SODIUM VALPROATE

VALPROS i-IV®

400 mg POWDER FOR INJECTION (IV)

ANTICONVULSANT / ANTIEPILEPTIC

FORMULATION
Each vial contains:
Sodium Valproate……400 mg

PHARMACOLOGIC CATEGORY
Anticonvulsant / Antiepileptic

PRODUCT DESCRIPTION
Sodium valproate 400 mg powder for injection is a white lyophilized powder for reconstitution. After reconstitution, the solution is clear and colorless.
This product is packed in a colorless type I glass vial, hermetically sealed with a gray chlorobutyl rubber stopper and a flip-off aluminum cap.
Sodium valproate 400 mg powder for injection is provided with a 4 mL sterile water for injection as solvent, packed in a transparent type I glass ampule.
This product contains 53.33 mg of sodium per vial.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
The mechanism by which sodium valproate exerts its effects is not known. However, its anticonvulsant effect may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter,γ-aminobutyric acid (GABA). This effect of sodium valproate on the GABA neurotransmitter is also believed to possibly contribute to its antimanic properties.

PHARMACOKINETICS
Equivalent doses of intravenous (IV) valproate and oral valproate products are expected to result in equivalent peak and trough plasma concentrations and total systemic exposure to the valproate ion when the IV valproate is administered as a 60 minute infusion. Although the rate of valproate ion absorption may vary with the specific formulation, any such differences should be of minor clinical importance under steady-state conditions achieved with chronic therapy for seizure disorders.
Distribution of sodium valproate is rapid and most likely restricted to the circulation and rapidly exchangeable extracellular water. Cerebrospinal fluid and breast milk levels were found to be 5 to 15% and about 1 to 10% of plasma levels, respectively**.** Plasma protein binding of valproate is concentration-dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin).
The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.
Sodium valproate is metabolized almost entirely in the liver. In adult patients on monotherapy, 30 to 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 to 20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in the urine.
Sodium valproate is almost completely metabolized prior to excretion. Plasma half-life is variable but generally appears to be 8 to 12 hours (range: 3.84 to 15.77 hours). It may be shorter in patients receiving other anticonvulsants or in children and patients receiving the medicine for long periods.

Special Population
Hepatic Impairment (see Boxed Warning, Contraindications and Warnings): Liver disease impairs the capacity to eliminate valproate. A study showed that the clearance of free valproate was decreased by 50% in patients with cirrhosis and by 16% in patients with acute hepatitis, compared with healthy subjects. In this study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Thus, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.
Renal Impairment: In patients with renal failure (creatinine clearance <10 mL/min), a slight reduction (27%) in the unbound clearance of valproate has been reported. However, hemodialysis typically reduces valproate concentrations by about 20%. 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.
Pediatric: Children between 3 months and 10 years old have 50% higher clearance of the drug expressed by weight (i.e., mL/min per kg) than adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults. Infants <2 months old have a markedly decreased ability to eliminate valproate compared with older children and adults. This may be due to reduced clearance (delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding).
Geriatrics: The capacity of elderly patients (68 to 89 years old) to eliminate valproate has been shown to be reduced compared with younger adults (22 to 26 years old). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in this age group.

INDICATIONS
Sodium valproate is indicated as an intravenous (IV) alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:
- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures.
- Monotherapy and adjunctive therapy in the treatment of patients with simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

DOSAGE AND ADMINISTRATION
Sodium valproate 400 mg injection is intended for intravenous (IV) use only. It is administered by slow IV injection (3 to 5 minutes) or slow IV infusion.
The use of sodium valproate injection for periods of more than 14 days has not been studied. Patients should be switched to oral valproate products as soon as it is clinically feasible.
Sodium valproate should be diluted with at least 500 mL of a compatible diluent (0.9% sodium chloride, 5% glucose and Lactated Ringer's solution). It should be administered intravenously at an infusion rate of 1 to 2 mg/kg body weight per hour. Any unused portion of the vial contents should be discarded.
Sodium valproate injection should not be injected intramuscularly as it may produce tissue necrosis.
Sodium valproate injection should not be administered at the same time as other IV additives via the same IV line. The IV solution is suitable for infusion by PVC, polyethylene or glass containers.
Dosing requirements vary according to age and body weight and should be adjusted individually to achieve adequate seizure control.

