Print Out : 70%

VALPROIC ACID

VALLEPSY®

250 mg/5 mL Syrup

Anticonvulsant

PRODUCT DESCRIPTION :
Valproic Acid (Vallepsy®) 250 mg/5 mL Syrup is a red color with sweet taste and grape odor solution.

COMPOSITION :
Each 5 mL contains Valproic Acid 250 mg.

PHARMACODYNAMIC & PHARMACOKINETIC PROPERTIES :
Valproic acid dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which Valproate exerts its antiepileptic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of Gamma-Aminobutyric Acid (GABA). Valproic acid and it salts are completely absorbed in gastrointestinal tract. The rate of absorption can be delayed if taken immediately after or with food. Valproic acid is widely metabolized in liver, primarily by glucoronidation and the rest by other complex metabolic pathway. Valproic acid does not appear to induce its metabolism, but the metabolism can be induced by other drug which induces the hepatic microsomal enzyme. Valproic acid excretes predominantly via the urine while small amount of it excreted via feces. Valproic acid is vastly binded to the protein plasma, ranges from 90-95% over plasma drug concentration of 50 µg / mL and lower to 80 - 85% at concentration of 100 µg / mL. The half-life of Valproic acid is about 5 to 20 hours. Valproic acid can pass through placental barrier and in small amount excreted to breast milk.

INDICATIONS:
Valproic acid is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that include absence seizures.
Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS:
Valproic Acid should not be administered to patients with hepatic disease or significant hepatic dysfunction.
Valproic Acid is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g. Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder.
Valproic Acid is contraindicated in patients with known hypersensitivity to the drug.
Valproic Acid is contraindicated in patients with known urea cycle disorders.
Valproic Acid is contraindicated in the following situation: Treatment of epilepsy: in pregnancy unless there is no suitable alternative treatment; in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned in **Pregnancy & Lactation** are met.
Treatment of mania and prophylaxis of migraine attacks: in pregnancy; in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned in **Pregnancy & Lactation** are met.
Valproic Acid is contraindicated in patients with porphyria.

DOSAGE AND MODE/ROUTE OF ADMINISTRATIONS:
Female children and women of childbearing potential: Valproic Acid must be initiated and supervised preferably by a specialist experienced in the management of epilepsy, mania or prophylaxis of migraine. Valproic Acid should not be used in female children, women of childbearing potential unless other treatments are ineffective or not tolerated.
Valproic Acid is prescribed and dispensed in accordance to the measures for prevention of pregnancy as mentioned in **Pregnancy & Lactation**.
After the treating physician determines the suitability of the patient, Valproic Acid should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

Prophylaxis of migraine attacks: Valproic acid should only be initiated and supervised by a specialist experienced in the management of migraine.
Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews.
Valproic acid is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of ten years, and in simple and complex absence seizures. As the valproic acid dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected.

Complex Partial Seizures (CPS): For adults and children ten years of age or older.
Monotherapy (Initial Therapy): Valproic acid has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day.
The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.
The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy: Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every two weeks. This reduction may be started at initiation of valproic acid therapy, or delayed by one to two weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy: Valproic acid may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.
In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium, no adjustment of carbamazepine or phenytoin dosage was needed. However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs, periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy.

Simple and Complex Absence Seizures: The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.
A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures will range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations.
As the valproic acid dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected.
Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

The following table is a guide for the initial daily dose of Valproic acid (15 mg/kg/day):

Weight		Total Daily Dose (mg)	Number of 250 mg Capsules or Teaspoonfuls of Syrup		
(Kg)	(Lb)		Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

General Dosing Advice: Geriatric: Due to a decrease in clearance of unbound valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response.

Dose-Related Adverse Events: The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related.
The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥110 mcg/mL (females) or ≥135 mcg/mL (males). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Valproic acid capsules, syrup and tablets are antiepileptics for oral administration.

