SODIUM VALPROATE
VALPROIC ACID

VALPROS®

500 mg CONTROLLED RELEASE TABLET
ANTICONVULSANT / ANTIEPILEPTIC

FORMULATION
Each film-coated controlled release tablet contains:
Sodium valproate .....333 mg
Valproic acid.....145 mg
(both ingredients together correspond to sodium valproate 500 mg)

PRODUCT DESCRIPTION
This product is a combination of sodium valproate and valproic acid in a controlled release format. It is a pink, oval, biconvex, film-coated tablet.

PHARMACOLOGY
Sodium valproate and valproic acid are antiepileptic drugs (AEDs). The mechanism by which valproate exerts its antiepileptic effects is not known. However, its anticonvulsant effect may be related, at least in part, to increase brain concentrations of the inhibitory neurotransmitter, γ - aminobutyric acid (GABA).

PHARMACOKINETICS
The controlled release formulation of sodium valproate + valproic acid reduces the possibility of fluctuations in plasma concentrations compared with conventional formulations.
Sodium valproate and valproic acid circulate in the plasma as the valproate ion and trough valproic acid plasma levels are used to monitor both.
After oral administration, sodium valproate is rapidly converted to valproic acid and valproic acid dissociates to the valproate ion in the gastrointestinal tract.
Absorption of valproate is rapid and complete. Peak plasma concentrations are achieved between 2 to 8 hours.
In healthy human subjects under fasting conditions, the mean C_{max} of valproic acid (21.29 µg/mL) was achieved 5.08 hours (t_{max}) after oral administration of a single dose of 500 mg controlled release tablet containing sodium valproate and valproic acid. The $AUC_{(0-t)}$ was 233.12 µg.hr/mL and the $AUC_{(0-\infty)}$ was 241.42 µg.hr/mL.
The relationship between dose and total valproic acid concentration is nonlinear; concentration does not increase proportionally with dose because of saturable protein binding. The pharmacokinetics of unbound drug are linear.
Valproate is rapidly distributed; distribution appears to be restricted to plasma and rapidly exchangeable extracellular water. The volume of distribution is 0.2 L/kg body weight. Valproate has been detected in the cerebrospinal fluid (CSF) (about 10% of plasma concentrations), saliva (about 1% of plasma concentrations), and milk (about 1to10% of plasma concentrations). The drug crosses the placenta.
Plasma protein binding of valproate is concentration dependent; the free fraction of the drug increases from 10% at a concentration of 40 mcg/mL to 18.5% at a concentration of 130 mcg/mL. Protein binding is between 80 to 95%.
Valproate is metabolized principally in the liver by beta (over 40%) and omega oxidation (up to 15 to 20%). The metabolites are excreted in urine; 30 to 50% of an administered dose is excreted as glucuronide conjugates. Less than 3% of an administered dose is excreted in urine unchanged. The major metabolite in urine is 2-propyl-3-ketopentanoic acid; minor urinary metabolites are 2-propylglutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid, and 2-propyl-4-hydroxypentanoic acid. Small amounts of drug are also excreted in feces and in expired air.
Valproate is eliminated by first-order kinetics. Mean plasma clearance of total or free valproic acid is 0.56 m^2 or 4.6 L/hr per 1.73 m^2, respectively. Plasma elimination half-life ($t_{1/2}$) was 4.95 hours.

INDICATIONS
- For the treatment of generalized, partial or other epilepsy.
- For the treatment and prevention of mania associated with bipolar disorders.