Recommended Daily Intravenous (IV) Dose:
Monotherapy
Adults:
Patients already satisfactorily treated with sodium valproate may be continued at their current dosage using continuous infusion. For example, a patient stabilized on 25 mg/kg body weight administered daily should be continued with an infusion rate of 1 mg/kg body weight per hour,
Other patients may be given a slow intravenous injection over 3 to 5 minutes, usually 400 to 800 mg depending on body weight (up to 10 mg/kg), followed by continuous infusion of 1 to 2 mg/kg body weight per hour to a maximum of 2,500 mg per day, according to the patient's clinical response.
Adjunctive Therapy
When starting sodium valproate in patients already on other anticonvulsants, these should be tapered slowly. Initiation of sodium valproate therapy should be gradual, with the target dose being reached after about two weeks. In some 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 known enzyme inducers have been withdrawn, it may be possible to maintain symptom control on a reduced dose of sodium valproate.

Special Population:
Pediatric:
20 to 30 mg/kg body weight per day
Where adequate control is not achieved within this range, the dose may be increased up to 40 mg/kg body weight per day but only in patients in whom plasma valproate levels can be monitored. Clinical chemistry and hematological parameters should be monitored if more than 40 mg/kg body weight per day**.**
Elderly:
Due to a decrease in unbound valproate clearance and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Subsequent dose should be increased more slowly. Likewise, regular monitoring of fluid and nutritional intake, dehydration, somnolence, and other adverse events is recommended. Dosage reduction or discontinuance of valproate should be considered in the elderly with decreased food or fluid intake and in those with excessive somnolence. The ultimate therapeutic dose in these patients should be determined on the basis of tolerability and clinical response.
Patients with impaired renal function:
Lower doses may be required since free drug levels may be high owing to lowered serum albumin and poor urinary excretion of free drug metabolites. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Or, as prescribed by a physician.

Preparation of Intravenous Injection/Infusion
To reconstitute, inject the solvent provided (4 mL) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by the sodium valproate, the concentration of the reconstituted preparation is 95 mg/mL. The reconstituted vial is stable for 8 hours at 25°C and for 24 hours at 5°C.

Compatibility and Stability
Sodium valproate powder for injection, once reconstituted and diluted in 500 mL of the IV solution (0.9% sodium chloride, 5% glucose and Lactated Ringer's solution), is stable for 6 hours at 25°C and for 24 hours when kept at 5°C.
- **Prior to administration, parenteral products should be inspected visually for particulate matter and discoloration.**
- **Shake the reconstituted solution before use.**
- **Observe strict aseptic technique when drawing up the contents of the vial. If contaminated, it has the potential to become a source of infection to patients.**

CONTRAINDICATIONS
- Hypersensitivity to sodium valproate or any ingredient of the product
- Urea cycle disorder
- Porphyria
- Pre-existing or acute hepatic dysfunction
- Personal or family history of severe hepatitis, particularly medicine related

WARNINGS AND PRECAUTIONS

HEPATOTOXICITY
Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. Experience has indicated that children under three 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.
TERATOGENICITY
Sodium valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of valproate products in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., migraine) is contemplated.
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, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Hepatotoxicity *(please see Boxed Warning)*
The incidents usually occurred during the first six months of therapy, the period of maximum risk being 2 to 12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients; the benefits of therapy should be weighed against the risks. Clinical symptoms are usually more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia, vomiting, abdominal pain, drowsiness, and jaundice. These are indications for immediate withdrawal of the medicine. Patients should be monitored closely for appearance of these symptoms and should be instructed to report any such signs to the clinician for investigation should they occur. Liver function tests should be done prior to therapy and at frequent intervals thereafter until 6 months after the controlling dose is reached, when less frequent monitoring may be appropriate. It is also advisable to monitor tests which reflect protein synthesis, e.g., prothrombin time, serum fibrinogen and albumin levels, particularly in those who seem most at risk and those with a prior history of hepatic disease. 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

