Depakote Sprinkle Capsules advertisement.

[s.l.]: [s.n.], 1989

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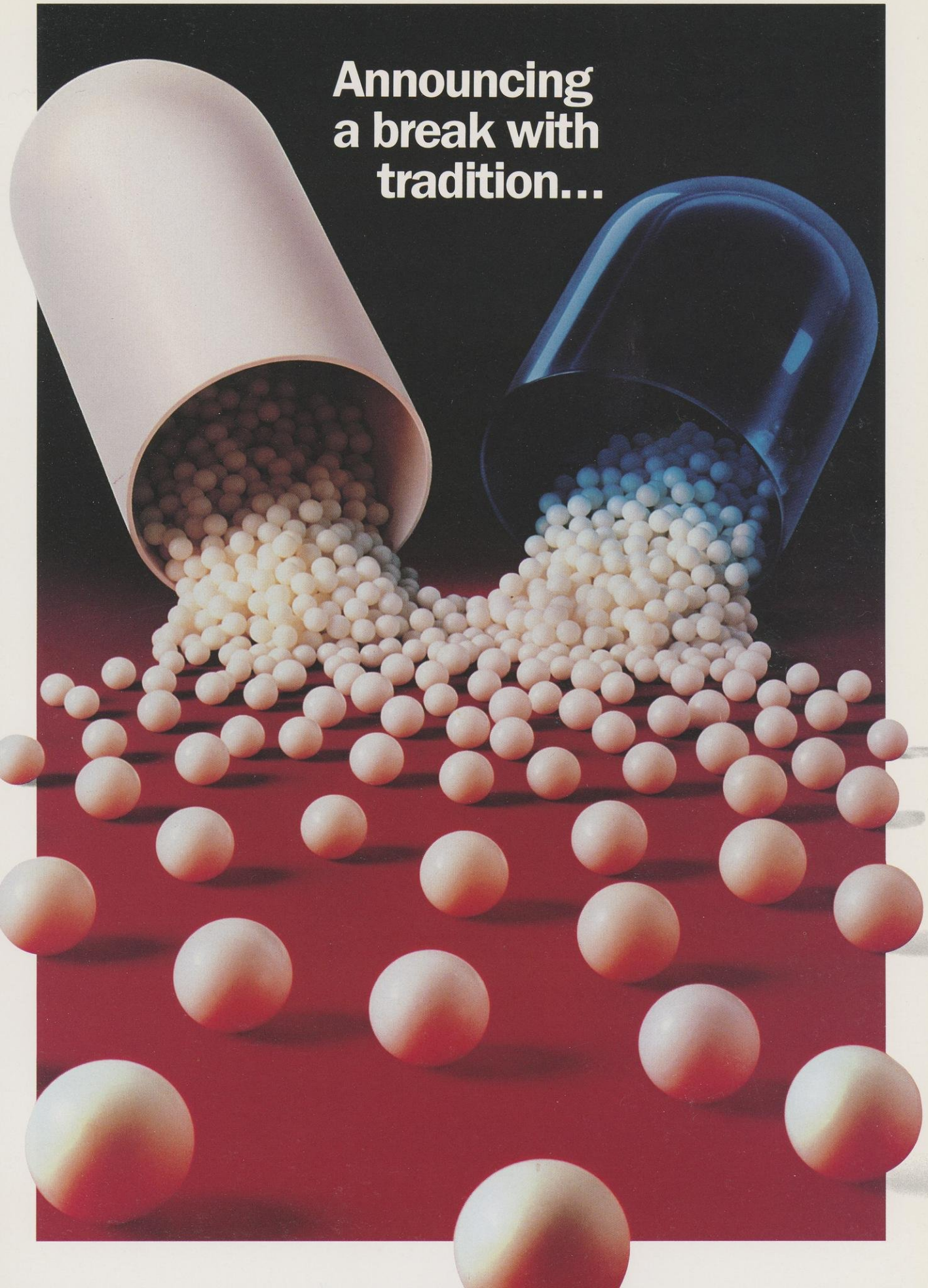

Announcing
a break with
tradition...

New!