DOSAGE AND ADMINISTRATION
General Dosing Recommendation:
The controlled release tablets should be swallowed whole and not crushed or chewed since this may cause inappropriate release and absorption of the drug.
Daily dosage requirements vary according to age and body weight. Dosage must be carefully and slowly adjusted according to individual requirements and response.
Sodium valproate + valproic acid controlled release tablets may be given once or twice daily.
Epilepsy
Therapeutic Dose Range: 1,000 mg to 2,000 mg/day (i.e., 20 to 30 mg/kg/body weight/ day)
Where adequate control is not achieved within this range, the dose may be further increased to 2,500 mg/day
Or, as prescribed by a physician.
Combined Therapy with Anticonvulsants
When sodium valproate + valproic acid is to be given to patients already on other anticonvulants, these should be tapered slowly; initiation of sodium valproate + valproic acid should then be gradual, with a target dose being reached after about two weeks.
In certain cases, it may be necessary to raise the dose by 5 to10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity (e.g., Phenytoin, phenobarbital and carbamazepine). Once the enzyme inducers have been withdrawn, it may be possible to maintain seizure control on a reduced dose of sodium valproate + valproic acid.
When barbiturates are being given concomitantly and if sedation is observed, the dosage of barbiturate should be reduced.
Bipolar Disorder
Recommended Initial Dose: 20 mg/kg/day
The dose may be adjusted according to individual clinical response. The maximum dose should not exceed 3,000 mg daily.
Recommended Maintenance Dose: 1,000 mg to 2,000 mg/day
Doses should be adjusted according to individual clinical response.
Prophylactic treatment should be established individually with the lowest effective dose.
Or, as prescribed by a physician.

SPECIAL POPULATION:
Elderly:
Although the pharmacokinetics of sodium valproate + valproic acid are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control.
In the elderly, the volume of distribution is increased and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the interpretation of plasma valproic acid levels.

Patients with Renal Insufficiency:
Dose reduction may be necessary. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

CONTRAINDICATIONS
- Known hypersensitivity to sodium valproate, valproic acid or to any ingredient in the product
- Patients with pre-existing, acute or chronic hepatic dysfunction or family history of severe hepatic dysfunction, particularly drug related
- Patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase-γ gene (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years old who are suspected of having a POLG-related disorder
- Patients with known urea cycle disorders
- Patients with porphyria

WARNINGS AND PRECAUTIONS
LIFE THREATENING ADVERSE REACTIONS
HEPATOTOXICITY
General Population: Hepatic failure resulting in fatalities has occurred in patients receiving valproate 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. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, particularly during the first six months.
Children under two years old are at a considerably increased risk of developing fatal hepatotoxicity, particularly 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 sodium valproate + valproic acid is used in this patient group, they should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patients groups.
Patients with Mitochondrial Disease: There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA polymerase-γ gene (POLG; e.g., Alpers Huttenlocher Syndrome). Sodium valproate + valproic acid is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years old who are clinically suspected of having a mitochondrial disorder. In patients over two years old who are clinically suspected of having a hereditary mitochondrial disease, sodium valproate + valproic acid should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with sodium valproate + valproic acid for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice.

FETAL RISK
Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following *in utero* exposure. Sodium valproate + valproic acid should only be used to treat pregnant women with epilepsy if other medications have failed to control their symptoms or are otherwise unacceptable. Sodium valproate + valproic acid should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is particularly important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using sodium valproate + valproic acid.

PANCREATITIS
Cases of life-threatening pancreatitis have been reported in both adults and children receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, sodium valproate + valproic acid should be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Hepatotoxicity
General information on hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproate. 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. Serum liver tests should be done prior to therapy and at frequent intervals thereafter, particularly during the first six months. However, healthcare providers 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 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.
In progressively older patient groups, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably.
Patients with known or suspected mitochondrial disease
Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase-γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents.
POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be done in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders.
Sodium valproate + valproic acid should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

