Epival®

(divalproex sodium)

PRESCRIBING INFORMATION

NAME OF DRUG: EPIVAL© (divalproex sodium)
Enteric-Coated Tablets

THERAPEUTIC CLASSIFICATION: Anticonvulsant

ACTION AND CLINICAL PHARMACOLOGY: EPIVAL© (divalproex sodium) has anticonvulsant properties, and is chemically related to valproic acid. Although its mechanism of action has not yet been established, it has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown. EPIVAL® dissociates into valproic acid in the gastrointestinal tract.
Peak serum levels of valproic acid occur in 3 to 4 hours.
The serum half-life ($t_{1/2}$) of valproic acid is typically in the range of 6 to 16 hours. Half-lives in the lower part of the above range are usually found in patients taking other drugs capable of enzyme induction. Enzyme induction may result in enhanced clearance of valproic acid by glucuronidation and microsomal oxidation. Because of these changes in valproic acid clearance, monitoring of valproate and concomitant drug concentrations should be intensified whenever enzyme-inducing drugs are introduced or withdrawn. A slight delay in absorption occurs when the drug is administered with meals but this does not affect the total absorption. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. Increases in doses may result in decreases in the extent of protein binding and variable changes in valproic acid clearance and elimination. In epilepsy, the therapeutic plasma concentration range is believed to be from 50 to 100 µg/mL. Occasional patients may be controlled with serum levels lower or higher than this range. A good correlation has not been established between daily dose, serum level and therapeutic effect.
In placebo-controlled clinical studies in acute mania, 79% of patients were dosed to a plasma concentration between 50 µg/mL and 125 µg/mL. Protein binding of valproate is saturable ranging from 90% at 50 µg/mL to 82% at 125 µg/mL.
Elimination of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The principal metabolite formed in the liver is the glucuronide conjugate. Other metabolites in the urine are products of C-3, C-4 and C-5 oxidation. The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxy-pentanoic acid, 2-propyl-3-hydroxy-pentanoic acid and 2-propyl-4-hydroxy-pentanoic acid.
(See WARNINGS regarding statement on fatal hepatic dysfunction.)

INDICATIONS AND CLINICAL USE:

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

Acute Mania: EPIVAL© (divalproex sodium) is indicated in the treatment of the manic episodes associated with bipolar disorder (DSM-III-R).
The effectiveness of EPIVAL© in long-term use, that is for more than 3 weeks, has not been systematically evaluated in controlled trials. EPIVAL© is not indicated for use as a mood stabilizer in patients under 18 years of age.

CONTRAINDICATIONS: EPIVAL© (divalproex sodium) should not be administered to patients with hepatic disease or significant dysfunction; it is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. These incidences usually occurred during the first six months of treatment with valproic acid. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease.
The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only valproate. Risk generally declined with increasing age. No deaths have been reported in patients over 10 years of age who received valproate alone.
If EPIVAL© is to be used for the control of seizures in children two years old or younger, it should be used with *extreme caution* and as a sole agent. The benefits of therapy should be weighed against the risks.
Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, vomiting, and in epileptic patients, loss of seizure control. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking EPIVAL© (divalproex sodium).
Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering EPIVAL® to patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.
In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decreases in concentration and serum ammonia for increases in concentration. If changes occur, divalproex sodium should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.
The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. The benefit of improved symptom control at higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Use in pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of human females receiving the drug during pregnancy. The incidence of neural tube defects in the fetus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid-exposed women having children with spina bifida is approximately **1-2%**. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (ANENCEPHALY AND SPINA BIFIDA).
Animal studies have demonstrated valproic acid-induced teratogenicity, and studies in human females have demonstrated placental transfer of the drug.
Multiple reports in the clinical literature indicate an association between the use of antiepileptic drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women, this incidence may be increased 2 to 3-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, cleft lip and/or palate, craniofacial abnormalities and neural tube defects. Nevertheless, the great majority of mothers receiving antiepileptic medications deliver normal infants.
Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed antiepileptics. Some reports indicate a possible similar association with the use of other antiepileptic drugs, including trimethadione, paramethadione, and valproic acid. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.
Patients taking valproic acid may develop clotting abnormalities. If valproic acid is used in pregnancy, the clotting parameters should be monitored carefully.
Antiepileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.
Epileptic women of childbearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation is indicated.
Risk-benefit must be carefully considered when treating women of childbearing age for bipolar disorder.
Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

Use in Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving EPIVAL® (divalproex sodium). It is not known what effect this may have on a nursing infant.

