VALPROIC ACID- valproic acid solution
Xttrium Laboratories Inc.

These highlights do not include all the information needed to use Valproic Acid Oral Solution safely and effectively. See full prescribing information for Valproic Acid Oral Solution.
Valproic Acid Oral Solution, USP
Initial U.S. Approval: 1978

HIGHLIGHTS OF PRESCRIBING INFORMATION

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WARNINGS: LIFE THREATENING ADVERSE REACTIONS

See full prescribing information for complete boxed warning.
• Hepatotoxicity, including fatalities, usually during the first 6 months of treatment. Children under the age of two
years and patients with mitochondrial disorders are at higher risk. Monitor patients closely, and perform serum
liver testing prior to therapy and at frequent intervals thereafter (5.1)
• Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ (5.2, 5.3, 5.4)
• Pancreatitis, including fatal hemorrhagic cases (5.5)

1 INDICATIONS AND USAGE

Valproic Acid Oral Solution is indicated for:

Monotherapy and adjunctive therapy of complex partial seizures; sole and adjunctive therapy of simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures (1)

2 DOSAGE AND ADMINISTRATION

Valproic Acid Oral Solution is intended for oral administration. (2.1)

Simple and Complex Absence Seizures: Start at 10 to 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/week until seizure control or limiting side effects (2.1)
Safety of doses above 60 mg/kg/day is not established (2.1, 2.2)

3 DOSAGE FORMS AND STRENGTH

Oral Solution: Equivalent of 250 mg valproic acid per 5 mL as the sodium salt

4 CONTRAINDICATIONS

- Hepatic disease or significant hepatic dysfunction (4, 5.1)
- Known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG) (4, 5.1)
- Suspected POLG-related disorder in children under two years of age (4, 5.1)

- Known hypersensitivity to the drug (4, 5.12)
- Urea cycle disorders (4, 5.6)
- Prophylaxis of migraine headaches: Pregnant women , women of child bearing potential not using effective contraception (4, 8.1)

5 WARNINGS AND PRECAUTIONS

- Hepatotoxicity; evaluate high risk populations and monitor serum liver tests (5.1)

• Birth defects, decreased IQ, and neurodevelopmental disorders following in utero exposure; should not be used to treat
women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant or to treat a woman of
childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise
unacceptable (5.2, 5.3, 5.4)
• Pancreatitis; Valproic Acid Oral Solution should ordinarily be discontinued (5.5)
• Suicidal behavior or ideation; Antiepileptic drugs, including Valproic Acid Oral Solution, increase the risk of suicidal thoughts
or behavior (5.7)

- Bleeding and other hematopoietic disorders; monitor platelet counts and coagulation tests (5.8) Hyperammonemia and

hyperammonemic encephalopathy; measure ammonia level if unexplained lethargy and vomiting or changes in mental
status, and also with concomitant topiramate use; consider discontinuation of valproate therapy (5.6, 5.9, 5.10)
• Hypothermia; Hypothermia has been reported during valproate therapy with or without associated hyperammonemia. This
adverse reaction can also occur in patients using concomitant topiramate (5.11)
• Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reaction; discontinue Valproic
Acid Oral Solution (5.12)
• Somnolence in the elderly can occur. Valproic Acid Oral Solution dosage should be increased slowly and with regular
monitoring for fluid and nutritional intake (5.14)

6 ADVERSE REACTIONS

• Most common adverse reactions (reported >5%) 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, increased appetite, infection, insomnia, nausea,
nervousness, nystagmus, peripheral edema, pharyngitis, rhinitis, somnolence, thinking abnormal, thrombocytopenia,
tinnitus, tremor, vomiting, weight gain, weight loss. (6.1)
• The safety and tolerability of valproate in pediatric patients were shown to be comparable to those in adults (8.4).
**To report SUSPECTED ADVERSE REACTIONS, contact Xttrium Laboratories, Inc. at 1-800-587-3721 or FDA at
1-800-FDA-1088 or www.fda.gov/medwatch**

