SODIUM VALPROATE

VALPROS® PEDIA
200 mg / 5 mL SYRUP
ANTICONVULSANT / ANTIEPILEPTIC

FORMULATION
Each 5 mL (1 teaspoonful) syrup contains:
Sodium valproate, BP..... 200 mg

PRODUCT DESCRIPTION
Sodium valproate (Valpros®Pedia) syrup is a red, syrupy liquid with a sweet cherry flavor, free from any visible foreign particles.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Sodium valproate is an anticonvulsant. Its anticonvulsant effect may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter, -aminobutyric acid (GABA). This effect of sodium valproate on the GABA neurotransmitter is also believed to possibly contribute to its antimanic properties.
Pharmacokinetics
Absorption of valproate is rapid and complete. After oral administration, sodium valproate is rapidly converted to valproic acid and valproic acid dissociates to the valproate ion in the gastrointestinal tract. Peak plasma concentrations are achieved between 1 to 4 hours after a single oral dose. Absorption of valproic acid is not affected by co-administration with milk products. Food slightly delays its absorption; however, this does not affect the total absorption of the drug. When administered on an empty stomach, local gastric irritation may occur due to the transformation of sodium valproate to valproic acid.
Valproate is rapidly distributed; distribution appears to be restricted to plasma and rapidly exchangeable extracellular water.
Valproate has been detected in the cerebrospinal fluid (CSF) (about 10% of serum concentrations),saliva (about 1% of plasma concentrations), and breast milk (about 1% to 10% 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 approximately 90%.
The relationship between dose and total valproic acid concentration is nonlinear; concentration does not increase proportionally with dose, but increases to a lesser extent, because of saturable protein binding. The pharmacokinetics of unbound drug is linear. The half-life of sodium valproate is within the range of 6 to 16 hours; its half-life in children is usually shorter.
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; 30-50% 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 L/hr per 1.73 m^2 or 4.6 L/hr per 1.73 m^2, respectively.
Hepatic Insufficiency: Hepatic insufficiency impairs the ability to eliminate valproic acid. Compared with healthy individuals, the clearance of valproic acid was decreased by 50% in a limited number of patients with liver cirrhosis and by 16% in a limited number of patients with acute hepatitis. Valproic acid's half-life was increased from 12 to 18 hours.
Renal Insufficiency: Drug clearance of sodium valproate may be reduced in patients with renal failure (i.e., creatinine clearance < 10 mL/min). Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.
Geriatrics: The capacity of elderly patients to eliminate valproate has been shown to be reduced; intrinsic clearance reduced by 39% and free fraction increased by 44%. Accordingly, the initial dose should be reduced in the elderly (see *Dosage and Administration*).
Pediatrics: Pediatric patients (i.e., 3 months to 10 years old) have 50% higher clearance of the drug expressed by weight (i.e., mL/min per kg). However, the pharmacokinetic parameters of valproic acid in children > 10 years old approximate those in the adult population. Infants (i.e., < 2 months old) have a markedly decreased clearance of valproic acid compared with older children and adults. This may be due to the delayed development of metabolic enzyme systems and an increased volume of distribution of valproic acid in these patients.

INDICATIONS
- ***Epilepsy***
  - Monotherapy or adjunctive therapy of complex partial seizures
  - Monotherapy or adjunctive therapy of simple or complex absence seizures, including petit mal, and is useful in primary generalized seizures with tonic-clonic manifestations
  - Adjunctive therapy of multiple seizure types, including absence seizures or tonic-clonic seizures
- ***Bipolar Disorder:*** Treatment of manic episodes, maintenance and prophylactic treatment of bipolar disorder