G.I. Irritation: Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Warnings
Female children/Female adolescents/Women of childbearing potential/Pregnancy: Valproic Acid has a high teratogenic potential and children exposed in utero to Valproic Acid have a high risk for congenital malformations and neurodevelopmental disorders.
Valproic Acid is contraindicated in the following situations: Treatment of epilepsy: in pregnancy unless there is no suitable alternative; in women of childbearing potential, unless the measures for prevention of pregnancy mentioned as follows and in Contraindications and Use in Pregnancy & Lactation are met.
Treatment of mania and prophylaxis of migraine attacks: in women of childbearing potential, unless the measures for prevention of pregnancy mentioned as follows and in **Contraindications** and in **Pregnancy & Lactation** are met.
The treating physician must ensure that: Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimize the risks.
The potential for pregnancy is assessed for all female patients.
The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to Valproic Acid in utero.
The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to Contraception as follows), without interruption during the entire duration of treatment with Valproic Acid.
The patient understands the need for regular (at least annual) review of treatment by the treating physician, preferably by a specialist experienced in the management of epilepsy, or mania or prophylaxis of migraine.
The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
The patient understands the hazards and necessary precautions associated with Valproic Acid use and the need to urgently consult her physician in case of pregnancy.
The patient has received the patient guide.
These conditions also concern women who are not currently sexually active unless the treating physician considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children: The treating physician must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using Valproic Acid experiences menarche.
In pregnancy (see **Pregnancy & Lactation**).
The treating physician must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to Valproic Acid in utero.
In patients who experienced menarche, the prescribing specialist must reassess the need for Valproic Acid therapy annually and consider alternative treatment options. If Valproic Acid is the only suitable treatment, the need for using effective contraception and all other measures as described in **Contraindications**, and in **Pregnancy & Lactation** should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach child bearing potential.
Pregnancy must be excluded before start of treatment with Valproic Acid.

Contraception: Women of childbearing potential who are prescribed Valproic Acid must use effective contraception, without interruption during the entire duration of treatment with Valproic Acid. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews preferably by a specialist: The treating physician should at least annually review whether Valproic Acid is the most suitable treatment for the patient.
The treating physician should ensure the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to Valproic Acid in utero.

Pregnancy planning: For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess Valproic Acid therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is. If switching is not possible, the woman should receive further counselling regarding the Valproic Acid risks for the unborn child to support her informed decision making regarding family planning.
For the indications mania and prophylaxis of migraine, if a woman is planning to become pregnant a specialist experienced in the management of mania and prophylaxis of migraine must be consulted and treatment with Valproic Acid should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy: In case of pregnancy, the patient should immediately contact a specialist/physician to re-evaluate treatment and consider alternative options.
Pharmacist must ensure that: the patients are advised not to stop Valproic Acid medication and to immediately contact a specialist in case of planned or suspected pregnancy.
Educational materials: In order to assist healthcare professionals and patients in avoiding exposure to Valproic Acid during pregnancy, the Marketing Authorization Holder has provided educational materials like a physician guide to reinforce the warnings and provide guidance regarding use of Valproic Acid in women of childbearing potential and the details of the pregnancy prevention program. A patient guide should be provided to all women of childbearing potential using Valproic Acid.
If the patient is thinking about becoming pregnant, or becomes pregnant, talk to a doctor straight away.
Do not stop taking this medicine unless the doctor tells to.

Special Precautions
Hepatotoxicity/Hepatic dysfunction: Conditions of occurrence: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid.
These incidents usually have occurred during the first six months of treatment.
Caution should be applied when administering valproic acid products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When divalproex sodium/valproate/valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy (seizure control) should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.
Suggestive signs: 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.
Detection: Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.
However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.
The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

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.
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 performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.
In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, divalproex sodium should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with valproic acid for the development of acute liver injury with regular clinical assessments and liver function test monitoring.

Pancreatitis: Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproic acid. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population that there have been cases in which pancreatitis recurred after rechallenge with valproate.
Patients and guardians experiencing abdominal pain, nausea, vomiting, and/or anorexia should be warned that these could 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.

Suicidal Behavior and Ideation: An increase in the risk of suicidal thoughts or behavior in patients taking antiepileptic drugs (AEDs) for any indication has been reported. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.
Anyone considering prescribing 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 an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behaviors 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 (and caregivers of patients), 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 thought about self-harm.
Behaviors of concern should be reported immediately to healthcare providers.

Interaction with Carbapenem Antibiotics: The concomitant use of INN and carbapenem agents is not recommended.

Thrombocytopenia: See **General** as follows.