7 DRUG INTERACTIONS

• Hepatic enzyme-inducing drugs (e.g., phenytoin, carbamazepine, phenobarbital, primidone, rifampin) can increase

valproate clearance, while enzyme inhibitors (e.g., felbamate) can decrease valproate clearance. Therefore increased
monitoring of valproate and concomitant drug concentrations and dosage adjustment are indicated whenever
enzyme-inducing or inhibiting drugs are introduced or withdrawn (7.1)
• Aspirin, carbapenem antibiotics, estrogen-containing hormonal contraceptives: Monitoring of valproate concentrations is
recommended (7.1)
• Co-administration of valproate can affect the pharmacokinetics of other drugs (e.g. diazepam, ethosuximide, lamotrigine,
phenytoin) by inhibiting their metabolism or protein binding displacement (7.2)
• Patients stabilized on rufinamide should begin valproate therapy at a low dose, and titrate to clinically effective dose (7.2)
• Dosage adjustment of amitriptyline/nortriptyline, propofol, warfarin, and zidovudine may be necessary if used
concomitantly with Valproic Acid Oral Solution (7.2)
• Topiramate: Hyperammonemia and encephalopathy (5.10, 7.3)

8 USE IN SPECIFIC POPULATIONS

• Pregnancy: Valproic Acid Oral Solution can cause congenital malformations including neural tube defects, decreased IQ, and
neurodevelopmental disorders (5.2, 5.3, 8.1)
• Pediatric: Children under the age of two years are at considerably higher risk of fatal hepatotoxicity (5.1, 8.4)
• Geriatric: Reduce starting dose; increase dosage more slowly; monitor fluid and nutritional intake, and somnolence (5.14,
8.5)

10 OVERDOSAGE

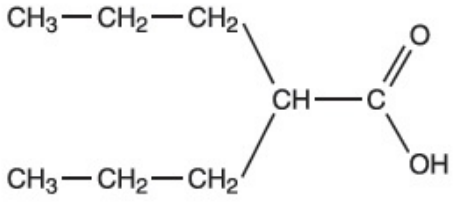
Overdosage with valproate may result in somnolence, heart block, deep coma, and hypernatremia. Fatalities have been reported; however, patients have recovered from valproate levels as high as 2,120 mcg/mL.

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.

11 DESCRIPTION

Valproic acid is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. Valproic acid has the following structure:



Valproic acid (pKa 4.8) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/mL) and very soluble in organic solvents.

Valproic Acid Oral Solution is an antiepileptic for oral administration. The oral solution contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt.

Inactive Ingredients

alcohol (less than 0.05%), artificial cherry flavor, artificial wild cherry flavor, corn syrup solids, FD&C Red No. 40, glycerin, hydrochloric acid, liquid sugar, methylparaben, potassium phosphate dibasic, propylene glycol, purified water, sodium benzoate and sodium hydroxide. The pH range is between 7.0 and 8.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Valproic acid dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic 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).

12.2 Pharmacodynamics

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.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

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.

12.3 Pharmacokinetics

Absorption/Bioavailability

Equivalent oral doses of divalproex sodium products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.

However, it is possible that differences among the various valproate products in T_{max} and C_{max} could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the divalproex sodium tablet (increase in T_{max} from 4 to 8 hours) than on the absorption of the divalproex sodium sprinkle capsules (increase in T_{max} from 3.3 to 4.8 hours).

While the absorption rate from the G.I. 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. Experience employing dosing

regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Co-administration 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 Dosage and Administration (2.1)]* . 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 *Drug Interactions (7.2)* for more detailed information on the pharmacokinetic interactions of valproate with other drugs].

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 drug are linear.

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/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/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 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

Effect of Age

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). For example, in one study, the half-life in children under 10 days ranged from 10 to 67 hours compared to a range of 7 to 13 hours in children greater than 2 months.

Children

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.

Elderly

The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26 years). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly *[see Dosage and Administration (2.2)]* .

Effect of Sex

There are no differences in the body surface area adjusted unbound clearance between males and females (4.8 ± 0.17 and 4.7 ± 0.07 L/hr per 1.73 m^2, respectively).

Effect of Race

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

Effect of Disease

Liver Disease

Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. 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. *[see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)]* .

Renal Disease

A slight reduction (27%) in the unbound clearance of 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Valproate was administered orally to rats and mice at doses of 80 and 170 mg/kg/day (less than the maximum recommended human dose on a mg/m^2 basis) for two years. The primary findings were an increase in the incidence of subcutaneous fibrosarcomas in high-dose male rats receiving valproate and a dose-related trend for benign pulmonary adenomas in male mice receiving valproate.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults.