DOSAGE AND ADMINISTRATION
General Dosing Considerations:
Daily doses vary according to age, body weight and seizure control. Dose must be carefully and slowly adjusted according to individual requirements and response. Sodium valproate may take several days to show an initial effect; in some cases, it may take from 2 to 6 weeks to exhibit its maximum effect. Measurement of plasma levels may be helpful where there is poor control or side effects are suspected.
Antiepileptic drugs (AEDs) should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.
Any changes in dose and administration or the addition or discontinuance of concomitant drugs should be accompanied by close monitoring of clinical status and valproate plasma concentrations.
Patients should be informed to take sodium valproate everyday as prescribed. If a dose is missed, it should be taken as soon as possible, unless it is almost time for the next dose. If a dose is skipped, the patient should not double the dose.
Patients who experience gastrointestinal irritation may benefit from administration of sodium valproate with food or by slowly building up the dose from an initial low level.
Sodium valproate syrup should be given in divided doses taken preferably with or after meals. It should not be diluted.
Epilepsy
As Monotherapy, usual requirements are:
Children > 20 kg: Initially, 400 mg per day (irrespective of weight) with spaced increases until control is achieved (usually within the range of 20 to 30 mg/kg body weight per day). If adequate control of seizure is not achieved within this range, the dose may be increased to 35 mg/kg body weight per day.
Children < 20 kg: 20 mg/kg body weight per day. Dose may be increased in severe cases, but only in patients in whom plasma valproate levels can be monitored. In patients receiving doses of > 40 mg/kg body weight per day, clinical chemistry and hematological parameters should be monitored.
Adult Dose: Initially, 600 mg per day increasing by 200 mg per day at 3-day intervals until control is achieved. This is generally within the range of 1,000 to 2,000 mg per day, (i.e., 20 to 30 mg/kg body weight per day). Where adequate control is not achieved within this range, the dose may be further increased to a maximum of 2,500 mg per day (in divided doses).
Combined Therapy: When sodium valproate is to be given to patients already on other anticonvulsants, these should be tapered slowly; initiation of sodium valproate should then be gradual, with a target dose being reached after about two weeks.
In certain cases, it may be necessary to increase the dose by 5 to 10 mg/kg body weight per 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.
When barbiturates are being given concomitantly and if sedation is observed, the dose of barbiturate should be reduced.
Bipolar Disorder in Adults ≥ 18 Years Old
Initially, 600 mg per day in 2 to 3 divided doses. From day 2, the dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. Daily dose is generally within the range of 1,000 to 2,000 mg per day, (i.e., 20 to 30 mg/kg body weight per day). If adequate control is not achieved within this range, the dose may be increased to a maximum of 2,500 mg per day.
Dosing in Special Populations
Elderly: Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced. Dose should be increased more slowly and with regular monitoring for fluid intake, dehydration, somnolence, urinary tract infection and other adverse events.
Elderly patients who experience excessive somnolence and those with decreased food or fluid intake should consider dose reductions or discontinuation of therapy. Therapeutic dose should be based on both the patient's tolerability and clinical response.
Renal Insufficiency: It may be necessary to decrease the dose. Dose should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

CONTRAINDICATIONS
- Hypersensitivity to sodium valproate or to any ingredient in the product
- Pre-existing or acute hepatic insufficiency or family history of severe hepatitis, particularly medicine-related
- Mitochondrial disorders caused by mutations in mitochondrial DNA polymerase (POLG; e.g., Alpers-Huttenlocher Syndrome) and children
- less than 2 years old who are suspected of having a POLG-related disorder
- Known urea cycle disorders
- Known hepatic porphyria
- Pregnant and breastfeeding women

WARNINGS AND PRECAUTIONS
Hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives, usually during the first 6 months of treatment. Children less than two years old 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. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreased considerably in progressively older patient (see *Warnings and Precautions*).
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- (POLG) gene (e.g., Alpers Huttenlocher Syndrome). Sodium valproate is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children < 2 years old who are clinically suspected of having a mitochondrial disorder (see *Contraindications*).

