Valproate
Sodium Injection, USP

500 mg per 5 mL (100 mg per mL) | NDC 70860-784-05

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- **BIG, BOLD AND BRIGHT —
TO HELP YOU SEE IT, SAY IT AND PICK IT RIGHT**
- **DIFFERENTIATION IN EVERY LABEL,
DESIGNED TO HELP REDUCE MEDICATION ERRORS**

PLEASE SEE IMPORTANT SAFETY INFORMATION ATTACHED, INCLUDING BOXED WARNING.

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THE NEXT GENERATION OF PHARMACY INNOVATION

Valproate Sodium Injection, USP

500 mg

NDC 70860-784-05
500 mg per 5 mL

DESCRIPTION	Single-dose vial
CONCENTRATION	100 mg per mL
CLOSURE	20 mm
UNIT OF SALE	10 vials
BAR CODED	Yes
STORAGE	Room Temperature

- AP RATED • PRESERVATIVE-FREE •
- NOT MADE WITH NATURAL RUBBER LATEX •

AccuraSEE™ PACKAGING & LABELING

CHOOSE AccuraSEE™ FOR YOUR PHARMACY

Our proprietary, differentiated and highly-visible label designs can assist pharmacists in accurate medication selection.

With a unique AccuraSEE label design for every Athenex product, we're helping your pharmacy to reduce the risk of medication errors. The idea is simple: "So what you see is *exactly* what you get."

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VALPROATE SODIUM Injection

INDICATION AND USAGE

Epilepsy
Valproate Sodium Injection is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:

Valproate Sodium Injection 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. Valproate Sodium Injection is also indicated for use as sole and adjunctive therapy in the treatment of patients with simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

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.

Important Limitations
Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, neural tube defects, and other major congenital malformations, which may occur very early in pregnancy, valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.

For prophylaxis of migraine headaches, valproate is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception.

WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity
General Population: Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When Valproate Sodium 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. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Patients with Mitochondrial Disease: There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase (POLG) gene (e.g. Alpers Huttenlocher Syndrome). Valproate Sodium Injection is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder.

In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Valproate Sodium Injection should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Valproate Sodium Injection for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice.

Fetal Risk
Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores and neurodevelopmental disorders following in utero exposure.

Valproate is therefore contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception. Valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.

Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. In such situations, effective contraception should be used.

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 a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

CONTRAINDICATIONS

- Valproate Sodium Injection should not be administered to patients with hepatic disease or significant hepatic dysfunction.
- Valproate Sodium Injection is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder.
- Valproate Sodium Injection is contraindicated in patients with known hypersensitivity to the drug.
- Valproate Sodium Injection is contraindicated in patients with known urea cycle disorders.
- For use in prophylaxis of migraine headaches: Valproate is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception.

WARNINGS and PRECAUTIONS

Hepatotoxicity-General Information on Hepatotoxicity- Hepatic failure resulting in fatalities has occurred in patients receiving valproate. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months of valproate therapy. However, healthcare providers should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering valproate products to patients with a prior history of hepatic disease.

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 Valproate Sodium 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. Use of Valproate Sodium Injection has not been studied in children below the age of 2 years.

In progressively older patient groups experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably.

Patients with Known or Suspected Mitochondrial Disease- Valproate Sodium Injection is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. 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 (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents.

In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Valproate Sodium Injection should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Valproate Sodium Injection for the development of acute liver injury with regular clinical assessments and serum liver test monitoring.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent.

Structural Birth Defects- Valproate can cause fetal harm when administered to a pregnant woman. Pregnancy registry data show that maternal valproate use can cause neural tube defects and other structural abnormalities. The rate of congenital malformations among babies born to mothers using valproate is about four times higher than the rate among babies born to epileptic mothers using other anti-seizure monotherapies. Evidence suggests that folic acid supplementation prior to conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population.

Decreased IQ Following In Utero Exposure- 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.

Use in Women of Childbearing Potential- Because of the risk to the fetus of decreased IQ, neurodevelopment disorders, and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death such as prophylaxis of migraine headaches. Women should use effective contraception while using valproate. Women of childbearing potential should be counseled regularly regarding the relative risks and benefits of valproate use during pregnancy. This is especially important for women planning a pregnancy and for girls at the onset of puberty; alternative therapeutic options should be considered for these patients.