Impairment of Fertility

In chronic toxicity studies in juvenile and adult rats and dogs, administration of valproate resulted in testicular atrophy and reduced spermatogenesis at oral doses of 400 mg/kg/day or greater in rats (approximately equal to or greater than the maximum recommended human dose (MRHD) on a mg/m ^{2} basis) and 150 mg/kg/day or greater in dogs (approximately equal to or greater than the MRHD on a mg/m ^{2} basis). Fertility studies in rats have shown no effect on fertility at oral doses of valproate up to 350 mg/kg/day (approximately equal to the MRHD on a mg/m ^{2} basis) for 60 days.

14 CLINICAL STUDIES

The studies described in the following section were conducted using divalproex sodium tablets.

14.1 Epilepsy

The efficacy of divalproex sodium in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials.

In one, multi-clinic, placebo controlled study employing an add-on design (adjunctive therapy), 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either divalproex sodium or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

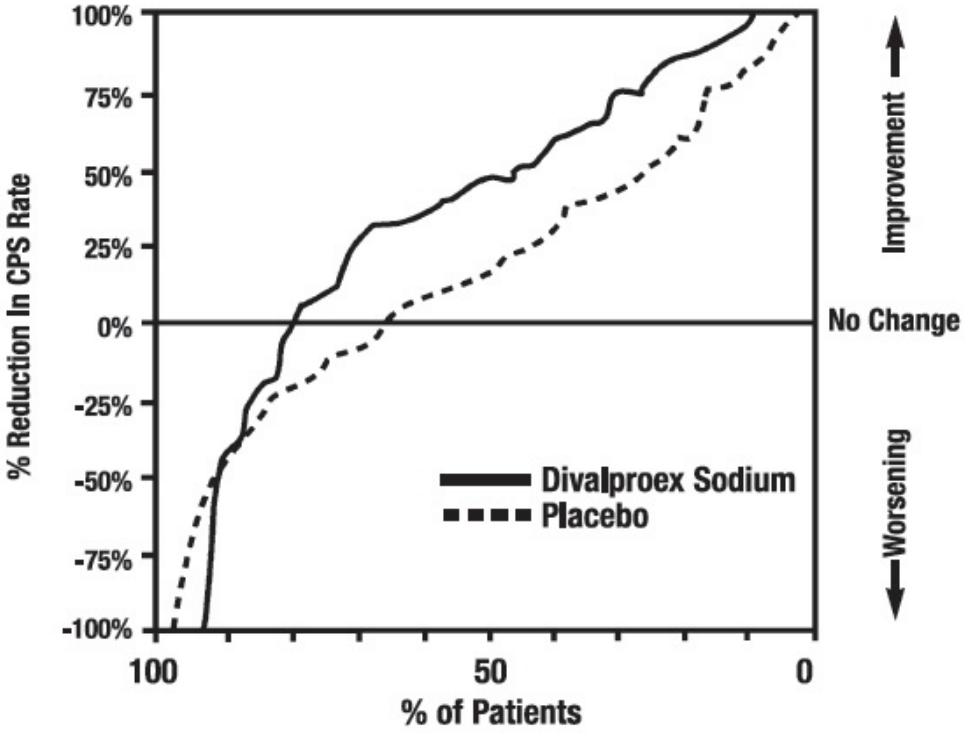
Table 5. Adjunctive Therapy Study Median Incidence of CPS per 8 Weeks

Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
Divalproex sodium	75	16.0	8.9 *
Placebo	69	14.5	11.5

* Reduction from baseline statistically significantly greater for divalproex sodium than placebo at $p \leq 0.05$ level.