Raised liver enzymes are not uncommon during treatment with valproate, particularly if used in conjunction with other anticoagulants, and are usually transient or respond to dosage reduction. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored more frequently. An abnormally low prothrombin rate, particularly in association with other relevant abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment and the substitution of alternative medicines to avoid precipitating convulsions. Uneventful recovery has been recorded in several cases where therapy with valproate has ceased, but death has occurred in some patients in spite of the medicine being withdrawn.
Sodium valproate 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 *(please see Boxed Warning)*
Severe pancreatitis, which may result in fatalities, has been very rarely reported. Some cases have occurred shortly after initial use while others have occurred after several years of use. There have also been cases in which pancreatitis recurred after rechallenge with sodium valproate.
Young children are at particular risk but this risk decreases with increasing age. Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.

Urea Cycle Disorders (UCD)
The use of valproate in patients with known UCD (a group of uncommon genetic abnormalities) is contraindicated. Hyperammonemic encephalopathy, which is sometimes fatal, has been reported after initiation of valproate in patients with UCD particularly ornithine transcarbamylase deficiency.

Metabolic investigations should be done prior to treatment. Evaluation for UCD should be considered in the following patients:
- 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;
- Signs and symptoms of UCD [e.g., cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen (BUN), protein avoidance];
- Family history of UCD or a family history of unexplained infant deaths (particularly males);
- 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.

Hyperammonemia
Hyperammonemia, which may be present in the absence of abnormal liver function tests, can occur in patients during valproate therapy**.**
Likewise, concomitant use of 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**.**
Hyperammonemia may occasionally present clinically, with or without lethargy or coma, as vomiting, ataxia and increasing clouding of consciousness. 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.

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. 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.

Post-traumatic Seizure
Sodium valproate injection should not be used in patients with acute head trauma for the prophylaxis of post-traumatic seizures.

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. 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.

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.

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. Patients typically presented with fever and rash associated with other organ system involvement. If this reaction is suspected, sodium valproate should be discontinued and an alternative treatment should be started.

Serious Skin Reactions
Serious skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported with concomitant lamotrigine and sodium valproate use.

Thrombocytopenia
The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of 110 mcg/mL or greater (females) or 135 mcg/mL or greater (males). 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.

Lupus erythematosus
Although immune disorders have been noted only exceptionally during the use of sodium valproate, the potential benefit of sodium valproate should be weighed against its potential risk in patients with systemic lupus erythematosus.

Effects on Ability to Drive and/or Operate Machines
Since valproate may produce central nervous system (CNS) depression, particularly 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).

HIV and CMV viruses Replication
In vitro studies showed 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. 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.

Abrupt Withdrawal
The possible risk of convulsions after sudden cessation of sodium valproate injection 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.

