiveness of divalproex sodium delayed-release tablets for the prophylaxis of migraines in patients over 65.

#### ADVERSE REACTIONS

##### Mania

The incidence of treatment-emergent events has been ascertained based on combined data from two placebo-controlled clinical trials of divalproex sodium delayed-release tablets in the treatment of acute mania. The adverse events were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, divalproex sodium delayed-release tablets and lithium carbonate. A total of 4%, 8%, and 11% of patients discontinued therapy due to intolerance in the placebo, divalproex sodium delayed-release tablets and lithium carbonate groups, respectively.

Table 2 summarizes these adverse events reported for patients in these trials where the incidence rate in the divalproex sodium

delayed-release tablets-treated group was greater than 5% and greater than the placebo incidence, or where the incidence in the divalproex sodium delayed-release tablets-treated group was statistically significantly greater than the placebo group. Vomiting was the only event that was reported by significantly (p < 0.05) more patients receiving divalproex sodium delayed-release tablets compared to placebo.

Adverse Event	Divalproex Sodium Delayed-release Tablets (n=97)	Placebo (n=97)
Nausea	22%	15%
Somnolence	19%	12%
Dizziness	12%	4%
Vomiting	12%	3%
Asthenia	10%	7%
Abdominal pain	9%	8%
Dyspepsia	9%	8%
Rash	6%	3%

<sup>1</sup>The following adverse events occurred at an equal or greater incidence for placebo than for divalproex sodium delayed-release tablets: back pain, headache, constipation, diarrhea, tremor, and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 89 divalproex sodium-treated patients in controlled clinical trials:

**Body as a Whole:** Chest pain, chills, chills and fever, neck pain, neck rigidity.  
**Cardiovascular System:** Hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation.  
**Digestive System:** Anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess.  
**Hemic and Lymphatic System:** Echinomycosis.  
**Metabolic and Nutritional Disorders:** Edema, peripheral edema.  
**Musculoskeletal System:** Arthralgia, arthrosis, leg cramps, twitching.  
**Nervous System:** Abnormal dreams, abnormal gait, agitation, ataxia, catatonal reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonnia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo.  
**Respiratory System:** Dyspnea, rhinitis.  
**Skin and Appendages:** Alopecia, discoid lupus erythematosus, dry skin, furunculosis, maculopapular rash, seborrhea.  
**Special Senses:** Amblyopia, conjunctivitis, deafness, dry/eye, ear pain, eye pain, tinnitus.  
**Urogenital System:** Dysmenorrhea, dysuria, urinary incontinence.

##### Migraine

Based on two placebo-controlled clinical trials and their long term extension, divalproex sodium delayed-release tablets were generally well tolerated with most adverse events rated as mild to moderate in severity. Of the 202 patients exposed to divalproex sodium delayed-release tablets 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 ≥ 1% of 248 divalproex sodium delayed-release tablets-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 3 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in the divalproex sodium delayed-release tablets-treated group was greater than 5% and was greater than that for placebo patients.

Body System/Event	Divalproex Sodium Delayed-release Tablets (N = 202)	Placebo (N = 81)
<b>Gastrointestinal System</b>		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal pain	9%	4%
Increased appetite	6%	4%
<b>Nervous System</b>		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%
Tremor	9%	0%
<b>Other</b>		
Weight gain	8%	2%
Back pain	8%	6%
Alopecia	7%	1%

<sup>1</sup>The following adverse events occurred in at least 5% of divalproex sodium delayed-release tablets-treated patients and at an equal or greater incidence for placebo than for divalproex sodium delayed-release tablets: flu syndrome and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 202 divalproex sodium-treated patients in the controlled clinical trials:

**Body as a Whole:** Chest pain, chills, face edema, fever, and malaise.  
**Cardiovascular System:** Vasodilation.  
**Digestive System:** Anorexia, constipation, dry mouth, flatulence, gastrointestinal disorder (unspecified), and stomatitis.  
**Hemic and Lymphatic System:** Echinomycosis.  
**Metabolic and Nutritional Disorders:** Peripheral edema, SGOT increase, and SGPT increase.  
**Musculoskeletal System:** Leg cramps and myalgia.  
**Nervous System:** Abnormal dreams, amnesia, confusion, depression, emotional lability, insomnia, nervousness, paresthesia, speech disorder, thinking abnormalities, and vertigo.  
**Respiratory System:** Cough increased, dyspnea, rhinitis, and sinusitis.  
**Skin and Appendages:** Pruritus and rash.  
**Special Senses:** Conjunctivitis, ear disorder, taste perversion, and tinnitus.  
**Urogenital System:** Cystitis, metrorrhagia, and vaginal hemorrhage.

##### Epilepsy

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

Table 4 lists treatment-emergent adverse events which were reported by ≥ 5% of divalproex sodium delayed-release tablets-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 divalproex sodium delayed-release tablets alone, or the combination of divalproex sodium delayed-release tablets and other antiepilepsy drugs.

Body System/Event	Divalproex Sodium Delayed-release Tablets (%) (n = 77)	Placebo (%) (n = 70)
<b>Body as a Whole</b>		
Headache	31	21
Asthenia	7	7
Fever	6	4
<b>Gastrointestinal System</b>		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
<b>Nervous System</b>		
Somnolence	27	11
Tremor	25	6
Dizziness	13	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
<b>Respiratory System</b>		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	4
Rhinitis	5	1
<b>Other</b>		
Alopecia	6	1
Weight Loss	6	0

Table 5 lists treatment-emergent adverse events which were reported by ≥ 5% of patients in the high dose group, in a controlled trial of divalproex sodium delayed-release tablets 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 divalproex sodium delayed-release tablets alone, or the combination of divalproex sodium delayed-release tablets and other antiepilepsy drugs.

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

<sup>1</sup>Headache 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 divalproex sodium delayed-release tablets 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, hypertonnia, 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

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 mild or moderate in intensity, but sometimes are serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, divalproex sodium delayed-release tablets and lithium carbonate. A total of 4%, 8%, and 11% of patients discontinued therapy due to intolerance in the placebo