VALPROIC ACID

CONVULZOR

250 mg / 5 mL Syrup

ANTIEPILEPTIC

Product Description:
Clear, colorless to light yellow solution with melon odor.

Formulation:
Each measuring spoonful/teaspoonful (5 mL) contains:
Valproic acid 250 mg

Pharmacology:
Pharmacodynamics
Valproic acid is a carboxylic acid. It 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).

Pharmacokinetics
Absorption
Valproic acid is rapidly and almost completely absorbed from the gastrointestinal tract. While the absorption rate from gastrointestinal tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected.
Total daily systemic bioavailability (extend absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inesequential from a practical clinical standpoint.
Coadministration of oral valproate products with food and substitution among the various divalproex sodium and valproic acid formulations should cause no clinical problems in the management of patients with epilepsy (see section **Dosage and Mode of Administration**). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

Distribution
Protein binding
The 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). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide) (see section **Drug Interactions**).

CNS distribution
Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

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

Excretion
Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hour/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hour/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to16 hours following oral dosing regimens of 250 to 1,000 mg.
The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special populations
Neonates
Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding).

Geriatric
The capacity of elderly patients to eliminate valproate has been shown to be reduced compared to younger adults. Intrinsic clearance is reduced by 39%; the free fraction of valproate is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly (see section **Dosage and Mode of Administration**).

Pediatric
Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Gender
There are no differences in the body surface area adjusted unbound clearance between males and females.

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

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

Hepatic impairment (see section **Contraindications** and **Warnings and Precautions**-Hepatotoxicity)
Liver disease impairs the capacity to eliminate valproate. The clearance of free valproate was decreased by 50% in patients with cirrhosis and by 16% in patients with acute hepatitis. 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. Accordingly, 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.

Plasma level and clinical effect
The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

Epilepsy
The therapeutic range in epilepsy is commonly considered to be 50 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Indications:
Valproic acid is indicated as 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. Valproic acid is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients 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 (see section **Warnings and Precautions** for statement regarding fatal hepatic dysfunction).

Dosage and Mode of Administration:
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 (see section **Drug Interactions**).

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 to 100 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 (see section **Warnings and Precautions**-Thrombocytopenia).

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 (50–100 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.
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 (see section **Drug Interactions**).

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 (see section **Drug Interactions**).
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.
Table 1 is a guide for the initial daily dose of valproic acid (15 mg/kg/day):

Table 1 Initial daily dose guide

Weight		Total daily dose (mg)	Number of measuring spoonful/teaspoonful(s) 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 responses (see section **Warnings and Precautions**-Somnolence in the elderly and section **Pharmacology**-Geriatric).

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) (see section **Warnings and Precautions**-Thrombocytopenia). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

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

Contraindications:
- Valproic acid should not be administered to patients with hepatic disease or significant hepatic dysfunction (see section **Warnings and Precautions**-Hepatotoxicity).
- 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 (see section **Warnings and Precautions**-Hepatotoxicity).
- Valproic acid is contraindicated in patients with known hypersensitivity to the drug (see section **Warnings and Precautions**-Multiorgan hypersensitivity reactions).
- Valproic acid is contraindicated in patients with known urea cycle disorders (see section **Warnings and Precautions**-Urea cycle disorders).
- Valproic acid is contraindicated in patients with porphyria.
- Valproic acid is contraindicated for use in prophylaxis of migraine headaches in pregnant women (see section **Warnings and Precautions**-Usage in pregnancy and **Pregnancy and Lactation**).

Warnings and Precautions:
Hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering valproic acid to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. 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 valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of 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.
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 (see section **Contraindications**).
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 (see section **Contraindications**).
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, ophthalmoplegia, 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.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. 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 and there have been cases in which pancreatitis recurred after rechallenge with valproate. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia 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.

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 the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low 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 (see section **Contraindications** and section **Warnings and Precautions**-Hyperammonemia and encephalopathy associated with concomitant topiramate use).

Suicidal behavior and ideation
An increase in the risk of suicidal thoughts or behavior in patients taking 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 for epilepsy than for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Anyone considering prescribing 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 increase 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, 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 thought about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Interaction with carbapenem antibiotics
Carbapenem antibiotics (ertapenem, imipenem, meropenem) may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. 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 (see section **Drug Interactions**-Carbapenem antibiotics).

Somnolence in the elderly
In elderly patients with dementia, there was a significantly higher proportion of valproate patients had a somnolence. In some patients with somnolence, there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. 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 (see section **Dosage and Mode of Administration**).

Thrombocytopenia
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia may be dose-related. The probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥110 mcg/mL (females) or ≥135 mcg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Women of childbearing potential
Because of the risk to the fetus of major congenital malformations (including neural tube defects), valproic acid 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 (see section **Pregnancy and Lactation**).
This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine).
Women of childbearing potential should use effective contraception while using valproate.