Figure 1 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for divalproex sodium than for placebo. For example, 45% of patients treated with divalproex sodium had a ≥ 50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 1



The second study assessed the capacity of divalproex sodium to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to divalproex sodium. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to divalproex sodium monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 mcg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

Table 6. Monotherapy Study Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose divalproex sodium	131	13.2	10.7 *
Low dose divalproex sodium	134	14.2	13.8

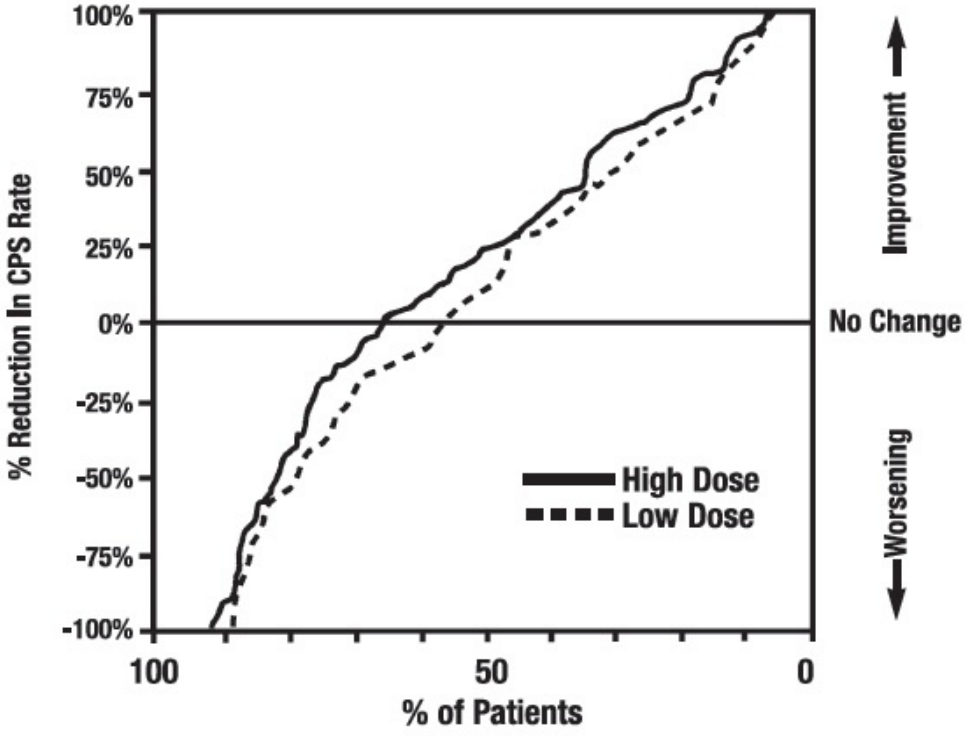
* Reduction from baseline statistically significantly greater for high dose than low dose at $p \leq 0.05$ level.

Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose divalproex sodium than for low dose divalproex sodium. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose divalproex sodium monotherapy, 63% of patients

experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose divalproex sodium.

Figure 2

Information on pediatric studies is presented in section 8.



15 REFERENCES

[1]Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurology 2013; 12 (3):244–252.

16 HOW SUPPLIED/STORAGE AND HANDLING

Valproic Acid Oral Solution, USP is available as a clear, cherry-flavored red oral solution containing the equivalent of 250 mg of valproic acid per 5 mL as the sodium salt in the following oral dosage forms:

16 fl oz (473 mL) bottles (NDC 0116-4021-16).

5 mL unit dose cups (NDC 0116-4021-05) packaged in trays of 10 unit dose cups each with either 4 or 10 trays to a case

10 mL unit dose cups (NDC 0116-4021-10) packaged in trays of 10 unit dose cups each with 10 trays to a case

RECOMMENDED STORAGE

Store at 20°–25°C (68°–77°F) [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP, with child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hepatotoxicity

Warn patients and guardians that nausea, vomiting, abdominal pain, anorexia, diarrhea, asthenia, and/or jaundice can be symptoms of hepatotoxicity and, therefore, require further medical evaluation promptly *[see Warnings and Precautions (5.1)].*

Pancreatitis

Warn patients and guardians that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly [see *Warnings and Precautions (5.5)*].

Birth Defects and Decreased IQ

Inform pregnant women and women of childbearing potential (including girls beginning the onset of puberty) that use of valproate during pregnancy increases the risk of birth defects and decreased IQ, and neurodevelopmental disorders in children who were exposed *in utero*. Advise women to use effective contraception while using valproate. When appropriate, counsel these patients about alternative therapeutic options. This is particularly important when valproate use is considered for a condition not usually associated with permanent injury or death such as prophylaxis of migraine headache [*see Contraindications (4)].*Advise patients to read the Medication Guide, which appears as the last section of the labeling [see *Warnings and Precautions (5.2, 5.3, 5.4)* and *Use in Specific Populations (8.1)*].