Fertility: The effect of valproate on testicular development and on sperm production and fertility in humans is unknown.
Long-term animal toxicity studies indicate that valproic acid is a weak carcinogen or promoter in rats and mice. The significance of these findings for man is unknown at present.

PRECAUTIONS:

Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia, inhibition of the second phase of platelet aggregation, platelet counts and coagulation tests are recommended before instituting therapy and at periodic intervals. It is recommended that patients receiving EPIVAL® (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery.
Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of EPIVAL® (divalproex sodium) dosage or withdrawal of therapy pending investigation.
Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs the divalproex sodium should be discontinued.
EPIVAL® (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.
There have been reports of altered thyroid function tests associated with valproic acid: the clinical significance of these is unknown.

Renal Impairment: Renal impairment is associated with an increase in the unbound fraction of valproate. In several studies, the unbound fraction of valproate in plasma from renally impaired patients was approximately double that for subjects with normal renal function. Hemodialysis in renally impaired patients may remove up to 20% of the circulating valproate.

Use in the Elderly: The safety and efficacy of EPIVAL® in elderly patients with epilepsy and mania has not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience with EPIVAL® in this population.

Driving and Hazardous Occupations: EPIVAL® (divalproex sodium) may produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: EPIVAL® (divalproex sodium) may potentiate the CNS depressant action of alcohol.
The concomitant administration of valproic acid with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine and dicumarol) may result in alteration of serum drug levels.

Aspirin and Warfarin: Caution is recommended when EPIVAL® is administered with drugs affecting coagulation (e.g., aspirin and warfarin). (See ADVERSE REACTIONS.)

Phenobarbital: There is evidence that valproic acid may cause an increase in serum phenobarbital levels, by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproic acid serum levels. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

Primidone: Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.

Phenytoin: There is conflicting evidence regarding the interaction of valproic acid with phenytoin. It is not known if there is a change in unbound (free) phenytoin serum levels. The dosage of phenytoin should be adjusted as required by the clinical situation. There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.
Because EPIVAL® (divalproex sodium) may interact with concurrently administered drugs which are capable of enzyme induction, periodic serum level determinations of these drugs are recommended during the early part of therapy.

Clonazepam: The concomitant use of valproic acid and clonazepam may produce absence status in patients with a history of absence-type seizures.

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

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

Carbamazepine: Concomitant use of carbamazepine with valproic acid may result in decreased serum concentrations and half-life of valproate due to increased metabolism induced by hepatic microsomal enzyme activity. Valproate causes an increase in the active 10, 11 -epoxide metabolite of carbamazepine by inhibition of its breakdown. Monitoring of serum concentrations is recommended when either medication is added to or withdrawn from an existing regimen. Changes in the serum concentration of the 10,11-epoxide metabolite of carbamazepine, however, will not be detected by routine serum carbamazepine assay.

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

Chlorpromazine: A single study has shown that the concomitant use of chlorpromazine with valproic acid may result in a decrease in valproic acid clearance. Valproic acid serum concentrations and effects should be monitored when valproic acid is co-administered

with chlorpromazine due to possible inhibition of valproic acid metabolism.

Selective serotonin re-uptake inhibitors (SSRIs): Some evidence suggests that SSRIs inhibit the metabolism of valproate, resulting in higher than expected levels of valproate.

Tricyclic antidepressants: The metabolism of amitriptyline and nortriptyline after a single dose of amitriptyline (50 mg) was inhibited by multiple dosing with valproic acid (500 mg twice daily) in sixteen healthy male and female volunteers. For the sum of amitriptyline and nortriptyline plasma concentrations, in the presence of valproic acid, the mean C_{max} and AUC were increased by 19% and 42%, respectively.

Lithium: In a double-blind, placebo-controlled, multiple dose crossover study in 16 healthy male volunteers, pharmacokinetic parameters of lithium were not altered by the presence or absence of EPIVAL°. The presence of lithium, however, resulted in an 11%-12% increase in the AUC and C_{max} of valproate. T_{max} was also reduced. Although these changes were statistically significant, they are not likely to have clinical importance.

Benzodiazepines: Valproic acid may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations. In two small studies in healthy volunteers, valproate produced a 17% decrease in the clearance of lorazepam, and 26% decrease in the clearance of unbound diazepam. Displacement of diazepam from plasma protein binding sites may also occur. During valproate administration the unbound fraction of diazepam in the serum increased approximately twofold.

