

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 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

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**).

ADVERSE REACTIONS

Epilepsy

The data described in the following section were obtained using DEPAKOTE (divalproex sodium) tablets.

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 2 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 a placebo-controlled trial of adjunctive therapy for the 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 2. Adverse Events Reported by $\geq 5\%$ 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 3 lists treatment-emergent adverse events which were reported by $\geq 5\%$ 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 3. Adverse Events Reported by $\geq 5\%$ 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

1 Headache was the only adverse event that occurred in $\geq 5\%$ 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

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. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

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

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, agranulocytosis, and acute intermittent porphyria.

Hepatic

Minor elevations of transaminases (e.g., 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

Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

Mania

Although DEPAKENE has not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE tablets.

Body as a Whole

Chills, neck pain, neck rigidity.

Cardiovascular System

Hypotension, postural hypotension, vasodilation.

Digestive System

Fecal incontinence, gastroenteritis, glossitis.

Musculoskeletal System

Arthrosis.

Nervous System

Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.

Skin and Appendages

Furunculosis, maculopapular rash, seborrhea.

Special Senses

Conjunctivitis, dry eyes, eye pain.

Urogenital System

Dysuria.

Migraine

Although DEPAKENE has not been evaluated for safety and efficacy in the treatment of prophylaxis of migraine headaches, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of DEPAKOTE tablets.

Body as a Whole

Face edema.

Digestive System

Dry mouth, stomatitis.

Urogenital System

Cystitis, metrorrhagia, and vaginal hemorrhage.

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 overdosage.

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

DOSAGE AND ADMINISTRATION

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

DEPAKENE (valproic acid) is administered orally. DEPAKENE is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the DEPAKENE dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see **PRECAUTIONS - Drug Interactions**).

Complex Partial Seizures

For adults and children 10 years of age or older.

Monotherapy (Initial Therapy)

DEPAKENE 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 DEPAKENE 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

DEPAKENE 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. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to DEPAKOTE tablets, 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

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. If the total daily dose exceeds 250 mg, it should be given in divided doses.

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 DEPAKENE 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.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight		Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup		
(Kg)	(Lb)		Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

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. 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 slowly building up the dose from an initial low level.

HOW SUPPLIED

DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid, bearing the trademark DEPAKENE for product identification, in bottles of 100 capsules (**NDC 0074-5681-13**), and as a red Oral Solution containing the equivalent of 250 mg valproic acid per 5 mL as the sodium salt in bottles of 16 ounces (**NDC 0074-5682-16**).

Store capsules at 59-77°F (15-25°C). Store Oral Solution below 86°F (30°C).

Patient Information Leaflet

Important Information for Women Who Could Become Pregnant About the Use of DEPAKOTE®, DEPAKOTE® ER, DEPAKOTE® Sprinkle Capsules, and DEPAKENE®.

Please read this leaflet carefully before you take any of these medications. This leaflet provides a summary of important information about taking these medications to women who could become pregnant. If you have any questions or concerns, or want more information about these medications, contact your doctor or pharmacist.

Information for Women Who Could Become Pregnant

These medications can be obtained only by prescription from your doctor. The decision to use any of these medications is one that you and your doctor should make together, taking into account your individual needs and medical condition.

Before using any of these medications, women who can become pregnant should consider the fact that these medications have been associated with birth defects, in particular, with spina bifida and other defects related to failure of the spinal canal to close normally. 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%.

These medications have also been associated with other birth defects such as defects of the heart, the bones, and other parts of the body. Information suggests that birth defects may be more likely to occur with these medications than some other drugs that treat your medical condition.

Information for Women Who Are Planning to Get Pregnant

- Women taking any of these medications who are planning to get pregnant should discuss the treatment options with their doctor.

Information for Women Who Become Pregnant

- If you become pregnant while taking any of these medications you should contact your doctor immediately.

Other Important Information

- Your medication should be taken exactly as prescribed by your doctor to get the most benefit from your medication and reduce the risk of side effects.
- If you have taken more than the prescribed dose of your medication, contact your hospital emergency room or local poison center immediately.
- Your 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.

This summary provides important information about the use of DEPAKOTE®, DEPAKOTE® ER, DEPAKOTE® Sprinkle Capsules, and DEPAKENE® to women who could become pregnant. If you would like more information about the other potential risks and benefits of these medications, 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 these medications, you should discuss them with your doctor.

Depakene Capsules are

Manufactured by:

Banner Pharmacaps, Inc.

High Point, NC 27265 U.S.A.

for:

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

Depakene Oral solution is

Manufactured by:

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

OR by:

DPT Laboratories, Ltd.

San Antonio, TX 78215, U.S.A.

For:

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

Depakene (valproic acid)

PRODUCT INFO

Product Code	0074-5682	Dosage Form	SOLUTION
Route Of Administration	ORAL	DEA Schedule	

INGREDIENTS

Name (Active Moiety)	Type	Strength
valproic acid (valproic acid)	Active	250 MILLIGRAM In 5 MILLILITER
glycerin	Inactive	
methylparaben	Inactive	
propylparaben	Inactive	
FD&C Red No.40 dye	Inactive	
water	Inactive	
sucrose	Inactive	
vanillin	Inactive	
artificial cherry flavor	Inactive	
sorbitol	Inactive	

IMPRINT INFORMATION

Characteristic	Appearance	Characteristic	Appearance
Color		Score	
Shape		Symbol	
Imprint Code		Coating	
Size			

PACKAGING

#	NDC	Package Description	Multilevel Packaging
1	0074-5682-16	473 MILLILITER In 1 BOTTLE	None

Depakene (valproic acid)

PRODUCT INFO

Product Code	0074-5681	Dosage Form	CAPSULE, LIQUID FILLED
Route Of Administration	ORAL	DEA Schedule	

INGREDIENTS

Name (Active Moiety)	Type	Strength
valproic acid (valproic acid)	Active	250 MILLIGRAM In 1 CAPSULE
corn oil	Inactive	
glycerin	Inactive	
methylparaben	Inactive	
propylparaben	Inactive	
FD&C Yellow No.6 dye	Inactive	
titanium dioxide	Inactive	
water	Inactive	
red iron oxide	Inactive	

IMPRINT INFORMATION

Characteristic	Appearance	Characteristic	Appearance
Color	ORANGE (Orange)	Score	1
Shape	CAPSULE	Symbol	false
Imprint Code	DEPAKENE	Coating	false
Size	19mm		

PACKAGING

#	NDC	Package Description	Multilevel Packaging
1	0074-5681-13	100 CAPSULE In 1 BOTTLE	None