INTERACTIONS WITH OTHER MEDICAMENTS
- **Alcohol:** Valproate may potentiate the CNS depressant activity of alcohol.
- **Aspirin:** Concomitant use of sodium valproate and aspirin may result in displacement of valproate from protein binding sites, resulting in an increased free valproate concentration. Also, aspirin appears to inhibit the metabolism of valproate. Caution is advised when patients on sodium valproate are prescribed with aspirin. Likewise, patients requiring long-term aspirin therapy may require a reduction in dosage of sodium valproate.
- **Vitamin K-dependent factor anticoagulants *(e.g., coumarin, warfarin)*:** Close monitoring of prothrombin time should be done in case of concomitant use of vitamin K-dependent factor anticoagulants with sodium valproate since valproate may possibly enhance the anticoagulant effect of these drugs.
  The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased after displacement from the plasma protein binding site by valproate. Prothrombin time should be closely monitored.
- **Carbapenem antibiotics *(e.g., ertapenem, imipenem, meropenem)*:** Decreases in blood levels of valproic acid have been reported when it is coadministered with carbapenem agents resulting in a 60 to 100% decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, coadministration of carbapenem agents in patients stabilized on valproic acid should be avoided. If treatment with these antibiotics cannot be avoided, serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy**.** Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates.
- **Rifampicin:** May decrease the valproate blood levels resulting in a lack of therapeutic effect. Valproate dosage adjustment may be necessary when it is coadministered with rifampicin.
- **Antidepressants *[e.g., monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)]:*** These may have the potential to inhibit the metabolism of valproate via the cytochrome P450 system. However, within normal therapeutic doses, any significant interaction is not expected. Antidepressants can lower the seizure threshold of non-stabilized epileptic patients, and so careful and regular monitoring of their condition is indicated.
  Fluoxetine may inhibit the metabolism of valproate as it does with TCAs, carbamazepine and diazepam.
- **Clozapine:** Caution is advised during concomitant use as competitive protein binding may potentiate an increase in clozapine or valproate levels.
- **Chlorpromazine:** May inhibit the metabolism of valproate.
- **Olanzapine:** Adding olanzapine to valproate may significantly increase the risk of certain adverse events associated with olanzapine (e.g., neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder, and somnolence).
- **Carbamazepine:** Valproate may displace carbamazepine from protein binding sites and may inhibit the metabolism of both carbamazepine and its metabolite carbamazepine 10, 11 epoxide and consequently potentiate carbamazepine toxicity. Clinical monitoring is recommended particularly at the beginning of combined therapy, with dosage adjustment when appropriate.
- **Felbamate:** May increase valproate serum concentrations. Valproate dosage should be monitored when given in conjunction with felbamate. Valproate may decrease felbamate mean clearance by up to 16%.
- **Lamotrigine:** Sodium valproate reduces lamotrigine metabolism and increases its mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular, serious skin rashes. Clinical monitoring is recommended and lamotrigine dosage should be decreased as appropriate.
- **Phenobarbital:** Sodium valproate increases phenobarbital plasma concentrations and sedation may occur, particularly in children. Clinical monitoring is recommended throughout the first 15 days of combined treatment with an immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital levels when appropriate.
  There is evidence of severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.
- **Primidone:** Sodium valproate increases primidone plasma levels causing an exacerbation of side effects (e.g., sedation); these signs cease with long-term treatment. Clinical monitoring is recommended particularly when initiating combined therapy with dosage adjustment as necessary.
- **Phenytoin:** Phenytoin total plasma levels are decreased by sodium valproate; the free form of phenytoin is increased leading to possible overdosage symptoms. Thus, clinical monitoring is recommended with the free form of phenytoin being measured.