FETAL RISK
Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following *in utero* exposure. Accordingly, the use of sodium valproate syrup in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus(see *Statement on Usage in High Risk Groups*).
PANCREATITIS
Cases of life-threatening pancreatitis have been reported in both adults and children receiving sodium 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.
Young children are at particular risk for pancreatitis. However, the risk is decreased with increasing age. Potential risk factors include severe seizures, neurological impairment or anticonvulsant polytherapy. Hepatic failure with pancreatitis increases the risk of fatal outcome. 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 should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.
General
Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.
Hepatic/Biliary/Pancreatic
Hepatotoxicity (see *Boxed Warnings*): 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 done 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.
To decrease the potential risk of liver toxicity, concomitant use of salicylates and sodium valproate should be avoided in children < 3 years old. In addition, salicylates should not be used in children <16 years old (see *aspirin/salicylate product information on Reye's syndrome*).
In patients > 2 years old who are clinically suspected of having a hereditary mitochondrial disease, sodium valproate should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with sodium valproate for the development of acute liver injury with regular clinical assessments and liver function testing. POLG mutation screening should be performed in accordance with current clinical practice.
Sodium valproate should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed despite discontinuation of the drug.
Pancreatitis (see *Boxed Warnings*)
Endocrine/Metabolic
Urea Cycle Disorders: The use of sodium valproate in patients with known urea cycle disorders is contraindicated. Hyperammonaemic encephalopathy, sometimes fatal, has been reported following initiation of valproate in patients with urea cycle disorders (a group of uncommon genetic abnormalities) particularly ornithine transcarbamylase deficiency. Prior to initiation of sodium valproate, evaluation for urea cycle disorder should be considered in the following patients:
- those with a history of unexplained encephalopathy or coma, encephalopathy associated with protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;
- those with signs and symptoms of urea cycle disorders [e.g., cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen (BUN), protein avoidance];
- those with a family history of urea cycle disorders or a family history of unexplained infant deaths (particularly males);
- those with other signs or symptoms of urea cycle disorders.

Discontinue sodium valproate and initiate prompt treatment in patients receiving sodium valproate who develop symptoms of unexplained hyperammonemic encephalopathy.
Hyperammonemia: Hyperammonemia, which may be present in the absence of abnormal liver function tests, can occur in patients during valproate therapy. Hyperammonemia may occasionally present clinically, with or without lethargy or coma, as vomiting, ataxia, increasing clouding of consciousness, and hypothermia. Should these symptoms occur, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for the treatment of hyperammonemia should be initiated(see *Urea Cycle Disorders*).
Asymptomatic elevations of serum ammonia are more common and when present, require close monitoring of serum ammonia levels. If elevation persists, discontinuation of sodium valproate should be considered.
Ornithine Transcarbamylase (OTC) Deficiency: Valproate may precipitate hyperammonemia symptoms in females with pre-existing OTC deficiency. As the symptoms may include seizures, any female with valproate-associated 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.
Concomitant Topiramate Use: Concomitant use of sodium valproate with topiramate has been shown to produce hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. This adverse event 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 increased risk for hyperammonemia with or without encephalopathy.
Hypothermia: Hypothermia, an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with sodium valproate therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with sodium valproate after starting topiramate treatment or after increasing the daily dose of topiramate. Hypothermia may be manifested by a variety of clinical abnormalities such as lethargy, confusion, coma, and significant alterations in other major organ systems (i.e., cardiovascular and respiratory). Consideration should be given to discontinuing valproate therapy in patients who develop hypothermia. Examination of blood ammonia levels should be included in the clinical management and assessment of patient.
Diabetes and Sucrose or Fructose Intolerance: Sodium valproate (Valpros® Pedia) syrup contains sucrose (which may be harmful to the teeth) and sorbitol. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.
When prescribing to diabetic patients, the sucrose content should be taken into account (see *Dosage and Administration*).
Weight Gain: Sodium valproate very commonly causes weight gain, which may be marked and progressive. Patients should be cautioned on the risk of weight gain at the initiation of therapy and appropriate measures should be made to minimize it.
Central Nervous System (CNS)
Brain Atrophy: There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy with neurological symptoms, in children, adults, and the elderly, receiving valproate therapy. In some cases, symptoms disappeared after valproate discontinuation but patients recovered with permanent sequelae. The motor and cognitive functions of patients on valproate should be routinely monitored and drug should be discontinued in the presence of suspected or apparent signs of brain atrophy.
Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including sodium valproate, 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 of worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Anyone considering prescribing sodium valproate or any other AED must balance this risk with the risk of untreated illness. 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.
Hematologic
The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥110 mcg/mL (females) or ≥135 mcg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.
Blood tests (e.g., blood cell count, including platelet count, bleeding time and coagulation tests) are recommended before initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of sodium valproate dose or withdrawal of therapy.
Musculoskeletal
Although immune disorders have only been rarely noted during the use of sodium valproate, the potential benefit should be weighed against its potential risk in patients with systemic lupus erythematosus.
Dermatologic and Hypersensitivity
Multi-organ Hypersensitivity Reaction: Although there have been rare reports of multi-organ hypersensitivity reactions associated with valproate therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40 days), many of these cases resulted in hospitalization and even death. Signs and symptoms of this disorder were diverse; however, patients typically 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 may occur. If this reaction is suspected, sodium valproate should be discontinued and an alternative treatment should be started.
Serious Skin Reactions: Serious skin reactions (e.g., Stevens-Johnson syndrome and Toxic Epidermal necrolysis) have been reported with concomitant lamotrigine and sodium valproate use.
Effects on Ability to Drive and/or Operate Machines
Since valproate may produce CNS depression, especially when combined with another CNS depressant such as alcohol, patients should be warned that sodium valproate may impair ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery or driving a motor vehicle).

