Dapakan Tablets
(Divalproex Sodium) **250 mg**
Equivalent to Valproic Acid

ڈیپاکان گولیاں
(ڈائی ویلپروایکس سوڈیم) ۲۵۰ ملی گرام
مساوی ویلپروئک ایسڈ

Dapakan Tablets
(Divalproex Sodium) **500 mg**
Equivalent to Valproic Acid

ڈیپاکان گولیاں
(ڈائی ویلپروایکس سوڈیم) ۵۰۰ ملی گرام
مساوی ویلپروئک ایسڈ

Dapakan Syrup
(Sodium Valproate) **250 mg / 5 ml**
Equivalent to Valproic Acid

ڈیپاکان سیرپ
(سوڈیم ویلپروئیٹ) ۲۵۰ ملی گرام/۵ ملی لیٹر
مساوی ویلپروئک ایسڈ

COMPOSITION
Dapakan Tablets 250 mg
Each Enteric coated tablet contains
Divalproex sodium equivalent to valproic acid ... 250 mg
Product Complies U.S.P. Specs.

Dapakan Tablets 500 mg
Each Enteric coated tablet contains
Divalproex sodium equivalent to valproic acid ... 500 mg
Product Complies U.S.P. Specs.

Dapakan Syrup 250 mg / 5 ml
Each 5 ml contains:
Sodium valproate equivalent to valproic acid ... 250 mg
Product Complies U.S.P. Specs.

DESCRIPTION
Dapakan Tablets contain divalproex sodium which is stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. Dapakan tablets are supplied in two dosage strengths containing divalproex sodium equivalent to 250 mg and 500 mg of valproic acid.

Dapakan Syrup contains sodium valproate equivalent to valproic acid 250 / 5 ml.

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

Pharmacokinetics
Absorption / Bioavailability Equivalent oral doses of Dapakan tablets and Dapakan syrup deliver equivalent quantities of valproate ion systemically. Due to enteric coating of Dapakan, absorption is delayed one hour following oral administration. Enteric coated Dapakan may reduce the incidence of the irritative gastrointestinal effects of valproate as compared to valproic acid capsules. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid), 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 difference among the various valproate products in T_{max} & C_{max} could be important upon initiation of treatment. For example, in single dose studies, the effects of feeding had a greater influence on the rate of absorption of the tablets (increases in T_{max} from 4 to 8 hours) than on the absorption of 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 effected. Experience employing dosing regimens from once-a-day to four-time-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 the partical clinical standpoint. Whether or not rate of absorption influences the efficacy of valproate as an antimanic or antimigraine agents is unknown. Co-administration of valproate products with food and substitution among the various valproate and valproic acid formulations should cause no clinical problems in the management of patents with epilepsy **(see DOSAGE AND ADMINISTRATION)**. Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drug should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

Distribution The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10 % at 40 µg / ml to 18.5 % at l30 µg / ml. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with the renal impairment, and in the presence of other drugs (e.g. aspirin). Conversely, valproate may displace certain protein bound drugs (e.g. phenytoin, carbamazepine, and warfarin). **(see PRECAUTIONS, Drug interactions)** approximate unbound concentrations in plasma (about 10 % of total concentration).

Metabolism Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30- 50 % of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40 % of the dose. Usually, less than 15-20 % of the dose is eliminated by other oxidative mechanisms. Less than 3 % of an administered dose is excreted unchanged in urine. The relationship between dose and total valproate concentration is nonlinear, concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination Elimination of Dapakan 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. Mean plasma clearance and volume of distribution for total valproate are 0.56 L / hr / 1.73 m^2 and 11 / L / l .73 m^2 respectively. Mean plasma clearance and volume of distribution for free valproate volume of distribution for free valproate are 4.6 L / hr / 1 .73 m^2 and 92 L / 1.73 m^2. 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 anti epileptic 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
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 glucuronosyl transferase 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 patents (i.e. between 3 months and 10 years) have 50 % higher clearance expressed on weight (i.e. ml / min / kg) than do adults. Over the age of 10 years, children have pharmacokinetic 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 DOSAGE AND ADMINISTRATION)**.

Gender There are no differences in the body surface area adjusted unbound clearance between males and females (4.8 ± 0.17 and 4.7±1.17 L / hr / 1.73 m^2, respectively).

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

Liver Disease **(See CONTRAINDICATIONS and WARNINGS)**. Liver disease impairs the capacity to eliminate valproate. Liver disease is also associated with decreased albumin concentrations and larger unbound fraction (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentration may be misleading since free concentrations may be substantially elevated in patients with hepatic disease where as total concentrations may appear to be normal.