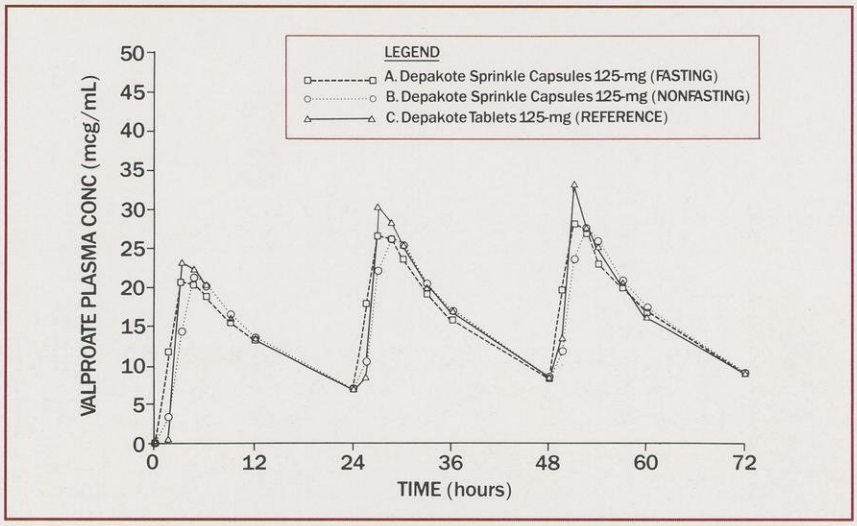
DEPAKOTE® divalproex sodium SPRINKLE CAPSULES 125 mg

An innovation in anticonvulsant dosage technology

All the advantages of Depakote® Tablets in an innovative pediatric dosage form

Formulated for consistent performance

- Therapeutically equivalent with Depakote® Tablets*
- Dose-to-dose consistency unaffected by food*



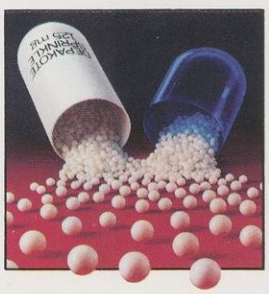
MEAN VALPROATE PLASMA CONCENTRATIONS FOLLOWING REPEATED DOSE ADMINISTRATION IN NORMAL SUBJECTS (N=11)†

Formulated for better taste and acceptance

- Overcomes the limitations of Depakene® (valproic acid) Syrup‡
- Better gastrointestinal tolerance
- Better patient compliance
  - –Eliminates unpleasant taste
  - –Improves convenience
  - –Makes midday dosing easier
- Less expensive than Depakene Syrup

Sprinkles on any soft food to make taking an anticonvulsant as easy as eating a snack.

Switch your patients to



New!

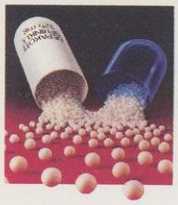
DEPAKOTE® divalproex sodium SPRINKLE CAPSULES 125 mg

Please see adjoining page for full prescribing information, including reported side effects of Depakote® and the warning concerning hepatotoxicity and the necessity for monitoring liver function. Please also see Clinical Pharmacology section for details on switching patients from Depakene to Depakote Sprinkle therapy.

*Carrigan PJ, Brinker DR, Lamm JE, Cavanaugh JH, Cloyd JC: Divalproex sodium: Evaluation of a multiparticulate ("sprinkle" capsule) pediatric dosage form. *Neurology* 1987;37 (suppl 1):96.

†Carrigan PJ, Brinker DR, Lamm JE, Cavanaugh JH, Cloyd JC: Divalproex sodium: Evaluation of a multiparticulate ("sprinkle" capsule) pediatric dosage form. Presented at the American Academy of Neurology Annual Meeting, New York, April 1987, Poster No. 60.

‡Cloyd JC, Kriel RL, Ong B, et al: Valproate absorption and patient acceptance of divalproex sodium-coated particles (sprinkle) in children with epilepsy. *Epilepsia* 1987;28(5):10.



New!

DEPAKOTE® divalproex sodium SPRINKLE CAPSULES 125 mg

AN INNOVATION IN ANTICONVULSANT DOSAGE TECHNOLOGY

DEPAKOTE® Sprinkle Capsules
DIVALPROEX SODIUM COATED PARTICLES IN CAPSULES

DEPAKOTE® Tablets
DIVALPROEX SODIUM DELAYED-RELEASE TABLETS

WARNING:
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 SEIZURE CONTROL SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE 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 LOSS OF SEIZURE CONTROL, 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.