INTERACTIONS WITH OTHER MEDICAMENTS
Caution is advised when using sodium valproate together with newer antiepileptics whose pharmacodynamics may not be well established.
Sodium valproate is an inhibitor of a variety of hepatic enzymes, including cytochrome P450, glucuronyl transferase and epoxide hydrolase. The following drug interactions are not exhaustive, as new interactions may be reported.

DRUG INTERACTIONS WITH SODIUM VALPROATE

Concomitant Drug	Effect	Clinical Comment
Acyclovir	↓valproate	Acyclovir apparently reduced plasma concentration of valproate to subtherapeutic levels, with increased seizure frequency and worsening of electroencephalography (EEG). Observe caution when these are taken concomitantly.
Alcohol	No interaction	Alcohol intake is not recommended since valproate may potentiate the CNS depressant activity of alcohol.

Concomitant Drug	Effect	Clinical Comment
Amitriptyline / Nortriptyline	In general: ↓ amitriptyline / nortriptyline Rarely: ↑ amitriptyline / nortriptyline	Concurrent use may increase amitriptyline or nortriptyline levels. Lowering the dose of amitriptyline or nortriptyline should be considered in the presence of valproate.
Other Antipsychotics, Monoamine Oxidase Inhibitors (MAOIs) and Tricyclic Antidepressants (TCAs)	↑ TCA	In addition to enhancing CNS depression when used concurrently with sodium valproate, antipsychotics, TCAs, and MAOIs may lower seizure threshold. Dose adjustments may be necessary to control seizures. Sodium valproate may inhibit the metabolism of TCAs. Clinical monitoring of free antidepressant levels may be necessary.
Aspirin Benzodiazepines (e.g., clonazepam, diazepam, lorazepam, midazolam)	↑ Valproate ↑ benzodiazepine	Aspirin is highly protein-bound, which may increase free valproic acid plasma levels. Observe caution when sodium valproate is administered with drugs affecting coagulation. Sodium valproate may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations.
Carbamazepine	↓ carbamazepine ↑ carbamazepine-10,11-epoxide ↓ valproate	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 when either medication is added to or withdrawn from an existing regimen, with dose adjustment when necessary.
Carbapenem Antibiotics (ertapenem, imipenem, meropenem, doripenem)	↓ valproate	This may result in loss of seizure control in epileptic patients or loss of efficacy in non-epileptics. In some cases of co-administration in epileptic patients, breakthrough seizures have occurred. Increasing sodium valproate dose may not be sufficient to overcome this interaction. The concomitant use of valproate and carbapenem agents is not recommended. If co-administration is essential, serum valproate concentrations should be monitored daily. Alternative antibacterial of anticonvulsant therapy should be considered if serum valproate concentrations drop significantly or seizure control deteriorates.
Chlorpromazine	↑ valproate	A 15% increase of valproate plasma levels was observed but this is not considered clinically important.
Cholestyramine	↓ valproate	May decrease the absorption of valproate.
Cimetidine	↑ valproate	Monitor valproate levels when treatment with cimetidine is instituted, increased, decreased, or discontinued. Sodium valproate dose should be adjusted accordingly.
Clonazepam	No reaction	The concomitant use of sodium valproate and clonazepam may induce absence seizures in patients with a history of absence type seizures.
Clozapine	↑ valproate or clozapine	Concomitant use may potentiate an increase in clozapine or valproate levels.
Diazepam	↑ diazepam	Sodium 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.
Erythromycin	↑ valproate	Concomitant use may increase valproate serum levels (as a result of reduced hepatic metabolism). Dose adjustment may be necessary when giving these drugs concomitantly.
Ethosuximide	↑ ethosuximide	Sodium valproate may inhibit ethosuximide metabolism, especially in the presence of other anticonvulsants. Patients receiving this combination should be monitored clinically.
Felbamate	↑ valproate	Felbamate may increase valproate serum concentrations. Decreasing the dose of sodium valproate may be necessary when felbamate therapy is initiated.