Usage in pregnancy
Since valproic acid has been associated with certain types of birth defects, 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 (see section **Pregnancy and Lactation**).
Valproate use is contraindicated during pregnancy in women being treated for prophylaxis of migraine headaches (see section **Contraindications**).
Women suffering from epilepsy or bipolar disorder who are pregnant or who plan to become pregnant should not be treated with valproate unless other treatments have failed to provide adequate symptom control or are otherwise unacceptable. In such women, the benefits of treatment with valproate during pregnancy may still outweigh the risks (see section **Pregnancy and Lactation**).
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. However, if cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Hepatic dysfunction
See section **Contraindications** and section **Warnings and Precautions**-Hepatotoxicity.

Hyperammonemia
Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hyperammonemia should also be considered in patients with hypothermia (see section **Warnings and Precautions**-Hypothermia). If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see section **Contraindications** and section **Warnings and Precautions**-Urea cycle disorders and Hyperammonemia and encephalopathy associated with concomitant topiramate use).
Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

Hyperammonemia and encephalopathy associated with concomitant topiramate use
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia (see section **Warnings and Precautions**-Hypothermia). 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 (see section **Contraindications** and section **Warnings and Precautions**-Urea cycle disorders and Hyperammonemia).

Hypothermia
Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with valproate therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproate after starting topiramate treatment or after increasing the daily dose of topiramate (see section **Drug Interactions**-Topiramate and section **Warnings and Precautions**-Hyperammonemia and encephalopathy associated with concomintant topiramate use and Hyperammonemia).
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 reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use of valproate products. In some cases, patients recovered with permanent sequelae (see section **Adverse Drug Reactions**). 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 (see section **Pregnancy and Lactation**).

General
Because of reports of thrombocytopenia (see section **Warnings and Precautions**-Thrombocytopenia), inhibition of the secondary phase if platelet aggregation, and abnormal coagulation parameters (e.g., low fibrinogen), platelet counts, and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving valproic acid be monitored for platelet count and coagulation parameters prior to planned surgery. There was an evidence of hemorrhage, bruising, or a disorder of hemostatis/coagulation for reduction of dosage or withdrawal of therapy.
Since valproate may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration of valproate and concomitant drugs are recommended during the early course of therapy (see section **Drug Interactions**).
Valproate is partially eliminated in the urine as a keto-metabolite, which may lead to a false interpretation of the urine ketone test.
There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.
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 the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

Multiorgan hypersensitivity reaction
Multiorgan hypersensitivity reactions have been rarely reported in close temporal association after the initiation of valproate therapy in adult and pediatric patients. 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), pruritis, 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 multiorgan hypersensitivity would indicate this to be a possibility.

Information for patients
Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia could be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.
Patients and guardians should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see section **Warnings and Precautions**-Hyperammonemia) and be told to inform the prescriber if any of these symptoms occur.
Since 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.
Since valproic acid has been associated with certain types of birth defects, 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 (see section **Warnings and Precautions**-Usage in pregnancy).

Pediatric use
Experience has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see section **Warnings and Precautions**-Hepatotoxicity). When valproic acid 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.

Geriatric use
A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.
Valproate therapy in elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see section **Warnings and Precautions**-Somnolence in the elderly).
The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see section **Dosage and Mode of Administration**).
This medicinal product contains sucrose. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose and galactose malabsorption, or sucrose-isomaltase insufficiency should not take this medicine.

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Last revised: dd/mm/yyyy

May be harmful to the teeth.
This medicinal product contains methylhydroxybenzoate. Those may cause allergic reactions (possibly delayed).
This medicinal product contains sorbitol.
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Pregnancy and Lactation:
Pregnancy (see sections **Contraindications** and **Warnings and Precautions**-Women of childbearing potential and Usage in pregnancy).

Risks associated with valproic acid:
In humans
Valproic acid may produce teratogenic effects, such as neural tube defects (e.g., spina bifida) in the offspring of human females receiving the drug during pregnancy. There are data that suggest an increased incidence of congenital malformations associated with the use of valproic acid during pregnancy. Therefore, valproic acid 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 antiepileptic drugs during pregnancy results in an increased incidence of birth defects in the offspring. Therefore, antiepileptic drugs should be administered to women of childbearing potential only if they are clearly shown to be essential in the management of their disease.
The incidence of neural tube defects in the fetus may be increased in mothers receiving valproate during the first trimester of pregnancy. The United States Centers for Disease Control (CDC) has estimated the risk of valproic acid exposed women having children with spina bifida to be approximately 1–2%.
Other congenital anomalies (e.g., craniofacial defects, cardiovascular malformations, hypospadias, and anomalies involving various body systems), compatible and incompatible with life, have been reported. There was an increased incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy. Available data indicate dose-dependency of this effect.
Valproate can cause decreased IQ scores following *in utero* exposure. Published epidemiological studies have indicated that children exposed to valproate *in utero* have lower cognitive test scores than children exposed *in utero* to either another antiepileptic drug or to no antiepileptic drugs.
There have been reports of developmental delay, autism, and/or autism spectrum disorder in the offspring of women exposed to valproic acid during pregnancy.
Exposure *in utero* to valproate products has been associated with cerebral atrophy with varying degrees/manifestations of neurological compromise, including developmental delays and psychomotor impairment (see section **Adverse Drug Reactions** and **Warnings and Precautions**).