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 occurs as a white powder with a characteristic odor.

DEPAKOTE tablets and Sprinkle capsules are antiepileptics for oral administration. DEPAKOTE Sprinkle capsules contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in a hard gelatin capsule. DEPAKOTE tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg or 500 mg of valproic acid.

Inactive Ingredients
125 mg Sprinkle capsules: cellulosic polymers, D&C Red No. 28, FD&C Blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide and triethyl citrate.

DEPAKOTE tablets: cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch) silica gel, talc, titanium dioxide and vanillin.

In addition, individual tablets contain:
125 mg tablets: FD&C Blue No. 1 and FD&C Red No. 40.
250 mg tablets: FD&C Yellow No. 6 and iron oxide.
500 mg tablets: D&C Red No. 30, FD&C Blue No. 2 and iron oxide.

CLINICAL PHARMACOLOGY
Divalproex sodium is an antiepileptic agent which dissociates to the valproate ion in the gastrointestinal tract. The mechanism by which valproate exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA).

Equivalent oral doses of DEPAKOTE (divalproex sodium) products and DEPAKENE (valproic acid) capsules deliver equivalent quantities of valproate ion systemically. However, the rate of valproate ion absorption may vary with the 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).

When subjects are in a fasting state, peak plasma concentrations of valproate ion are observed approximately 3 to 4 hours following administration of all DEPAKOTE products.

Experiments indicate that feeding can influence the rate of systemic absorption of valproate. In studies in which the contents of DEPAKOTE (divalproex sodium) Sprinkle capsules were sprinkled on applesauce, feeding was found to delay the time to peak plasma concentration by approximately 1.5 hours.

Compared to DEPAKOTE tablets, however, DEPAKOTE Sprinkle capsules (in the fasting state) exhibit a slower rate of absorption, resulting in lower peak plasma concentration (i.e., fluctuations between minimum and maximum plasma valproate concentrations are attenuated).

While absorption rate from the GI tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate in chronic use is not affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Accordingly, coadministration of oral valproate products with food, and substitution among the various DEPAKOTE and DEPAKENE formulations should cause no clinical problems (see DOSAGE 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.

The plasma half-life of valproate is typically in the range of six to sixteen hours. Half-lives in the lower part of the range are usually found in patients taking other antiepileptic drugs capable of enzyme induction.

Valproate is primarily metabolized in the liver. The major metabolic routes are glucuronidation, mitochondrial beta oxidation, and microsomal oxidation. The major metabolites formed are the glucuronide conjugate, 2-propyl-3-keto-pentanoic acid, and 2-propyl-hydroxypentanoic acids. Other unsaturated metabolites have been reported. The major route of elimination of these metabolites is in the urine.

Patients on monotherapy will generally have longer half-lives and higher concentrations of valproate at a given dosage than patients receiving polytherapy. This is primarily due to enzyme induction caused by other antiepileptics, which results in enhanced clearance of valproate by glucuronidation and microsomal oxidation. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

The therapeutic range is commonly considered to be 50 to 100 mcg/ml of total valproate, although some patients may be controlled with plasma concentrations that fall outside this range. Valproate is highly bound (90%) to plasma proteins in the therapeutic range; however, protein binding is concentration-dependent and decreases at high valproate concentrations. The binding is variable among patients, and may be affected by fatty acids or by highly bound drugs such as salicylate. Some clinicians favor monitoring free valproate concentrations, which may more accurately reflect CNS penetration of valproate. As yet, a consensus on the therapeutic range of free concentrations has not been established; however, monitoring total and free valproate may be informative when there are changes in clinical status, concomitant medication or valproate dosage.

INDICATIONS AND USAGE
DEPAKOTE (divalproex sodium) is 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.

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

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

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

WARNINGS
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 nonspecific symptoms such as loss of seizure control, 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. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control 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.

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, ANTIEPILEPTIC 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%.[1] THIS RISK IS SIMILAR TO THAT FOR NON-EPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROATE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be 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. 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.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS
Hepatic Dysfunction: See BOXED WARNING, CONTRAINDICATIONS AND WARNINGS.

General: Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If clinically significant elevation occurs, DEPAKOTE products should be discontinued.

Since valproate may interact with concurrently administered antiepileptic drugs, periodic plasma concentration determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See 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.