Fluoxetine	↑ valproate	Fluoxetine may inhibit the metabolism of sodium valproate
Haloperidol	↔ valproate	Concomitant use had no significant changes in valproate trough levels.
Lamotrigine	↑ lamotrigine ↓ valproate	Valproate may reduce lamotrigine metabolism. Clinical monitoring is recommended and lamotrigine dose should be decreased as appropriate. Serious skin reactions (e.g., Stevens-Johnson syndrome and toxic dermal necrolysis) have been reported with concomitant lamotrigine and sodium valproate administration.
Lithium	↔ lithium	Concomitant use had no effect on the steady-state kinetics of lithium.
Lorazepam	↓ lorazepam	Concomitant use results in decreased lorazepam plasma clearance. However, the decrease is not considered clinically important.
Mefloquine and chloroquine	↑ valproate	These drugs increase sodium valproate metabolism and may lower the seizure threshold; therefore, epileptic seizures may occur in cases of combined therapy. Dose adjustment of sodium valproate may be necessary.
Olanzapine	↓ olanzapine	Clinical significance of this observation is unknown.
Oral contraceptive steroids	No interaction	Concomitant use did not reveal any pharmacokinetic interaction.
Paracetamol	↔ paracetamol	Sodium valproate had no effect on any of the pharmacokinetic parameters of paracetamol.
Phenobarbital	↑ phenobarbital	Valproate may block the metabolism of barbiturates resulting in increased phenobarbital plasma levels, which particularly in children, may be associated with sedation. There is also evidence for severe CNS depression, with or without elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Rare cases of coma have been reported in patients receiving sodium valproate alone or in combination with phenobarbital. A reduction in dose of phenobarbital and/or sodium valproate may be necessary. Clinical monitoring is recommended throughout the first two weeks of concomitant use.
Phenytoin	↑ phenytoin	Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of sodium valproate and phenytoin. Most reports have noted a decrease in total plasma phenytoin concentration; however increases in total phenytoin levels have been reported. The dose of phenytoin should be adjusted as required by the clinical situation.
Primidone	↑ phenobarbital	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 dose adjustment when appropriate. Primidone is metabolized into a barbiturate (phenobarbital), and may also be involved in a similar or identical interaction with sodium valproate as phenobarbital.
Rifampicin	↓ valproate	Rifampicin may decrease valproate blood levels resulting in a lack of therapeutic effect. Thus, sodium valproate dose adjustment may be necessary when it is co-administered with rifampicin.
Ritonavir	↓ valproate	Reduction of therapeutic effect of valproate was observed in a patient with bipolar disorder with the initiation of HIV treatment with lopinavir/ritonavir, zidovudine, and lamivudine.
Selective Serotonin Re-uptake Inhibitors (SSRIs)	↑ valproate	SSRIs may inhibit the metabolism of sodium valproate, resulting in higher than expected levels of valproate.
Temozolomide	↑ temozolomide	A small decrease in the clearance of temozolomide has been observed; however, this effect is not clinically significant.
Tolbutamide	↑ 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. The clinical relevance of this displacement is unknown.
Topiramate	Effect unknown	Concomitant use with valproate has been associated with hyperammonemia with or without encephalopathy and hypothermia in patients who have tolerated either drug alone. Patients treated with these two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy (see *Warnings & Precautions*).
Vitamin K-dependent factor anticoagulant (e.g., coumarin, warfarin)	Effect unknown	The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. Close monitoring of prothrombin time should be done in case of concomitant use of vitamin K-dependent factor anticoagulant.
Zidovudine	↑ zidovudine	Sodium valproate may increase zidovudine plasma concentrations leading to increased zidovudine toxicity