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

Plasma Levels and Clinical Effect
The relationship between plasma concentration and clinical response is not well documented.

One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species. For example, because the plasma protein binding of valproate is concentration dependant, the free fraction increases from approximately 10 % at 40 µg / ml to 18.5 % at l30 µg / ml. Higher than expected free fraction 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 l00 µg / 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 50 and 125 µg / ml **(See DOSAGE AND ADMINISTRATION)**.

INDICATIONS
Epilepsy Dapakan is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures, as well as in generalized tonic clonic (grand mal) juvenile myoclonic and partial (focal, local) simple / complex seizures. In accordance with the international classification of seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2 - 15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

Mania Dapakan tablets are indicated for the treatment of the manic episodes 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 safety effectiveness of Dapakan for long term use in mania, i.e. more than three weeks, has not been systematically evaluated in controlled clinical trials. Therefore physicians who elect to use Dapakan for extended periods should continually reevaluate the long-term usefulness of the drugs for the individual patient

Migraine Dapakan tablets are indicated for prophylaxis of migraine headaches. There is no evidence that Dapakan is useful in the acute treatment of migraine headaches. Because valproic acid may be a hazard to the fetus. Dapakan should be considered for women of childbearing potential only after risk has been thoroughly discussed with the patient and weighted against the potential benefits of treatment (See WARNINGS-Us-age in Pregnancy).

CONTRAINDICATIONS

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

Dapakan 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 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 valproate products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children those with congenital metabolic disorder, 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 considerable increased risk of developing fatal hepatotoxicity, especially those with the aforementioned condition. When valproate is used in this patient group it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risk. Above this age group experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patients 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 and thrombocytopenia) may be dose-related. The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy According to published and unpublished reports, valproic acid may produce teratogenic effects, such as neural tube defects (e.g., spinal bifida) 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 Center for Disease Control (CDC) has estimated the risk of valproic acid exposed women having children with spinal bifida to be approximately 1 to 2 %. Other congenital anomalies (e.g. craniofacial defects, cardiovascular malformations and anomalies involving various body systems), compatible and incompatible with life, have been reported, sufficient data to determine the incidence of these congenital anomalies is not available. The higher incidence of congenital anomalies in antiepileptic drug-treated women with seizure disorders can not be regarded as a cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in contributing to congenital anomalies.

Patients taking valproate may develop clotting abnormalities. A patient who had low fibrinogen when taking multiple anticonvulsants including valproate gave birth to an infant with afibrinogenemia who subsequently died of hemorrhage. If valproate is used in pregnancy, the clotting parameters should be monitored carefully.

Hepatic failure, resulting in the death of a newborn and of an infant, have been reported following the use of valproate during pregnancy.

Animal studies 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 abruptly in patients in whom the drugs is administered to prevent major seizures because of the strong possibility of precipitating status epileptics 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. However, 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 the benefits of therapy against the risks in treating or counseling women to childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Tests to detect neural tube and other defects using current accepted procedure should be considered a part of routine prenatal care in child bearing women receiving valproate.

PRECAUTIONS
Hepatic Dysfunction See CONTRAINDICATIONS AND WARNINGS.

General
Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters (e.g. low fibrinogen); platelet counts, and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving valproate be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising or disorder of hemostasis / coagulation is an indication for reduction of the Dapakan 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. Asymptomatic elevations of ammonia are more common than symptomatic elevations and when present require more frequent monitoring. If clinically significant symptoms occur, Dapakan therapy should be modified or discontinued. Since valproate may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy (See PRECAUTIONS Drug Interactions).

Valproate is partially eliminated in the urine as a ketometabolite 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. Suicidal ideation may be a manifestation of preexisting psychiatric disorders, and close supervision of high risk patents should accompany initial drug therapy.

Information for patients
Since valproate 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 know that they do not become drowsy from the drug.

Drug Interactions
Drugs that affect the level expression of hepatic enzymes, particularly those that elevate levels of glucuronosyl transferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone),can double the clearance of valproate. Thus patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs. In contrast, drugs that are inhibitors of cytochrome P_{450} isozymes, e.g. antidepressants, may be expected to have little effect on valproate clearance because cytochrome P_{450} microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and β-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentration 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.

Alcohol Dapakan may potentiate the CNS depressant activity of alcohol.

Aspirin A study involving the co-administration of aspirin at antipyretic doses with valproate to pediatric patients revealed a decreases in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased four-fold in the presence of aspirin compared to valproate alone.

Carbamazepine / carbamazepine-10, 11- Epoxide Serum levels of carbamazepine decreased 17 % while that carbamazepine-10,11-epoxide increased by 45 % upon co-administration of valproate to epileptic patients.