ADVERSE REACTIONS:

Epilepsy: The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other antiepileptics, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal: Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor (may be dose-related), dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash, photosensitivity, generalized pruritus, erythema multiforme, Stevens-Johnson syndrome and petechiae have rarely been noted.

Endocrine: There have been reports of irregular menses and secondary amenorrhea, breast enlargement, galactorrhea and parotid gland swelling in patients receiving valproic acid. Abnormal thyroid function tests have been reported (see PRECAUTIONS).

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

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (see PRECAUTIONS). This may be reflected in altered bleeding time. Petechiae, bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis, macrocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia, including macrocytic with or without folate deficiency, bone marrow suppression and acute intermittent porphyria have been reported.

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

Metabolic: Hyperammonemia (see PRECAUTIONS), hyponatremia and inappropriate ADH secretion. Hyperglycinemia has been reported and associated with a fatal outcome in a patient with preexisting non-ketotic hyperglycinemia.

Genitourinary: Enuresis

Pancreatic: There have been reports of acute pancreatitis occurring in association with therapy with valproic acid.

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

Other: Edema of the extremities has been reported.

Bipolar Disorder: The incidence of adverse events has been ascertained based on data from two short-term (21 day) placebo-controlled clinical trials of divalproex sodium in the treatment of acute mania, and from two long-term (up to 3 years) retrospective open trials.

Most Commonly Observed: During the short-term placebo-controlled trials, the six most commonly reported adverse events in patients (N=89) exposed to divalproex sodium were nausea (22%), headache (21%), somnolence (19%), pain (15%), vomiting (12%), and dizziness (12%).
In the long-term retrospective trials (634 patients exposed to divalproex sodium), the six most commonly reported adverse events were somnolence (31%), tremor (29%), headache (24%), asthenia (23%), diarrhea (22%), and nausea (20%).

Associated with Discontinuation of Treatment: In the placebo-controlled trials, adverse events which resulted in valproate discontinuation in at least one percent of patients were nausea (4%), abdominal pain (3%), somnolence (2%), and rash (2%).
In the long-term retrospective trials, adverse events which resulted in valproate discontinuation in at least one percent of patients were alopecia (2.4%), somnolence (1.9%), nausea (1.7%), and tremor (1.4%). The time to onset of these events was generally within the first two months of initial exposure to valproate. A notable exception was alopecia, which was first experienced after 3-6 months of exposure by 8 of the 15 patients who discontinued valproate in response to the event.

Controlled Trials: Table 1 summarizes those treatment-emergent adverse events reported for patients in the placebo-controlled trials when the incidence rate in the divalproex sodium group was at least 5%. (Maximum treatment duration was 21 days; maximum dose in 83% of patients was between 1000 mg - 2500 mg per day).

Table 1

Treatment-Emergent Adverse Event Incidence (≥ 5%) in Short-Term Placebo-Controlled Trials

Body System/Event	*Percentage of Patients*	
	divalproex sodium (N=89)	placebo (N=97)
Body as a Whole		
Headache	21.3	30.9
Pain	14.6	15.5
Accidental injury	11.2	5.2
Asthenia	10.1	7.2
Abdominal Pain	9.0	8.2
Back Pain	5.6	6.2
Digestive System		
Nausea	22.5	15.5
Vomiting	12.4*	3.1
Diarrhea	10.1	13.4
Dyspepsia	9.0	8.2
Constipation	7.9	8.2
Nervous System		
Somnolence	19.1	12.4
Dizziness	12.4	4.1
Tremor	5.6	6.2
Respiratory System		
Pharyngitis	6.7	9.3
Skin and Appendages		
Rash	5.6	3.1

*Statistically significant at $p \leq 0.05$ level.

Adverse Events in Elderly Patients: In elderly patients (above 65 years of age), there were more frequent reports of accidental injury, infection, pain, and to a lesser degree, somnolence and tremor, when compared to patients 18-65 years of age. Somnolence and tremor tended to be associated with the discontinuation of valproate.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: In a reported case of overdosage with valproic acid after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.
Naloxone has been reported to reverse the CNS depressant effects of valproic acid overdosage.
Because naloxone could theoretically also reverse the antiepileptic effects of EPIVAL°, it should be used with caution in patients with epilepsy.
Since EPIVAL° tablets are enteric-coated, the benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION:

Epilepsy: EPIVAL° (divalproex sodium) is administered orally. The recommended initial dosage is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases.
The maximal recommended dosage is 60 mg/kg/day. When the total daily dose is 125 mg or greater, it should be given in a divided regimen (see Table 2).
The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by improved seizure control must be weighed against the increased incidence of adverse effects.