  There have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin in patients with epilepsy. The dosage of phenytoin should be adjusted as required by the clinical situation.
- **Topiramate:** Concomitant use of valproate and topiramate has been associated with hyperammonemia with and without encephalopathy. Concomitant use of these drugs has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported. In patients taking valproate and topiramate, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.
- **Clonazepam:** The concomitant use of sodium valproate and clonazepam may induce absence status in patients with a history of absence type seizures.
- **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.
- **Lorazepam:** Concomitant use with sodium valproate may cause a decrease in lorazepam plasma clearance.
- **Zidovudine:** In patients who were seropositive for human immunodeficiency virus (HIV), the clearance of zidovudine was decreased by 38% after administration of valproate; the half-life of zidovudine was unaffected.
- **Temozolomide:** Concomitant use of temozolomide and sodium valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.
- **Mefloquine and chloroquine:** Increase valproate metabolism and thus epileptic seizures may occur with combined therapy. The dosage of sodium valproate may need adjustment.
- **Cimetidine or erythromycin:** Valproate plasma levels may be increased when used concomitantly with cimetidine or erythromycin as a result of reduced hepatic metabolism.
- **Cholestyramine:** May decrease the absorption of valproate.
- **Ethosuximide:** There is evidence that sodium valproate may inhibit ethosuximide metabolism, particularly in the presence of other anticonvulsants. Patients receiving this combination should be monitored clinically.
- **Oral contraceptive:** Sodium valproate usually has no enzyme-inducing effect; thus, sodium valproate injection does not reduce the efficacy of oestroprogestative agents in women receiving hormonal contraception, including oral contraceptive pill.
- **Interference with clinical laboratory and other tests:** Sodium valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies. This may give false positive in the urine testing of possible diabetics.
  There have been reports of altered thyroid function test results associated with sodium valproate. The clinical significance of this is unknown.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
- **PREGNANCY** (please see Boxed Warning)
  Pregnancy Category D. **Data suggest that there is an increased incidence of congenital malformations associated with the use of valproate by women with seizure disorders during pregnancy when compared to the incidence in women with seizure disorders who do not use AEDs during pregnancy, the incidence in women with seizure disorders who use other AEDs and the background incidence for the general population. Therefore, valproate should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.**
  There are multiple reports in the clinical literature that indicate the use of AEDs during pregnancy results in an increased incidence of congenital malformations in offspring.
  Antiepileptic drugs, including valproate, should be administered to women of childbearing potential only if they are clearly shown to be essential in the management of their medical condition.
  Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.
  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.
  Pregnant women who receive folic acid supplementation may be at decreased risk for congenital neural tube defects in their offspring compared to pregnant women not receiving folic acid. Whether the risk of neural tube defects in the offspring of women receiving valproate specifically is reduced by folic acid supplementation is unknown.
  Dietary folic acid supplementation both prior to and during pregnancy should be routinely recommended to patients contemplating pregnancy.
  Other Adverse Pregnancy Effects
  Patients taking valproate may develop clotting abnormalities. If valproate is used in pregnancy, the clotting parameters should be monitored carefully.
  Patients taking valproate may develop hepatic failure. Fatal hepatic failures, in a newborn and in an infant, have been reported after the maternal use of valproate during pregnancy.
  There have been reports of developmental delay, autism and/or autism spectrum disorder in the offspring of women exposed to valproate during pregnancy**.**