Laboratory Test Alterations

- Sodium valproate is excreted mainly through the kidneys, partly in the form of ketone bodies. This may give false positives in the urine testing of possible diabetics.
- Altered thyroid function test results (including both hyperthyroidism and hypothyroidism) have been associated with sodium valproate. The clinical significance of this is unknown.

In vitro studies suggest that valproate stimulates the replication of the human immunodeficiency virus (HIV) and cytomegalovirus (CMV) viruses under certain experimental conditions. However, the clinical consequence is not yet known. However, these data should be considered when interpreting the results from regular monitoring of the viral load in HIV infected patients taking sodium valproate or when following CMV infected patients clinically.

- Protein binding of valproate is reduced in the elderly, in patients with renal impairment, and in the presence of other drugs (e.g., Aspirin). Accordingly, measurements of plasma levels of valproate may be misleading in these patients; an actual drug exposure may be higher than measured values.
- Decreased coagulation factors (at least one), abnormal coagulation tests (e.g., prolonged prothrombin time, activated partial thromboplastin, prolonged thrombin time, prolonged INR).

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy and Lactation(see *Boxed Warnings*)
Pregnancy Category D

Valproate can produce teratogenic effects. Sodium valproate should not be used in women of childbearing potential unless clearly necessary (i.e., other treatments are ineffective or not tolerated). This is especially 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 valproate.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is used to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. Even minor seizures may pose some hazard to the developing embryo or fetus. However, discontinuation of the drug may be considered prior to and during pregnancy in individual cases if the seizure severity and frequency do not pose a serious threat to the patient.

If appropriate, folic acid supplementation should be given both prior to and during pregnancy at relevant doses (5 mg/day) as it may minimize the risk of neural tube defects.

Congenital Malformations: The strongest association of maternal valproate usage with congenital malformations is with neural tube defects. However, 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.

Neural Tube Defects: The incidence of neural tube defects in the fetus is increased in mothers receiving valproate during the first trimester of pregnancy. Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in pregnant women receiving valproate.

Cerebral Atrophy and Decreased IQ Following in *utero* Exposure: Reports of cerebral atrophy with various forms of neurological problems including developmental delays and psychomotor impairment have also been reported in children who were exposed in *utero* to valproate products.

Clinical evidence suggests that valproate exposure in utero can cause decreased IQ in children. Because women in the study were exposed to antiepileptic drugs throughout pregnancy, whether the risk for decreased IQ was related to a particular time period during pregnancy could not be assessed.

Risk in the Neonate: Very rare cases of hemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This hemorrhagic syndrome is related to hypofibrinogenemia. Afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Patients taking valproate may develop hepatic failure. Fatal hepatic failures, in a newborn and in an infant, have been reported following the maternal use of valproate during pregnancy.

Serious reports of hypoglycemia and hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy. Most neonates also displayed other congenital anomalies including hypospadias, complex facial dysmorphism, limb anomalies, severe cardiac anomalies, etc.