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

Ethosuximide Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg. day) to healthy volunteers was accompanied by a 25 % increase in elimination half-life of ethosuximide and a 15 % decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Felbamate Increase in average steady state valproate concentrations of 28 to 54 % may occur when felbamate is added to epileptic patients stabilized on valproate. A decrease in valproate dosage may be necessary when felbamate therapy is initiated. Lower doses of valproate may be necessary when used concomitantly with felbamate.

Lamotrigine The elimination half-life of lamotrigine was increased from 26 to 70 hours when valproate was co-administered. The dose of lamotrigine should be reduced when co-administered with valproate.

Lithium Co-administration of valproate (5000 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers has no effect on the steady-state kinetics of lithium.

Phenobarbital There is evidence that valproic acid can cause a decrease in non-renal clearance (50 % increase in half-life and 30 % decrease in plasma clearance of phenobarbital [60 mg single-dose]). This phenomenon can result in sever CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproate serum levels.

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.

Phenytoin Valproate displaces phyenytion from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytion (250 mg) in normal volunteers was associated with a 60 % increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30 % in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25 %. In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Primidone Primidone is metabolized into barbiturate and therefore, may also be involved in a similar or identical interaction with valproate as Phenobarbital.

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 valproate therapy is instituted in patients taking anticoagulants.

Carcinogenesis
Valproic acid was administered to Sprague Dawely rats and ICR (HNICR) mice at doses of 0, 80 and 170 mg / kg / day for two years. Although 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 human is unknown.

Mutagenesis
Valproate was not mutagenic in an in vitro bacterial assay (ames test) did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an in vivo cytogenetic study in rats. Increased frequencies of Sister Chromatid Exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of increase in SCE frequency is not know.

Nursing Mothers
Valproate is excreted in breast milk, concentrations in breast milk have been reported to be 1 to 10 % of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when valproate is administered to a nursing woman.

Pregnancy
See WARNINGS.

Pediatric
Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity specially those with the aforementioned conditions (see WARNINGS). When valproate is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatatoxicity 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 Dapakan for the treatment of acute mania has not been studied in individuals below the age of 18 years.

The safety and effectiveness of Dapakan for the prophylaxis of migraine has not been studied in individuals below the age of 16 years.

Geriatric
There is insufficient information available to discern the safety and effectiveness of Dapakan for the prophylaxis of migraine in patients over 65.

ADVERSE EVENTS
Other Patients Population

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

Since Dapakan has usually been used with other antiepilepsy drugs, in the treatment of epilepsy, it is not possible in most cases to determine whether the following adverse reactions can be ascribed to Dapakan alone, or the combination of drugs.

Migraine Divalproex sodium was generally well tolerated with most adverse events rated as mild to moderate in severity.

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. Diarrhoea, 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 enteric-coated Dapakan may result in reduction of gastrointestinal side effects in some patients.

CNS Effects Sedative effects have been noted in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. ***Trémor*** has been reported in patients receiving valproate and may be dose related.

Hallocination ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo and incardination have rarely been noted. Rare cases of coma have been noted in patients receiving valproate alone or in conjunction with Phenobarbital, Encephalopathy, ***with or without fever or hyperammonemia*** has been reported without evidence of hepatic dysfunction or inappropriate valproate plasma levels. Most patients recovered, with noted improvement of symptoms, upon discontinuation of the drug.

Reversible cerebral atrophy and dementia have been reported in association with valproate therapy.

Dermatologic Transient increases in hair loss have been observed. ***Skin rash,*** photosensitivity generalized pruritis, erythema, multiforme, ***Steven-Johnson Syndrome (SJS)*** and ***Toxic Epidermal Necrolysis (TEN)*** have been rarely reported.

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

Musculoskeletal Weakness has been reported.

Hematologic Thromboocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation.**(See PRECAUTIONS-General).**This may be reflected in altered bleeding time. Petechiae, bruising, hematoma formation, and frank hemorrhage have been reported. ***Relative lymphocytosis, macrocytosis, anemia including microcytic with or without folate deficiency, pancytopenia aplastic anemia, hypofibrinogenemia*** and ***acute intermittent prophyria*** have been noted. ***Leukopenia*** and ***eosinophilia, anemia and bone marrow suppression*** have been reported.

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

Respiratory system Dyspnea, rhinitis.

Skin and Appendages Alopecia, discoid lupus erythematosus, dry skin, furunculosis, maculopapular rash, seborrhea.

Special Senses Abnormal vision, amblyopia, conjunctivitis, deafness, dry eyes, ear disorder, ear pain, eye pain, tinnitus.