Pancreatitis
Young children are at particular risk but this risk decreases with increasing age. Severe seizures, neurological impairment or anticonvulsant polytherapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.
Urea Cycle Disorders (UCD)
Sodium valproate + valproic acid is contraindicated in patients with known UCD.
Hyperammonemic encephalopathy, sometimes fatal, has been reported after initiation of valproate therapy in patients with UCD, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase (OTC) deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen (BUN), or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); and 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying UCD.
Ornithine Transcarbamylase Deficiency
The females who are heterozygous for OTC deficiency have a spectrum of clinical and biochemical findings, depending on the extent of inactivation of the X-chromosome. Females may show a range of symptoms due to hyperammonemia which, may be episodic, and therefore difficult to diagnose. The acute symptoms include headaches, vomiting, irritability, bizarre behavior, lethargy, ataxia, tremors, seizures (generalized tonic-clonic or focal) and coma. Valproate may precipitate hyperammonemia symptoms in those who have pre-existing OTC deficiency. As the symptoms may include seizures, any female with valproate-associated symptomatic hyperammonemia should be evaluated for OTC deficiency. Investigations should include measurement of plasma amino acids and the immediate cessation of valproate should result in clinical improvement.
Hyperammonemia
There has been report of hyperammonemia in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hyperammonemia should also be considered in patients who present with hypothermia. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying UCD.
Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.
Concomitant use of topiramate and valproate has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in levels of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse reaction is not due to pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.
Hypothermia
Hypothermia, defined as an unintentional drop in body temperature to <35°C (95°F), has been reported in association with valproate therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproate after starting topiramate treatment or after increasing the daily dose of topiramate. Consideration should be given to stopping valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities, including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.
Suicidal Behavior and Ideation
AEDs, including sodium valproate + valproic acid, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Anyone considering prescribing sodium valproate + valproic acid or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
Thrombocytopenia
The frequency of adverse effects, particularly elevated liver enzymes and thrombocytopenia, may be dose-related. 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 sodium valproate + valproic acid 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.
Weight Gain
Patients should be warned of the risk of weight gain at the initiation of therapy, and appropriate strategies should be adopted to minimize the risk.
Surgery
Prolongation of bleeding time, sometimes with thrombocytopenia, has occurred with valproate therapy. Platelet function should be monitored before surgery is undertaken in patients receiving sodium valproate + valproic acid.
Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding.
Multi-Organ Hypersensitivity Reactions
Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days: range 1 to 40 days). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, hepato-renal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience among drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.
Carnitine Palmitoyltransferase (CPT) Type II Deficiency
Patients with an underlying CPT type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate.
Monitoring Drug Plasma Concentration
Periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy since valproate may interact with concurrently administered drugs which are capable of enzyme induction.
Abrupt withdrawal
The possible risk of fits after sudden cessation of sodium valproate + valproic acid should be considered. If it is the only anticonvulsant used and has to be withdrawn for more than 12 hours because of surgery, control of epilepsy may be lost.
Effect on Ability to Drive or Operate Machinery
Use of sodium valproate + valproic acid may provide seizure control such that the patient may be eligible to hold a driving license. However, patients should be warned of the risk of transient drowsiness, particularly in cases of anticonvulsant polytherapy, too high starting dose, too rapid dose escalation, or association with benzodiazepines.