Hyperammonemia: Hyperammonemia has been reported in association with valproate sodium/valproic acid 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 measured. Hyperammonemia should also be considered in patients who present with hypothermia (see Hypothermia as follows). If ammonia is increased, valproic acid therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders.
Asymptomatic elevations of ammonia are more common and, when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproic acid therapy should be considered.
Urea Cycle Disorders (UCD): Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency.
Prior to 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 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 BUN, protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 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 urea cycle disorders.

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use: Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level 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 event is not due to a 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. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons.

Hypothermia: Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with valproic acid 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.
Brain Atrophy: There have been post marketing reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use valproate products; in some cases, 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.

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.

General: Laboratory tests: 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. Prior to planned surgery, it is recommended that patients receiving valproic acid be monitored for platelet count and coagulation parameters. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.
Since divalproex sodium/valproate sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy.
Valproic acid is partially eliminated in the urine as a keto-metabolite that may lead to a false interpretation of the urine ketone test.
There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.
Recommended tests: Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.
Since divalproex sodium/valproate sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy.
There are in vitro studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions.
The clinical consequence, if any, is not known. Additionally, the relevance of these in vitro findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.
Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate.
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The therapeutic benefit that may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.
It seems prudent not to use valproate sodium in patients with acute head trauma for the prophylaxis of post-traumatic seizures until further information is available.

Multi-Organ Hypersensitivity Reactions: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multi-organ hypersensitivity reactions have been rarely reported in close temporal association after the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40). 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 amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.
Aggravated convulsions: As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately.

Information for Female patients: Since valproic acid has been associated with certain types of birth defects and development risk, female patients of childbearing age considering the use of valproic acid should be advised of the risks associated with the use of valproic acid during pregnancy.
Use in Children: Experience with oral valproate has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When valproic acid injection is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.
Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.
The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.
In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, valproic acid should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with valproic acid for the development of acute liver injury with regular clinical assessments and liver function test monitoring.
The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.
Use in the Elderly: No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from pre-existing medical illness and concomitant medication use among these patients.
Somnolence in the elderly: A study of elderly patients with dementia revealed 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.
In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.

Effects on Ability to Drive and Use Machines
Valproic Acid may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

OVERDOSE:
Overdosage with valproate may result in somnolence, heart block, hypotension and circulatory collapse/shock, and deep coma. Fatalities have been reported; however, patients have recovered from valproate levels as high as 2,120 mcg/mL.
In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.
Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

DRUG INTERACTIONS:
Effects of Co-Administered Drugs on Valproate Clearance: Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases (such as ritonavir), may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.
In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation. Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme-inducing drugs are introduced or withdrawn. The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs For Which a Potentially Important Interaction Has Been Observed: Aspirin: A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and in inhibition if metabolism of valproate. Valproate free fraction was increased four-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.
Carbapenem Antibiotics: A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics (ertapenem, imipenem, meropenem) and may result in loss of seizure control. The mechanism of this interaction

is not well understood. 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.
Estrogen-Containing Hormonal Contraceptives: Estrogen-containing hormonal contraceptives may increase the clearance of valproate, which may result in decreased concentration of valproate and potentially increased seizure frequency. Prescribers should monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products, preferably during on-off intervals of the hormonal contraceptive cycle.
Felbamate: A study involving the co-administration of 1,200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentrations by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2,400 mg/day increased the mean valproate peak concentrations to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.
Rifampin: A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after five nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate.
Valproate dosage adjustment may be necessary when it is co-administered with rifampin.
Protease inhibitors: Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma level when coadministered.
Cholestyramine: Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