Information for Patients: Since DEPAKOTE products 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.

Drug Interactions: Valproate may potentiate the CNS depressant activity of alcohol.

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

THERE IS EVIDENCE THAT VALPROATE CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL CONCENTRATIONS BY IMPAIRMENT OF NONRENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF VALPROATE AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION 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 is metabolized to a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF VALPROATE AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL WITH SUBSEQUENT INCREASE IN TOTAL PHENYTOIN CONCENTRATIONS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN CONCENTRATIONS HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide concentrations. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Caution is recommended when valproate is used with drugs affecting coagulation (e.g., aspirin, warfarin). See ADVERSE REACTIONS.

Evidence suggests that there is an association between the use of certain antiepileptics and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing antiepileptics effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. While valproate is not a significant enzyme inducer, and, therefore, would not be expected to decrease concentrations of steroid hormones, clinical data about the interaction of valproate with oral contraceptives is minimal.[2]

Carcinogenesis: Valproic acid was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80 and 170 mg/kg/day 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: Studies on valproate have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for valproate.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day 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. Caution should be exercised when divalproex sodium is administered to a nursing woman.

ADVERSE REACTIONS
Since divalproex sodium has usually been used with other antiepileptic drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to divalproex sodium alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have 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.[3]

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), ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness and incoordination. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus and erythema multiforme. A case of fatal epidermal necrolysis has been reported in a 6 month old infant taking valproate and several other concomitant medications.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity 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 and frank hemorrhage (see PRECAUTIONS – *General* and *Drug Interactions*). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia and bone marrow suppression.

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).

Pancreatic: Acute pancreatitis (including rare fatal cases).

Metabolic: Hyperammonemia (see PRECAUTIONS).

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

Other: Edema of the extremities.

OVERDOSAGE
Overdosage with valproate may result in deep coma.

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.

DOSAGE AND ADMINISTRATION
DEPAKOTE tablets and Sprinkle capsules are administered orally. 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 a divided regimen.

Administration of Sprinkle Capsules: DEPAKOTE Sprinkle capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoonful) of soft food such as applesauce or pudding. The drug/food mixture should be swallowed immediately (avoid chewing) and not stored for future use. Each capsule is oversized to allow ease of opening.

Conversion from DEPAKENE to DEPAKOTE: In patients previously receiving DEPAKENE (valproic acid) therapy, DEPAKOTE products should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on a DEPAKOTE product, a dosing schedule of two or three times a day may be elected in selected patients.[4]

DEPAKOTE products provide equal extent of absorption, although they may not produce identical trough and peak valproate concentrations. DEPAKOTE tablets produce slightly higher peak concentrations than DEPAKOTE Sprinkle capsules. Such differences in the maximum and minimum valproate plasma concentrations are unlikely to be of clinical significance; however, changes in dosage, administration of valproate or concomitant medications should be accompanied by increased monitoring of plasma concentrations of valproate and other medications, as well as the patient's clinical status.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum concentration and therapeutic effect. However, therapeutic valproate serum concentrations for most patients will range from 50 to 100 mcg/ml. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

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

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
DEPAKOTE Sprinkle capsules (divalproex sodium coated particles in capsules), 125 mg, are white opaque and blue, and are supplied in bottles of 100 (**NDC** 0074-6114-13) and Abbo-Pac® unit dose packages of 100 (**NDC** 0074-6114-11).

DEPAKOTE tablets (divalproex sodium delayed-release tablets) are supplied as:

125 mg salmon pink-colored tablets:
Bottles of 100 ..... (**NDC** 0074-6212-13)
Abbo-Pac® unit dose packages of 100 ..... (**NDC** 0074-6212-11)

250 mg peach-colored tablets:
Bottles of 100 ..... (**NDC** 0074-6214-13)
Bottles of 500 ..... (**NDC** 0074-6214-53)
Abbo-Pac® unit dose package of 100 ..... (**NDC** 0074-6214-11)

500 mg lavender-colored tablets:
Bottles of 100 ..... (**NDC** 0074-6215-13)
Bottles of 500 ..... (**NDC** 0074-6215-53)
Abbo-Pac® unit dose packages of 100 ..... (**NDC** 0074-6215-11)

Store capsules below 86°F (30°C).

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Revised: Sept., 1989

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