Breastfeeding: Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentration. Consideration should be given to discontinuing breastfeeding when sodium valproate is administered to a breastfeeding woman.

Use in Children (< 18 years old)

The safety and efficacy of sodium valproate should be weighed against the risk of liver damage or pancreatitis in pediatric patients prior to initiation of therapy (see *Boxed Warnings*).

The safety and efficacy of valproate for acute manic episodes in patients < 18 years old with bipolar disorder have not been established.

Use in the Elderly (≥65 years old)

The safety and efficacy of sodium valproate in elderly patients with epilepsy has not been evaluated in clinical trials. Exercise caution in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience in this population (see *Dosage and Administration*).

A case review study showed that a higher percentage of patients > 65 years old reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with somnolence and tremor.

The safety and efficacy of sodium valproate for the prevention of migraine headaches in elderly patients > 65 years old have not been established. Its safety and efficacy in elderly patients with epilepsy and mania has not been established. Because of limited experience with sodium valproate in this population, caution should be exercised.

UNDESIRABLE EFFECTS(see *Warnings and Precautions; Statement on Usage for High Risk Groups*)

Body as a whole: *Very Common* - Infection. *Common* - Fever, back pain, malaise, chills, neck pain, neck rigidity, facial edema. *Rare* - Myelodysplastic syndrome (may be reversible). *Other Reported Effects* - Hypothermia, fever with chills, sweating, cyst, accidental injury, fatigue.

Cardiovascular: *Common* - Chest pain, tachycardia, hypertension, palpitation, hypotension, postural hypotension, vasodilation. *Other Reported Effects* - Bradycardia, arrhythmia.

Gastrointestinal: *Very Common* - Nausea. *Common* - Diarrhea, vomiting, indigestion, abdominal pain, abdominal cramps, dyspepsia, constipation, flatulence, hematemesis, eructation, acute pancreatitis (may be hemorrhagic with a rapid progression from initial symptoms to death),periodontal abscess, fecal incontinence, gastroenteritis, glossitis, stomatitis, dry mouth. *Uncommon* - Pancreatitis (sometimes lethal), dysphagia, gum hemorrhage, mouth ulceration.

Hematologic: *Common* - Anemia (including macrocytic with or without folate deficiency), thrombocytopenia, hemorrhage, ecchymosis, petechiae. *Uncommon* - Pancytopenia, leukopenia, vasculitis. *Rare* - Bone marrow failure (i.e., red cell aplasia, agranulocytosis, macrocytic anemia, macrocytosis). *Other Reported Effects* - Red cell hypoplasia, neutropenia, reduction in blood fibrinogen and/or increase in prothrombin time, bruising, bleeding, hematoma formation, epistaxis, frank hemorrhage, relative lymphocytosis, hypofibrinogenemia, eosinophilia, aplastic anemia, acute intermittent porphyria, bone marrow suppression, inhibition of platelet aggregation resulting in prolonged bleeding time.

Hepatic: *Common* - Liver injury, severe liver damage (including hepatic failure), minor elevations of transaminases (i.e., alanine aminotransferase, ALT; aspartate aminotransferase, AST) and lactate dehydrogenase (LDH). *Other Reported Effects* - Increased serum bilirubin, abnormal changes in other liver function tests, hepatitis.

Musculoskeletal: *Common* - Myalgia, leg cramps, arthralgia, twitching, myasthenia, arthrosis. *Uncommon* - Decreased bone mass (potentially leading to osteoporosis and osteopenia), fractures. *Rare* - Systemic lupus erythematosus, muscular weakness, reversible skeletal muscle weakness. *Other Reported Effects* - Weakness, bone pain.

Metabolic/Nutritional: *Common* - Hyponatremia, weight gain, anorexia with some weight loss,increased appetite. *Uncommon* - Inappropriate antidiuretic hormone (ADH) secretion, peripheral edema, angioedema. *Rare* - Hyperammonemia, hypothyroidism, reversible Fanconi syndrome, galactorrhea. *Other Reported Effects* - Parotid gland swelling, decreased carnitine concentrations, hyperglycemia, abnormal thyroid test results, hypoglycemia.