Drugs For Which Either No Interaction or a Likely Clinically Unimportant Interaction Has Been Observed:
Antacids: A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac-160 mEq doses) did not reveal any effect on the extent of absorption of valproate.
Chlorpromazine: A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg b.i.d.) revealed a 15% increase in trough plasma levels of valproate.
Haloperidol: A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg b.i.d.) revealed no significant changes in valproate trough plasma levels.
Cimetidine and Ranitidine: Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs: Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyltransferases.
The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs For Which a Potentially Important Valproate Interaction Has Been Observed:
Amitriptyline/Nortriptyline: Administration of a single oral 50 mg dose of amitriptyline to 15 normal
volunteers (ten males and five females) who received valproate (500 mg b.i.d.) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.
Carbamazepine/carbamazepine-10,11-Epoxide: Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.
Clonazepam: The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.
Diazepam: Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism.
Co-administration of valproate (1,500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.
Ethosuximide: Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1,600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.
Lamotrigine: In a steady-state study involving ten healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.
Phenobarbital: Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg b.i.d. for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.
There is evidence for 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.
Phenytoin: Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg t.i.d.) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate.
In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.
Valproic acid metabolites levels may be increased in case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia.
Primidone: Primidone is metabolized into a barbiturate and therefore, may also be involved in a similar interaction with valproate as phenobarbital.
Propofol: A clinically significant interaction between valproate and propofol may occur leading to an increased blood level of propofol. Therefore, when co-administered with valproate, the dose of propofol should be reduced.
Nimodipine: Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50 %.
Tolbutamide: From in vitro experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.
Topiramate and acetazolamide: Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonemia.
Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy. Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. Blood ammonia levels should be measured in patients with reported onset of hypothermia.
Warfarin: In an in vitro study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if divalproex sodium therapy is instituted in patients taking anticoagulants.
Zidovudine: In six patients, who were seropositive for HIV, the clearance of zidovudine (100 mg every eight hours) was decreased by 38% after administration of valproate (250 or 500 mg every eight hours); the half-life of zidovudine was unaffected.
Quetiapine: Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.

Drugs For Which Either No Interaction or a Likely Clinically Unimportant Interaction Has Been Observed:
Acetaminophen: Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.
Clozapine: In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.
Lithium: Co-administration of valproate (500 mg b.i.d.) and lithium carbonate (300 mg t.i.d.) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.
Lorazepam: Concomitant administration of valproate (500 mg b.i.d.) and lorazepam (1 mg b.i.d.) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.
Olanzapine: Valproic acid may decrease the olanzapine plasma concentration.
Rufinamide: Valproic acid may lead to an increase in plasma level of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

PREGNANCY AND LACTATION:
Valproic Acid is contraindicated as treatment for mania and prophylaxis of migraine during pregnancy.
Valproic Acid is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
Valproic Acid is contraindicated for use in women of childbearing potential unless the measures for prevention of pregnancy as mentioned in Contraindications and Precautions are met.

Pregnancy: Valproate was shown to cross the placental barrier both in animal species and in humans.
Pregnancy Exposure Risk related to valproic acid: Both valproate monotherapy and valproic acid polytherapy are frequently associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproic acid is associated with a greater risk of congenital malformations than valproic acid monotherapy.
Congenital malformations: Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproic acid monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16-13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established based on available data.
Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.
In utero exposure to valproate may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Monitoring of signs and symptoms of ototoxicity is recommended.

Developmental disorders: Data have shown that exposure to valproic acid in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
Studies in preschool children exposed in utero to valproic acid show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems, possibly indicating neurodevelopmental disorders.
Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics.
Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproic acid that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.
Available data suggest that children exposed to valproate in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the general population.
Female children, female adolescents and woman of childbearing potential: If a Woman wants to plan a Pregnancy: For epilepsy indication: During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
For epilepsy and/or mania/bipolar disorder indication: In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed.
For epilepsy and/or mania/bipolar disorder indication: If a woman plans a pregnancy or becomes pregnant, valproate therapy should be stopped.
For epilepsy and/or mania/bipolar disorder indication: In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

If a woman plans a pregnancy: For the indication epilepsy, if a woman is planning to become pregnant, a specialist (preferably) experienced in the management of epilepsy, must reassess Valproic Acid therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the Valproic Acid risks for the unborn child to support her informed decision making regarding family planning.
For the indication(s) mania and prophylaxis of migraine, if a woman is planning to become pregnant, preferably a specialist experienced in the management of mania or prophylaxis of migraine must be consulted and treatment with Valproic Acid should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