In animals
Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 mcg/mL (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development.

Risks in the neonates
Pregnant women taking valproate may develop clotting abnormalities, including thrombocytopenia, hypofibrinogenemia, and/or decrease in other coagulation factors, which may result in hemorrhagic complications in the neonate including death (see section **Warnings and Precautions**-Thrombocytopenia and General).
If valproate is used in pregnancy, the clotting parameters should be monitored carefully.
Hepatic failure resulting in the death of a newborn and of an infant, has been reported following the use of valproate during pregnancy.
Cases of hypoglycemia have been received for neonates whose mothers have taken valproate during pregnancy.
Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.
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.

Breastfeeding
Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1–10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when valproic acid is administered to a nursing woman (see section **Warnings and Precautions**-Usage in pregnancy).

Effects on Ability to Drive and Use Machines:
Since valproic acid products 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.

Drug Interactions:
Effects of coadministered 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
Coadministration of aspirin at antipyretic doses with valproate to pediatric patients may decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased four-fold in the presence of aspirin. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased in the presence of aspirin. Caution should be observed if valproate and aspirin are to be coadministered.

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 (see section **Warnings and Precautions**-Interactions with carbapenem antibiotics).

Felbamate
Coadministration of felbamate with valproate to patients with epilepsy may increase the mean valproate peak concentration. Increasing the felbamate dose may increase the mean valproate peak concentration. A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin
The administration of a single dose of valproate with rifampin may increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is coadministered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed
Antacids
Coadministration of valproate with commonly administered antacids did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine
The administration of chlorpromazine to schizophrenic patients already receiving valproate may increase in trough plasma levels of valproate.

Haloperidol
The administration of haloperidol to schizophrenic patients already receiving valproate has 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 coadministration 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 dose of amitriptyline in patients who received valproate resulted in a decrease in plasma clearance of amitriptyline and a decrease in the net clearance of nortriptyline. Rare 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 while that of carbamazepine-10,11-epoxide (CBZ-E) increased upon coadministration 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. Coadministration of valproate increased the free fraction of diazepam. Plasma clearance and volume of distribution for free diazepam were reduced 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 with valproate was accompanied by an increase in elimination half-life of ethosuximide and a decrease in its total clearance. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine
The elimination half-life of lamotrigine increased with valproate coadministration. The dose of lamotrigine should be reduced when coadministered 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. Coadministration of valproate with phenobarbital result an increase in half-life and a decrease in plasma clearance of phenobarbital. The fraction of phenobarbital dose excreted unchanged increased in the 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.

Primidone
Primidone is metabolized to a barbiturate and therefore, may also be involved in a similar interaction with valproate as phenobarbital.

Phenytoin
Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Coadministration of valproate with phenytoin was associated with an increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 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.

Tolbutamide
The unbound fraction of tolbutamide was increased when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Topiramate
Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see section **Contraindications** and **Warnings and Precautions**-Urea cycle disorders, Hyperammonemia and encepalopathy associated with concomitant topiramate use, and Hyperammonemia).
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 (see section **Warnings and Precautions**-Hypothermia and Hyperammonemia).

Warfarin
Valproate increased the unbound fraction of warfarin. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproic acid therapy is instituted in patients taking anticoagulants.

Zidovudine
In patients who were seropositive for HIV, the clearance of zidovudine was decreased after administration of valproate; the half-life of zidovudine was unaffected.

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, no interaction was observed when valproate was coadministered with clozapine.

Lithium
Coadministration of valproate and lithium carbonate had no effect on the steady-state kinetics of lithium.

Lorazepam
Concomitant administration of valproate and lorazepam was accompanied by a decrease in the plasma clearance of lorazepam.

Olanzapine
Administration of a single dose of olanzapine with valproic acid did not affect olanzapine C_{max} and elimination half-life. However, olanzapine AUC was lower in the presence of valproic acid. The clinical significance of these observations is unknown.

Oral contraceptive steroids
Administration of a single-dose of ethinylestradiol/levonorgestrel with valproate therapy for 2 months did not reveal any pharmacokinetic interaction.