Table 2
Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Dosage (mg) equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	1000	250	250	500
75-89.9	165-197.9	1250	500	250	500

As the dosage of divalproex sodium is raised, blood levels of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS, under *Drug Interactions*).
Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. The tablets should be swallowed without chewing.

Acute Mania: The recommended initial dose is 250 mg three times a day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations.
In placebo-controlled trials, 84% of patients received and tolerated maximum daily doses of between 1000 mg/day to 2500 mg/day. The maximum recommended dosage is 60 mg/kg/day.
The relationship of plasma concentration to clinical response has not been established for EPIVAL°. In controlled clinical studies, 79% of patients achieved and tolerated serum valproate concentrations between 50 µg/mL and 125 µg/mL.
When changing therapy involving drugs known to induce hepatic microsomal enzymes (e.g., carbamazepine) or other drugs with valproate interactions (see PRECAUTIONS, Drug Interactions), it is advisable to monitor serum valproate concentrations.

Conversion from Depakene° to EPIVAL°: EPIVAL° (divalproex sodium) dissociates into valproic acid in the gastrointestinal tract. Divalproex sodium tablets are uniformly and reliably absorbed, however, because of the enteric-coating, absorption is delayed by an hour when compared with Depakene (valproic acid) capsules. The bioavailability of divalproex sodium tablets is equivalent to that of Depakene (valproic acid) capsules.
In patients previously receiving Depakene° (valproic acid) therapy, EPIVAL° should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on EPIVAL°, a dosing schedule of two or three times a day may be elected in selected patients.

PHARMACEUTICAL INFORMATION:

Drug Substance

Tradename: EPIVAL°

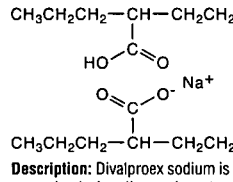
Proper Name: Divalproex sodium

USAN Names: INN: Valproate semisodium
BAN: Semisodium valproate

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

Molecular Weight: 310.14 *Molecular Formula:* $C_{16}H_{31}NaO_4$

Structural Formula:



Description: Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. It is a white powder with a characteristic odor, freely soluble in many organic solvents and in aqueous alkali solutions.

Non-Medicinal Ingredients: **EPIVAL° Enteric-Coated Tablets:** Cellulosic polymers, silica gel, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), 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.

Storage Recommendations: Store between 15°- 30°C (59°- 86°F).

AVAILABILITY OF DOSAGE FORMS: EPIVAL° (divalproex sodium) particle coated tablets are available as salmon-pink coloured tablets of 125 mg in bottles of 100 tablets; peach-coloured tablets of 250 mg and lavender-coloured tablets of 500 mg in bottles of 100 and 500 tablets.

INFORMATION FOR THE CONSUMER: Since EPIVAL° (divalproex sodium) 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 a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

References: 1. Dean JC. Valproate. In: Wyllie E, ed. The Treatment of Epilepsy: Principles and Practices. Philadelphia, Pa: Lea & Febiger, 1993:915-22. **2.** Wilder BJ, Ramsay RE, Murphy JV, et al. Comparison of valproic acid and phenytoin in newly diagnosed tonic-clonic seizures. *Neurology* 1983;33:1474-6. **3.** Turnbull DM, Howel D, Rawlins MD, et al. Which drug for the adult epileptic patient: phenytoin or valproate? *Br Med J* 1985;290:815-9. **4.** Covanis A, Gupta AK, Jeavons PM. Sodium valproate: monotherapy and polytherapy. *Epilepsia* 1982;23:693-720. **5.** Kakegawa N, Miyakoshi M, Seino M. Monopharmacy by sodium valproate (SV) and the blood concentration. In: Program and Abstracts of the XI Epilepsy International Symposium; September 30, 1979; Firenze, Italy. Abstract:153. **6.** Dreifuss FE, Langer DH. Side effects of valproate. *Am J Med* 1988;84 Suppl 1A:34-41. **7.** Epival Product Monograph. Abbott Laboratories, Limited.

ABBOTT LABORATORIES, LIMITED
P.O. BOX 6150, STATION CENTRE-VILLE
MONTRÉAL, QUÉBEC H3C 3K6

Product Monograph available on request.

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