Pregnant women: Valproic Acid as treatment for mania and prophylaxis of migraine attacks is contraindicated for use during pregnancy. Valproic Acid as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment, as evaluated and decided by the treating physician.
If a woman using Valproic Acid becomes pregnant, she must be immediately referred to a specialist (preferably) to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of Valproic Acid in pregnancy and after careful consideration of alternative treatment preferably by the specialist, in exceptional circumstances a pregnant woman must receive Valproic Acid for epilepsy, it is recommended to: Use the lowest effective dose and divide the daily dose of Valproic Acid into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.
All patients with a Valproic Acid exposed pregnancy and their partners should consider specialized prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.
The available evidence does not suggest that folate supplementation before the pregnancy may prevent the risk of neural tube defects which may occur in all pregnancies.
Risk in the neonate: Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken Valproic acid during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors.
Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
Cases of hypoglycemia have been reported in neonates whose mothers have taken Valproic acid during the third trimester of their pregnancy.
Cases of hypothyroidism have been reported in neonates whose mothers have taken Valproic acid during pregnancy.
Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding: Valproic acid is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from divalproex sodium therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility: Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using Valproic acid. Valproic acid administration may also impair fertility in men. Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

ADVERSE DRUG REACTIONS:
The following adverse reactions possibly related to valproates are displayed by MedDRA system organ class classification. Frequency groupings are classified according to the subsequent conventions:
Very common : ≥ 1/10
Common : ≥ 1/100 to <1/10
Uncommon : ≥ 1/1,000 to <1/100
Rare : ≥ 1/10,000 to <1/1,000
Very rare : < 1/10,000
Not known : cannot be estimated from the available data