INTERACTIONS WITH OTHER MEDICAMENTS
- **Alcohol:** Valproate may potentiate the CNS depressant activity of alcohol. Concomitant use is not recommended.
- **Antiepileptic drugs** (e.g., phenytoin, carbamazepine, phenobarbital, lamotrigine, primidone, felbamate): Several AEDs often used in conjunction with valproate have the ability to increase the intrinsic clearance of valproate, presumably by enzymatic induction of metabolism.
  Valproate may displace carbamazepine from protein binding sites and may inhibit the metabolism of both carbamazepine and its metabolites, potentiating the toxic effects of carbamazepine. Clinical monitoring is recommended particularly at the beginning of combined therapy, with dosage adjustment when necessary.
  Valproate reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and lamotrigine dosage should be decreased as appropriate.
  Valproate may block the metabolism of barbiturates resulting in increased phenobarbital plasma levels, which particularly in children, may be associated with sedation. Concomitant use of phenobarbital and sodium valproate + valproic acid can cause CNS depression without significant elevation of serum level of either drug. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.
  Concomitant use of phenytoin and sodium valproate + valproic acid may lead to breakthrough seizures. Most reports have noted a decrease in total plasma phenytoin concentration, however increases in total phenytoin levels have been reported. An initial fall in total phenytoin levels with subsequent increase in phenytoin levels has also been reported. Furthermore, a decrease in total serum phenytoin with an increase in the free versus protein bound phenytoin levels has been reported with possible overdose symptoms (valproate displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore, clinical monitoring is recommended. When phenytoin plasma levels are determined, the free form should be evaluated. The dosage of phenytoin may require adjustment when given concomitantly with valproate as required by the clinical situation.
  Valproate increases primidone plasma levels with exacerbation of its adverse effects (e.g., sedation); these signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.
  Valproate may decrease felbamate mean clearance by up to 16%. On the other hand, combination of felbamate and sodium valproate + valproic acid decreases valproate clearance by 22% to 50% and consequently increase the valproate plasma concentrations. Valproate dosage should be monitored when given in combination with felbamate.
- **Anticoagulants**: The concomitant use of sodium valproate with drugs that exhibit extensive protein binding (e.g., aspirin, warfarin) may result in alteration of serum drug levels.
  The effect of valproate on anticoagulants is unknown. Caution is recommended when administering anticoagulants and other products which have anticoagulant properties.
  Concomitant use of sodium valproate + valproic acid and aspirin may result in displacement of valproate from protein binding sites, resulting in a rise in free levels of valproate. In addition, aspirin appears to inhibit the metabolism of valproate. Caution is advised when aspirin is given concomitantly with sodium valproate + valproic acid. Patients requiring long-term aspirin therapy may require a reduction in sodium valproate + valproic acid dose.
- **Carbapenem antibiotics** (e.g., panipenem, meropenem, imipenem): Decreases in blood levels of valproate have been reported when it is co-administered with carbapenem agents resulting in a 60 to 100% decrease in valproate levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, concomitant use of carbapenem agents in patients stabilized on valproate should be avoided. If treatment with these antibiotics cannot be avoided, close monitoring of valproate blood levels should be done.
- **Cimetidine or Erythromycin:** Concomitant use may increase valproate serum levels (as a result of reduced hepatic metabolism).
- **Cholestyramine:** May decrease the absorption of valproate.
- **Ethosuximide:** Valproate may inhibit ethosuximide metabolism, particularly in the presence of other anticonvulsants. Patients receiving this combination should be monitored clinically.
- **Mefloquinone and chloroquine:** These drugs increase valproate metabolism and may lower the seizure threshold; therefore, epileptic seizures may occur in cases of combined therapy. Dose adjustment of sodium valproate + valproic acid may be necessary.
- **Psychotropic agents** [e.g., monoamine oxidase inhibitors (MAOIs), antipsychotics (e.g., clozapine, haloperidol, olanzapine, quetiapine), antidepressants (e.g., fluoxetine), and benzodiazepines (e.g., clonazepam, diazepam, lorazepam, midazolam): Valproate may potentiate the effects of psychotropic agents; therefore, clinical monitoring is advised and the dose of these drugs should be reduced accordingly.
  Concomitant use of clozapine and sodium valproate + valproic acid may potentiate an increase in clozapine or valproate levels.
  A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate revealed no significant changes in valproate trough plasma levels.
  Concomitant use of olanzapine and sodium valproate + valproic acid may result in significant increase in the risk of adverse events associated with olanzapine e.g., neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder, and somnolence.
  Concomitant use of sodium valproate + valproic acid and quetiapine may increase the risk of neutropenia/leukopenia.
  Fluoxetine may inhibit the metabolism of sodium valproate + valproic acid as it does with TCAs, carbamazepine, and diazepam.
  The concomitant use of sodium valproate + valproic acid and clonazepam may produce absence status.
  Valproate displaces diazepam from its plasma binding sites and inhibits its metabolism. Monitoring of free diazepam levels may be necessary if the patient becomes sedated.
  Concomitant use of sodium valproate + valproic acid and lorazepam results in decreased lorazepam plasma clearance.
  Concomitant use of sodium valproate + valproic acid results in increased free plasma midazolam leading to an increase in of the midazolam response.
- **Lithium:** Sodium valproate + valproic acid has no effect on serum lithium levels.
- **Rifampicin:** Rifampicin may decrease valproate blood levels resulting in a lack of therapeutic effect. Therefore, sodium valproate + valproic acid dosage adjustment may be necessary when it is co-administered with rifampicin.
- **Temozolomide:** Concomitant use with sodium valproate + valproic acid may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.
- **Tolbutamide:** *In vitro* studies showed that the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with sodium valproate + valproic acid. The clinical relevance of this displacement is unknown.
- **Topiramate:** Concomitant use with sodium valproate + valproic acid has been associated with encephalopathy and/or hyperammonemia. Patients treated with these drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.
- **Tricyclic Antidepressants (TCAs)** (e.g., chlorpromazine, amitriptyline/nortriptyline): Valproate may inhibit the metabolism of TCAs. Clinical monitoring of free antidepressant levels may be necessary.
  Chlorpromazine may inhibit the metabolism of sodium valproate + valproic acid.
  Concomitant use of amitriptyline and sodium valproate + valproic acid resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Concomitant use of these drugs has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking sodium valproate + valproic acid concomitantly with amitriptyline. Lowering the amitriptyline/nortriptyline dose in the presence of sodium valproate + valproic acid should be considered.
- **Vitamin K-dependent factor anticoagulant:** The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased after displacement from plasma protein binding sites by valproate. The prothrombin time should be closely monitored.
- **Zidovudine:** Sodium valproate + valproic acid may increase zidovudine plasma concentrations leading to increased zidovudine toxicity.
- **Antacids:** Concomitant use with sodium valproate + valproic acid did not reveal any effect on the extent of valproate absorption.
- **Paracetamol:** Concomitant use with sodium valproate + valproic acid had no effect on the pharmacokinetics of paracetamol.
- **Oral contraceptives steroids:** Concomitant use with sodium valproate + valproic acid did not reveal any pharmacokinetic interaction.