Urogenital System Dysmenorrhea, dysuria, urinary incontinence.

Body as a Whole Accidental injury, allergic reaction, chest pain, chills, face edema, fever, malaise and neck pain.

Cardiovascular System Vasodilatation.

Digestive System Anorexia, constipation, dry mouth, flatulence, gastrointestinal disorder (unspecified), and stomatitis.

Hemic and Lymphatic System Ecchymosis.

Metabolic and nutritional Disorders Peripheral edema, SCOT increase, and SGPT increase.

Musculoskeletal System Leg cramps and myalgia.

Nervous System Abnormal dreams, amnesia, confusion, depression, emotional liability, 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.

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 tanderm hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastnc 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
General Dapakan tablets are administered orally and should be swallowed whole, without chewing.

Epilepsy Monotherapy **(Initial Therapy):**Divalproex sodium 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 / day 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 optimal, 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, concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25 % every two weeks. This reduction may be started at initation of divalproex sodium therapy, or delayed by one to two 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: Divalproex sodium may be added to the patients 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 divalproex sodium, no adjustement of carbamazepine or phenytoin dosage was needed. However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see Drug interactions), periodic plasma concentration determines the course of therapy **(see PRECAUTIONS Drug interactions).**

Other Patients Populations 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 exceed 250 mg. it should be given in a divided regimen.

The following table is guide for the initial daily dose of Dapakan Syrup (Sodium Valproate) (15 mg / kg / day).

Weight		Total daily Dose (mg)	Teaspoonfuls of syrup		
(Kg)	(lb)		Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250 mg	0	0	1
25 - 39.9	55 - 87.9	500 mg	1	0	1
40 - 59.9	88 - 131.9	750 mg	1	1	1
60 - 74.9	132 - 164.9	1000 mg	1	1	2
75 - 89.9	165 - 197.9	1250 mg	2	1	2

A good correlation has not been established between daily dose serum concentration, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with epilepsy will range from 50 to 100 µg / ml. Some patients may be controlled with lower or higher serum concentrations **(see CLINICAL PHARMACOLOGY)**. As the Dapakan dosage is titrated upward, blood concentrations of Phenobarbital and / or phyenytoin may be affected **(see PRECAUTIONS).**

Antiepilepsy Anitepileptic 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 epileptics with attendant hypoxia and threat to life. **(See WARNINGS)**.

Conversion from Dapakan syrup to Dapakan tablets In patients previously receiving Dapakan syrup, Dapakan tablets should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on Dapakan tablet, a dosing schedule of two or three times a day may be elected in selected patients.

Mania The recommended dose is 750 mg daily in divided doses. 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 clinical trials of acute mania, patients were dosed to a clinical trials of acute mania, patients were dosed to a clinical response with a trough plasma concentration between 50 and 125 µg / ml. Maximum concentrations were generally achieved within 14 days. The maximum recommended dosage is 60 mg / kg / day.

There is no body of evidence available from controlled trials to guide a clinican in the longer term management of a patient who improves during Divalproex sodium treatment of an acute manic episode. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the benefits of Divalproex sodium in such longer-term treatment. Although there are no efficacy data that specifically address longer-term antimanic treatment with Divalproex sodium, the safety of Divalproex sodium in longer-term use is supported by data from record reviews involving approximately 360 patients treated with Divalproex sodium for greater than 3 months.

Migraine The recommended starting dose is 250 mg twice daily. Some patents may benefit form doses up to 1000 mg / day. In the clinical trials, there was no evidence that higher doses led to greater efficacy.

General Dosing Advice
Dosing in Elderly Patients Due to a decrease in unbound clearance of valproate, the starting dose should be reduced, the ultimate therapeutic dose should be achieved on the basis of clinical response.

Dose Related Adverse Events The frequency of adverse effects (particulay elevated liver enzymes and thrombocytopenia) may be dose-related. 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.

STORAGE Store below 30°C in a dry place, protect from light. To be dispensed on the prescription of a registered medical practitioner only. Keep out of the reach of children.

HOW SUPPLIED
Dapakan Tablets 250 mg:
Enteric-coated tablets in Alu-Alu blister of 3 x 10s and 10 x 10s in carton

Dapakan Tablets 500 mg:
Enteric-coated tablets in Alu-Alu blister of 2 x 10s and 10 x 10s in carton

Dapakan Syrup 250 mg / 5 ml:
Supplied in 60 ml, bottle in carton.
Supplied in 120 ml, bottle in carton.

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
صرف مستند معالج کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:

Platinum
Pharmaceuticals (Pvt.) Ltd.
A 20,North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Mfg. Lic No. 000415 QAR No. AW22-0991