CNS: *Very Common* - Tremor. *Common* - Extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, confusion, aggression, euphoria, agitation, disturbance in attention, asthenia, dizziness, emotional lability, thinking abnormalities, amnesia, depression, anxiety, abnormal gait, hypertonia, incoordination, abnormal dreams, personality disorder, catatonic reaction, hypokinesia, increased reflexes, tardive dyskinesia, vertigo. *Uncommon* - Coma, encephalopathy (with or without fever or hyperammonemia), lethargy, reversible Parkinsonism, ataxia, paresthesia. *Rare* - Hallucinations, excitement, increased alertness, hyperactivity, reversible dementia associated with cerebral atrophy, cognitive disorder, sedation, abnormal behavior, psychomotor hyperactivity, learning disorder, encephalopathy with or without fever. *Other Reported Effects* - Dysarthria, asterixis, hypesthesia, incoordination, reversible and irreversible cerebral and cerebellar atrophy, emotional upset, psychosis/acute psychosis, hostility, behavioral deterioration, insomnia, nervousness, suicidal behavior, spasmodic dysphonia.

Respiratory: *Common* - Flu syndrome, infection, bronchitis, rhinitis, pharyngitis, dyspnea, sinusitis, increased cough, pneumonia, epistaxis. *Uncommon* - Pleural effusion, hiccups.

Dermatologic and Hypersensitivity: *Common* - Hypersensitivity, transient alopecia (hair loss), pruritus, rash (including maculopapular), dry skin, furunculosis, seborrhea. *Rare* - Toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, multi-organ hypersensitivity. *Very Rare* - Hirsutism, acne. *Other Reported Effects* - Generalized pruritus, anaphylaxis, discoid lupus erythematosus, cutaneous vasculitis, photosensitivity, erythema nodosum.

Special senses: *Common* - Hearing loss (either reversible or irreversible), diplopia, amblyopia/blurred vision, tinnitus, taste perversion, abnormal vision, nystagmus, otitis media, conjunctivitis, dry eyes, eye pain. *Other Reported Effects* - Ear pain, ispots before the eyesî, otic disorder, ocular disorder, photophobia.

Urogenital/Reproductive: *Common* - Dysmennorrhea, urinary incontinence, urinary frequency, vaginitis, dysuria, metrorrhagia, cystitis, vaginal hemorrhage. *Uncommon* - Secondary amenorrhea. *Rare* - Male infertility, polycystic ovary disease, enuresis, gynecomastia, hyperandrogenism. *Other Reported Effects* - Irregular menses, urinary tract infection, developmental delay, autism and/or autism spectrum disorder in the offspring of women exposed to valproate during pregnancy, interstitial nephritis.

OVERDOSE AND TREATMENT

There have been reports of accidental and deliberate valproate overdosage. Signs and symptoms of overdosage include somnolence, heart block or deep coma.

At plasma concentrations of up to 5 or 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness. Signs of acute massive overdose (with plasma concentrations 10 to 20 times the maximum therapeutic levels) usually include CNS depression or coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function and metabolic acidosis. Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. There have also been cases of intracranial hypertension related to cerebral edema. Deaths have occurred after massive overdose.

Hemodialysis or tandem hemodialysis with hemoperfusion have been used successfully. As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. Management of overdose should consist of general supportive therapy, particularly maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. However, naloxone should be used with caution since it could also theoretically reverse the anticonvulsant effects of valproate.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS
Store at temperatures not exceeding 30ºC. Protect from light.
Keep the product out of sight and reach of children.

AVAILABILITY
Sodium Valproate (Valpros® Pedia) - 100 mL amber plastic bottle- DR-XY45101.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by Square Pharmaceuticals Ltd.
Square Road, Salgaria, Pabna, Bangladesh
Imported and Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines
Date of Revision: February 2016
Date of First Authorization: February 22, 2016
MED156538IN03 2000016761 *Reg. IPOPHIL