Other Interactions:
- Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test. Altered thyroid function tests associated with valproate has also been reported.
- *In vitro* studies suggest that valproate stimulates the replication of the human immunodeficiency virus (HIV) and cytomegalovirus (CMV) viruses under certain experimental conditions. The clinical consequence, if any, is not known. In addition, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be taken into consideration when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.
- There have been reports of altered thyroid function test results associated with valproate. The clinical significant of this is unknown.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
PREGNANCY AND LACTATION
Pregnancy
Pregnancy Category D. Women of childbearing potential should not be started on sodium valproate + valproic acid without specialist neurological advice.
Adequate counseling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the fetus. Women who are taking sodium valproate + valproic acid and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.
If pregnancy is planned, consideration should be given to cessation of sodium valproate + valproic acid treatment, if appropriate.
When sodium valproate + valproic acid treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed.
Risk associated with epilepsy and antiepileptics
In offspring born to mothers with epilepsy receiving antiepileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3%) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardiovascular malformations.
No sudden discontinuation in the antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the fetus.
AEDs should be withdrawn under specialist supervision.
Risk associated with seizures
During pregnancy, maternal tonic-clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.
Risk associated with valproate
Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias, and multiple anomalies involving various body systems in offspring born to mothers treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other AEDs. Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73%. Available date indicate dose dependency of this effect.
Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.
Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.
Autism spectrum disorders have also been reported in children exposed to valproate *in utero*.
In view of the above data, the following recommendations should be taken into consideration:
- Sodium valproate + valproic acid should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e., in situations where other treatments are ineffective or not tolerated). This assessment is to be made before sodium valproate + valproic acid is prescribed for the first time, or when a woman of child-bearing potential treated with sodium valproate + valproic acid plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of sodium valproate and valproic acid during pregnancy.
  If a woman plans a pregnancy or becomes pregnant, sodium valproate + valproic acid therapy should be reassessed whatever the indication:
  - In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. The use of a prolonged release formulation may be preferable to any other treatment form.
  - In addition, folate supplementation should be started before pregnancy at relevant dosage (5 mg per day) for at least four weeks prior to and 12 weeks after conception. Evidence suggests that folic acid decreases the risk for congenital neural tube defects in the general population. It is not known whether the risk of neural tube defects or decreased IQ in the offspring of women receiving valproate is reduced by folic acid supplementation. Dietary folic acid supplementation both prior to conception and during pregnancy should be routinely recommended for patients using valproate.
  - Specialized prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.
- The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1,000 mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak levels.
- Pregnancies should be carefully screened by ultrasound, and other techniques, if appropriate.
- In bipolar indication, cessation of valproate therapy should be considered.