LACTATION
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.
PEDIATRIC
The safety of intravenous sodium valproate has not been studied in children below 2 years old. If a decision is made to use sodium valproate injection in this age group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks.
The safety and efficacy of sodium valproate for the treatment of manic episodes in bipolar disorder have not been evaluated in patients below 18 years old.
GERIATRIC
A case review study showed that a higher percentage of patients above 65 years old reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with somnolence and tremor, It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant drug use among these patients.
A study in elderly patients with dementia showed drug related somnolence and discontinuation for somnolence. The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence.
No unique safety concerns were identified in patients >65 years old receiving intravenous sodium valproate.

ADVERSE EFFECTS
Body as a Whole: Pain (unspecified), peripheral edema
Cardiovascular: Chest pain, vasodilation, vasculitis
Endocrine/Metabolic/Nutritional: Weight gain, hyperammonemia, hyponatremia
Nervous/Psychiatric: Headache, dizziness, nervousness, sedation, ataxia, paresthesia, hypesthesia, extrapyramidal symptoms including parkinsonism, tremor, reversible dementia, somnolence, hallucination, convulsion, encephalopathy, coma, euphoria, lethargy, confusion, abnormal gait, aggression, alertness increased, hyperactivity, behavioral deterioration
Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting, pancreatitis, gastralgia
Hematologic: Thrombocytopenia; anemia; leukopenia; pancytopenia; bone marrow failure, including red cell aplasia; agranulocytosis; blood fibrinogen reduced; increased prothrombin time
Hepatic: Hepatic dysfunction; severe liver damage, including hepatic failure; increased liver enzymes
Respiratory: Pharyngitis, pneumonia
Skin and appendages: Injection site inflammation, injection site pain, injection site reaction, sweating, transient hair loss, hirsutism, acne, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema, drug rash with eosinophilia systemic symptoms (DRESS) syndrome, allergic reactions
Special senses: Hearing loss, taste perversion
Urogenital/Reproductive: Fanconi's syndrome, amenorrhea, irregular periods, gynecomastia
Adverse events that have been reported with all dosage forms of valproate:
Body as a Whole: Asthenia, fever, hypothermia, chills, infection, malaise, fatigue, edema of the extremities, face edema
Cardiovascular: Tachycardia, bradycardia, hypertension, hypotension, postural hypotension, vasodilation, palpitation
Endocrine/Metabolic/Nutritional: Anorexia, weight loss, increased appetite, syndrome of inappropriate secretion of ADH (SIADH), parotid gland swelling, abnormal thyroid function tests, decreased carnitine concentrations, hyperglycinemia
Nervous / Psychiatric: Drowsiness, hypertonia, incoordination, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, asterixis, insomnia, abnormal dreams, amnesia, dementia, dysarthria, vertigo, cerebral atrophy, emotional lability, thinking abnormal, emotional upset, depression, anxiety, stupor, personality disorder, excitement, psychosis, hostility, agitation
Gastrointestinal: Periodontal abscess, dry mouth, glossitis, stomatitis, abdominal cramps, dyspepsia, indigestion, constipation, gastroenteritis, flatulence, hematemesis, eructation, fecal incontinence
Hematologic: Ecchymosis, petechia, neutropenia, altered bleeding time, bruising, hematoma formation, epistaxis, hemorrhage, lymphocytosis, macrocytosis, hypofibrinogenemia, eosinophilia, anemia including macrocytic anemia with or without folate deficiency, aplastic anemia, acute intermittent porphyria, bone marrow suppression, lupus erythematosus
Hepatic: Serum bilirubin increased
Musculoskeletal: Back pain, neck pain, neck rigidity, myalgia, twitching, arthralgia, arthrosis, leg cramps, myasthenia, weakness, bone pain
Respiratory: Flu syndrome, bronchitis, rhinitis, dyspnea, sinusitis, cough increased
Skin and appendages: Alopecia, rash, pruritus, dry skin, photosensitivity, furunculosis, maculopapular rash, seborrhea
Special senses: Diplopia, amblyopia/blurred vision, abnormal vision, spots before eyes, conjunctivitis, dry eyes, eye pain, nystagmus, deafness, otitis media, tinnitus
Urogenital/Reproductive: Urinary incontinence, urinary frequency, enuresis, dysuria, cystitis, vaginitis, vaginal hemorrhage, dysmenorrhea, metrorrhagia, galactorrhea

OVERDOSAGE & MANAGEMENT
Cases of accidental and suicidal overdosage have been reported. Fatalities are rare.
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 of 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.
Management of overdose should consist of general supportive therapy, particularly maintenance of adequate urinary output. Establish airway and breathing and evaluate circulatory status. Assisted mechanical ventilation may be required in cases of respiratory depression. Hemodialysis and hemoperfusion have been used successfully**.**
Provided that adequate supportive treatment is given, full recovery usually occurs. Particular attention should be given to the maintenance of an adequate urinary output. Hepatic and pancreatic function should be monitored.
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.

AVAILABILITY
Sodium Valproate 400 mg powder for Injection - Box of USP type 1 glass vial with 4mL diluent ampoule containg water for injection.
CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.
STORAGE CONDITIONS
Store at temperatures not exceeding 30°C. Keep the product out of reach and sight of children.
Single dose. Discard any remaining portion.

Manufactured by
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