Congenital malformations and developmental disorders:	
Unknown	Porphyria acute
Blood and lymphatic system disorders	
Common	Thrombocytopenia
Uncommon	Anemia, hypochromic anemia, leukopenia, thrombocytopenic purpura
Unknown	Agranulocytosis, anemia folate deficiency, anemia macrocytic, aplastic anemia, bone marrow failure, eosinophilia, hypofibrinogenemia, lymphocytosis, macrocytosis, pancytopenia, platelet aggregation inhibition
Investigations	
Common	Weight decreased, weight increased
Uncommon	Alanine aminotransferase increased[1], Aspartate aminotransferase increased[1], Blood creatinine increased, Blood folate, decreased, Blood lactate dehydrogenase increased[1], Blood urea increased, Drug level increased, Liver function test abnormal[1], Protein bound iodine increased, White blood cell
Unknown	Blood bilirubin increased[1], Carnitine decreased, Thyroid function test abnormal
Nervous system disorders	
Very Common	Somnolence, Tremor
Common	Amnesia, Ataxia, Dizziness, Dysgeusia, Headache, Nystagmus, Paresthesia, Speech disorder
Uncommon	Aphasia, Coordination abnormal, Dysarthria, Encephalopathy[2], Hyperkinesia, Hyperreflexia, Hypertonia, Hypoesthesia, Hyporeflexia, Seizure[3], Stupor, Tardive dyskinesia, Visual field defect
Unknown	Asterixis, Cerebellar atrophy[4], Cerebral atrophy, Cognitive disorder, Coma, Extrapyramidal disorder, Disturbance in attention, Memory impairment, Parkinsonism, Psychomotor hyperactivity, Psychomotor skills impaired, Sedation5
Ear and labyrinth disorders	
Common	Tinnitus
Uncommon	Deafness[6], Ear disorder, Hyperacusis, Vertigo
Unknown	Ear pain
Respiratory, thoracic, and mediastinal disorders	
Uncommon	Cough, Dyspnea, Dysphonia, Epistaxis
Unknown	Pleural effusion
Gastrointestinal disorders	
Very Common	Nausea[7]
Common	Abdominal pain, Constipation, Diarrhea, Dyspepsia[7], Flatulence, Vomiting[7]
Uncommon	Aphasia, Coordination abnormal, Dysarthria, Encephalopathy[2], Hyperkinesia, Hyperreflexia, Hypertonia, Hypoesthesia, Hyporeflexia, Seizure[3], Stupor, Tardive dyskinesia, Visual field defect
Unknown	Gingival disorder, Gingival hypertrophy, Parotid gland enlargement
Renal and urinary disorders	
Uncommon	Hematuria, Micturition urgency, Pollakuria, Urinary incontinence
Unknown	Enuresis, Fanconi syndrome9, Renal failure, Tubulointerstisial nephritis
Skin and tissue disorders	
Common	Alopecia[10], Ecchymosis, Pruritus, Rash
Uncommon	Acne, Dermatitis exfolative, Dry skin, Eczema, Erythema nodosum, Hyperhidrosis, Nail disorder, Petechiae, Seborrhea
Unknown	Cutaneous vasculitis, Drug Rash with Eosinophilia and Systemic Symptoms syndrome (DRESS), Erythema multiforme, Hair disorder, Nail bed disorder, Photosensitivity reaction, Stevens-Johnson syndrome, Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle spasm, Muscle twitching, Muscular weakness
Unknown	Bone density decreased, Bone pain, Ostopenia, Osteoporosis, Rhabdomyolysis, Systemic Lupus Erythematosus
Endocrine disorders	
Unknown	Hyproandrogenism[11], Hypothyroidism, Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
Common	Decreased appetite, Increased appetite
Uncommon	Hyperkalemia, Hypernatremia, Hypoglycemia, Hyponatremia, Hypoproteinemia
Unknown	Biotin deficiency, Dyslipidemia, Hyperammonemia, Insulin resistance, Obesity
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	Hemangioma of skin
Uncommon	Myelodysplastic syndrome
Vascular disorders	
Uncommon	Orthostatic hypotension, Pallor, Peripheral vascular disorder, Vasodilatation
General disorders and administration site conditions	
Very common	Asthenia
Common	Gait disturbance, Edema peripheral
Uncommon	Chest pain, Chills, Face edema, Injection site inflammation[13], Injection site pain[13], Injection site reaction[13], Pyrexia
Unknown	Gait disturbance, Edema peripheral
Hepatobiliary disorders	
Unknown	Hepatotoxicity
Reproductive system and breast disorders	
Uncommon	Amenorrhea, Dysmenorrhea, Erectile dysfunction, Menorrhagia, Menstrual disorder, Metrorrhagia, Vaginal hemorrhage
Unknown	Breast enlargement, Galactorrgea, infertility male12, Menstrutation irregular, Polycystic ovaries
Psychiatric disorders	
Common	Abnormal dreams, Affect lability, Confusional state, Depression, Insomnia, Nervousness, Thinking abnormal
Uncommon	Agitation, Anxiety, Apathy, Catatonia, Delirium, Euphoric mood, Hallucination, Hostility, Personality disorder
Unknown	Abnormal behavior, Aggression, Emotional distress, Learning disorder, Psychotic disorder
Cardiac disorders	
Uncommon	Bradycardia, Cardiac arrest, Cardiac failure congestive, Tachycardia
Eye disorders	
Common	Amblyopia, Diplopia
Uncommon	Chromatopia, Dry eye, Eye disorder, Eye pain, Lacrimation disorder, Miosis, Photopobia, Visual impairment
Immune system disorders	
Unknown	Anaphylactic reaction, Hypersensitivity
Infections and infestations	
Common	Infection
Uncommon	Bronchitis, Furuncle, Gastroenteritis, Herpes simplex, Influenza, Rhinitis, Sinusitis
Unknown	Otitis media, Pneumonia, Urinary tract infection
Injury, poisoning and procedural complications	
Common	Injury

1) May reflect potentially serious hepatoxicity
2) Encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders. Encephalopathy in the absence of elevated ammonia levels was also observed.
3) Here, consider aggravated seizure.
4) Reversible and irreversible. Cerebral atrophy seen in children exposed to valproate in utero led to various forms of neurological events, including developmental delays and psychomotor impairment.
5) Noted in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication
6) Either reversible and irreversible
7) These effects are usually transient and rarely require discontinuation of therapy
8) Includes acute pancreatitis including fatalities
9) Occuring primarily in children
10) Reversible
11) With events of hirsutism, virilism, acnea, male pattern alopecia, androgen increased
12) Including azoospermia, abnormal semen analysis, decreased sperm count, spermatozoa morphology abnormal, aspermia, and decrease spermatozoa mobility
13) ADRs specific to sodium valproate injection

STORAGE CONDITIONS:
Store below 30°C and protect from light.

PACKAGING AVAILABLE:
Amber glass bottle x 120 mL (Box of 1's) with 10 mL pipette.

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

ADR REPORTING:
For suspected adverse drug reaction, report to the FDA : www.fda.gov.ph

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NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:

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