Adverse Drug Reactions:
Epilepsy
Complex partial seizures (CPS)
Divalproex sodium was generally well tolerated with most adverse events rated as mild to moderate in severity. The following additional adverse events were reported in patients complex partial seizures treated with divalproex sodium.

Body as a whole
Headache, asthenia, fever, back pain, chest pain, malaise.

Cardiovascular system
Tachycardia, hypertension, palpitation.

Digestive system
Nausea, vomiting, abdominal pain, diarrhea, anorexia, dyspepsia, constipation, increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.

Hemic and lymphatic system
Thrombocytopenia, ecchymosis, petechia.

Metabolic and nutritional disorders
Weight gain, weight loss, peripheral edema, SGOT increased, SGPT increased.

Musculoskeletal system
Myalgia, twitching, arthralgia, leg cramps, myasthenia.

Nervous system
Somnolence, tremor, dizziness, diplopia, amblyopia/blurred vision, ataxia, nystagmus, emotional lability, thinking abnormal, amnesia, nervousness, depression, anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.

Respiratory system
Flu syndrome, infection, bronchitis, rhinitis, pharyngitis, dyspnea, sinusitis, cough increased, pneumonia, epistaxis.

Skin and appendages
Rash, pruritus, dry skin, alopecia.

Special senses
Tinnitus, taste perversion, abnormal vision, deafness, otitis media.

Urogenital system
Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Other patient populations
Adverse events that have been reported with all dosage forms of valproate are listed below by body system.
Gastrointestinal
The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

CNS effects
Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hyperesthesia, vertigo, incoordination, memory impairment, cognitive disorder, and Parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances 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 (see section **Warnings and Precautions**-Urea cycle disorders, Hyperammonemia and encephalopathy associated with concomitant topiramate use, and Hyperammonemia).
There have been reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use of valproate products. In some cases the patient recovered with permanent sequelae (see section **Warnings and Precautions**-Brain atrophy). Cerebral atrophy seen in children exposed to valproate *in utero* led to various forms of neurological events including developmental delays and psychomotor impairment (see section **Pregnancy and Lactation**).

Dermatologic
Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6-month-old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35-year-old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (see section **Drug Interactions**).

Psychiatric
Emotional upset, depression, psychosis, aggression, psychomotor hyperactivity, hostility, agitation, disturbance in attention, abnormal behavior, learning disorder, and behavioral deterioration.

Musculoskeletal
Weakness.
Reports have been received of decreased bone mass, potentially leading to osteoporosis and osteopenia, during long-term therapy with anticonvulsant medications, including valproate. Supplemental calcium and vitamin D may be of benefit to patients who are on chronic valproate therapy.

Hematologic
Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechia, bruising, hematoma formation, epistaxis, and hemorrhage (see section **Warnings and Precautions**-General and **Drug Interactions**-Warfarin). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

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

Endocrine
Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests including hypothyroidism (see section **Warnings and Precautions**-General). There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic
Acute pancreatitis, including fatalities (see section **Warnings and Precautions**-Pancreatitis).

Metabolic
Hyperammonemia (see section **Warnings and Precautions**-Hyperammonemia), hyponatremia, and inappropriate ADH secretion.
There have been rare reports of Fanconi's syndrome occurring chiefly in children.
Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.
Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary
Enuresis and urinary tract infection.

Special senses
Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Neoplasma benign, malignant, and unspecified (including cysts and polyps)
Myelodysplastic syndrome.

Respiratory, thoracic, and mediastinal disorders
Pleural effusion.

Other
Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, increased cough, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

Mania
Although valproic acid has not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported in patients whom treated with valproic acid tablets.

Body as a whole
Chills, neck pain, neck rigidity.

Cardiovascular system
Hypotension, postural hypotension, vasodilation.

Digestive system
Fecal incontinence, gastroenteritis, glossitis.

Musculoskeletal system
Arthrosis.

Nervous system
Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.

Skin and appendages
Furunculosis, maculopapular rash, seborrhea.

Special senses
Conjunctivitis, dry eyes, eye pain.

Urogenital system
Dysuria.

Migraine
Although valproic acid has not been evaluated for safety and efficacy in the treatment of prophylaxis of migraine headaches, the following adverse events not listed above were reported in patients whom treated with valproic acid tablets.

Body as a whole
Face edema.

Digestive system
Dry mouth, stomatitis.

Urogenital system
Cystitis, metrorrhagia, and vaginal hemorrhage.

Overdose and Treatment:
Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however, patients have recovered from valproate levels as high as 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.

Storage Condition:
Store at temperatures not exceeding 30ºC.

Availability:
Valproic Acid (CONVULZOR) 250 mg / 5 mL Syrup: USP Type III Amber Colored Glass Bottle x 100 mL (Box of 1's).

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

ON MEDICAL PRESCRIPTION ONLY.

Keep out of reach of children.

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

Please seek medical attention immediately at the first sign of any adverse drug reaction.

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