To prevent major seizures, valproate should not be discontinued abruptly, as this can precipitate status epilepticus with resulting maternal and fetal hypoxia and threat to life.

Evidence suggests that folic acid supplementation prior to conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population. It is not known whether the risk of neural tube defects or decreased IQ in the offspring of women receiving valproate is reduced by folic acid supplementation. Dietary folic acid supplementation both prior to conception and during pregnancy should be routinely recommended for patients using valproate.

Pancreatitis- Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, Valproate Sodium Injection should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Urea Cycle Disorders- Valproate Sodium Injection is contraindicated in patients with known urea cycle disorders (UCD).

Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy.

Bleeding and Other Hematopoietic Disorders- Valproate is associated with dose-related thrombocytopenia. The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects. Valproate use has also been associated with decreases in other cell lines and myelodysplasia.

Measurements of complete blood counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving Valproate Sodium Injection be monitored for blood counts and coagulation parameters prior to planned

surgery and during pregnancy. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia- Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests and should also be considered in patients who present with hypothermia. If ammonia is increased, valproate therapy should be discontinued.

Asymptomatic elevations of ammonia are more common and, require close monitoring. If the elevation persists, discontinuation of valproate therapy should be considered.

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use- Concomitant administration of topiramate and valproate has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

Hypothermia- Hypothermia, defined as an unintentional drop in body 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. Consideration should be given to stopping valproate in patients who develop hypothermia.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity Reactions- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multi-Organ Hypersensitivity, has been reported in patients taking valproate. DRESS may be fatal or life- threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy in association with other organ system involvement, (e.g., hematological abnormalities). Early manifestations of hypersensitivity may be present even though rash is not evident. Valproate should be discontinued and not be resumed if an alternative etiology for the signs or symptoms cannot be established.

Interaction with Carbapenem Antibiotics- Carbapenem antibiotics (for example, ertapenem, imipenem, meropenem; this is not a complete list) may reduce serum valproate concentrations to subtherapeutic levels, resulting in loss of seizure control.

Somnolence in the Elderly- In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.

Post-traumatic Seizures- A study was conducted to evaluate the effect of IV valproate in the prevention of post-traumatic seizures in patients with acute head injuries. Patients were randomly assigned to receive either IV valproate given for one week (followed by oral valproate products for either one or six months per random treatment assignment) or IV phenytoin given for one week (followed by placebo). In this study, the incidence of death was found to be higher in the two groups assigned to valproate treatment compared to the rate in those assigned to the IV phenytoin treatment group (13% vs. 8.5%, respectively). Many of these patients were critically ill with multiple and/or severe injuries, and evaluation of the causes of death did not suggest any specific drug-related causation. Further, in the absence of a concurrent placebo control during the initial week of intravenous therapy, it is impossible to determine if the mortality rate in the patients treated with valproate was greater or less than that expected in a similar group not treated with valproate, or whether the rate seen in the IV phenytoin treated patients was lower than would be expected. Until further information is available, it seems prudent not to use Valproate Sodium Injection in patients with acute head trauma for the prophylaxis of post-traumatic seizures.

Monitoring: Drug Plasma Concentration- Since valproate 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.

Effect on Ketone and Thyroid Function Tests- 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.

Effect on HIV and CMV Viruses Replication- 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 the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

ADVERSE REACTIONS

The most common adverse in at least 5% of patients are: abdominal pain, alopecia, amblyopia/blurred vision, amnesia, anorexia, asthenia, ataxia, bronchitis, constipation, depression, diarrhea, diplopia, dizziness, dyspepsia, dyspnea, ecchymosis, emotional lability, fever, flu syndrome, headache, infection, insomnia, nausea, nervousness, nystagmus, peripheral edema, pharyngitis, rhinitis, somnolence, thinking abnormal, thrombocytopenia, tinnitus, tremor, vomiting, weight gain, and weight loss.

Additional adverse reactions not included above that occurred in >0.5% of patients treated with Valproate Sodium Injection include: chest pain, euphoria, hypesthesia, injection site inflammation, injection site pain, injection site reaction, pain, sweating, taste perversion, and vasodilation.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, deep coma, and hypernatremia. Fatalities have been reported; however, patients have ecovered from valproate serum concentrations as high as 2120 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. 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.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch. Or call 1-800-FDA-1088.

Please see full prescribing information for VALPROATE SODIUM Injection.