Risk in the neonate
There have been rare reports of hemorrhagic syndrome in neonates whose mothers have taken sodium valproate + valproic acid during pregnancy. This syndrome is related to thrombocytopenia, hypofibrinemia and/or to a decrease in other coagulation factors. Afibrinemia has also been reported and may be fatal. Hypofibrinemia is possibly associated with a decrease of coagulation factors. Phenobarbital and other enzyme inducers may also induce hemorrhagic syndrome. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.
Cases of hypoglycemia have been reported in neonates whose mothers have taken valproate during the third trimester of pregnancy.
Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
Withdrawal syndrome (e.g., agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions, and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of pregnancy.

Lactation
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 breast-fed infant. As a general rule, breastfeeding should not be undertaken while a patient is receiving sodium valproate + valproic acid.

PEDIATRIC
The potential benefit of sodium valproate + valproic acid should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy. The concomitant use of salicylates should be avoided in children under 3 years old due to the risk of liver toxicity and the concomitant use of barbiturates may require dosage adjustment. Monotherapy is recommended in these children, when prescribing sodium valproate + valproic acid. Young children are at particular risk for pancreatitis; however, this risk decreases with increasing age.
The safety and efficacy of sodium valproate for the treatment of manic episodes in bipolar disorder have not been evaluated in patients less than 18 years old.

GERIATRIC
A study involving elderly patients with dementia, a significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patient with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and higher blood urea nitrogen (BUN). In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.

UNDESIRABLE EFFECTS
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): Myelodysplastic syndrome
Blood and Lymphatic System Disorders: Thrombocytopenia, anemia, aplastic anemia, leukopenia, pancytopenia with or without bone marrow depression, decreased blood fibrinogen, red cell hypoplasia, neutropenia; bone marrow failure, including pure red cell aplasia, agranulocytosis; anemia including macrocytic with or without folate deficiency, anemia macrocytosis, ecchymosis, petechia, lymphocytosis, bone marrow suppression, acute intermittent porphyria
Immune System Disorders: Angioedema, anaphylaxis, allergic reaction, cutaneous vasculitis
Endocrine Disorders: Hypothyroidism, hyperandrogenism (e.g., hirsutism, virilism, androgen increased), parotid gland swelling, hyperglycemia
Gastrointestinal Disorders: Nausea, upper abdominal pain, diarrhea, gingival disorder (mainly gingival hyperplasia), stomatitis, vomiting, abdominal cramp, upper abdominal pain, anorexia, increased appetite, pancreatitis, constipation, gastralgia, dyspepsia, flatulence, hematemesis, eructation, periodontal abscess, taste perversion, fetal incontinence, gastroenteritis, glossitis, dry mouth
Hepatobiliary Disorders: Hepatic dysfunction, including hepatic failure; liver injury, AST and ALT increased
Metabolism and Nutrition Disorders: Hyperammonemia, asymptomatic elevations of ammonia, hyponatremia, syndrome of inappropriate secretion of ADH (SIADH)
Psychiatric Disorders: Depression, excitement, hyperactivity, behavioral disorders, confusional state, hallucinations, aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity, learning disorder, emotional lability, thinking abnormal, anxiety, abnormal gait, personality disorder, emotional upset, psychosis, hostility, behavioral deterioration, developmental delay
Nervous System Disorders: Drowsiness, sedation, tremor, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness, ataxia, coma, encephalopathy, lethargy, paresthesia, reversible dementia associated with reversible cerebral atrophy and cognitive disorder; reversible parkinsonism, extrapyramidal disorder which may not be reversible; twitching, hypertonia, incoordination, abnormal dreams, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo
Eye Disorders: Diplopia, amblyopia/blurred vision, abnormal vision, conjunctivitis, dry eyes, eye pain
Ear and Labyrinth Disorders: Deafness, either reversible or irreversible, tinnitus, otitis media, hearing loss
Cardiac Disorders: Chest pain, tachycardia, hypertention, palpitation, hypotension, postural hypotension, bradycardia
Vascular Disorders: Hemorrhage, vasculitis, vasodilation
**Respiratory, Thoracic and Mediastinal Dis