Pregnancy Registry:

Advise women of childbearing potential to discuss pregnancy planning with their doctor and to contact their doctor immediately if they think they are pregnant.

Encourage women who are taking valproic acid oral solution to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 or visit the website, http://www.aedpregnancyregistry.org [see *Use in Specific Populations (8.1)*].

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and families that AEDs, including valproic acid, may increase the risk of suicidal thoughts and behavior and to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to the healthcare providers [see *Warnings and Precautions (5.7)*].

Hyperammonemia

Inform patients of the signs and symptoms associated with hyperammonemic encephalopathy and to notify the prescriber if any of these symptoms occur [see *Warnings and Precautions(5.9, 5.10)*].

CNS Depression

Since valproate products may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), advise patients 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.

Multiorgan Hypersensitivity Reactions

Instruct patients that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug-related and should be reported to the physician immediately [see *Warnings and Precautions (5.12)*].

MEDICATION GUIDE

Valproic Acid Oral Solution

Read this Medication Guide before you start taking valproic acid oral solution and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about valproic acid oral solution?

Do not stop taking valproic acid oral solution without first talking to your healthcare provider.

Stopping valproic acid oral solution suddenly can cause serious problems.

Valproic acid oral solution can cause serious side effects, including:

1. Serious liver damage that can cause death, especially in children younger than 2 years old.

The risk of getting this serious liver damage is more likely to happen within the first 6 months of treatment.

Call your healthcare provider right away if you get any of the following symptoms:

- nausea or vomiting that does not go away
- loss of appetite
- pain on the right side of your stomach (abdomen)
- dark urine
- swelling of your face
- yellowing of your skin or the whites of your eyes

In some cases, liver damage may continue despite stopping the drug.

2. Valproic acid oral solution may harm your unborn baby.

- If you take valproic acid oral solution during pregnancy for any medical condition, your baby is at risk for serious birth defects that affect the brain and spinal cord and are called spina bifida or neural tube defects. These defects occur in 1 to 2 out of every 100 babies born to mothers who use this medicine during pregnancy. These defects can begin in the first month, even before you know you are pregnant. Other birth defects that affect the structures of the heart, head, arms, legs, and the opening where the urine comes out (urethra) on the bottom of the penis can also happen. Decreased hearing or hearing loss can also happen.
- Birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors.
- Taking folic acid supplements before getting pregnant and during early pregnancy can lower the chance of having a baby with a neural tube defect.
- If you take valproic acid oral solution during pregnancy for any medical condition, your child is at risk for having a lower IQ and may be at risk for developing autism or attention deficit/hyperactivity disorder.
- There may be other medicines to treat your condition that have a lower chance of causing birth defects, decreased IQ, or other disorders in your child.
- Women who are pregnant must not take valproic acid oral solution to prevent migraine headaches.
- **All women of child-bearing age (including girls from the start of puberty)should talk to their healthcare provider about using other possible treatments instead of valproic acid oral solution. If the decision is made to use valproic acid oral solution, you should use effective birth control (contraception).**
- Tell your healthcare provider right away if you become pregnant while taking valproic acid oral solution. You and your healthcare provider should decide if you will continue to take valproic acid oral solution while you are pregnant.
- **Pregnancy Registry:** If you become pregnant while taking valproic acid oral

solution, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling toll-free 1-888-233-2334 or by visiting the website, http://www.aedpregnancyregistry.org/. The purpose of this registry is to collect information about the safety of antiepilectic drugs during pregnancy.

3. Inflammation of your pancreas that can cause death.

Call your healthcare provider right away if you have any of these symptoms:

- severe stomach pain that you may also feel in your back
- nausea or vomiting that does not go away

4. Like other antiepileptic drugs, valproic acid oral solution may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attetion to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about your symptoms.

Do not stop valproic acid oral solution without first talking to a healthcare provider. Stopping valproic acid oral solution suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What is valproic acid oral solution?

Valproic acid oral solution is a prescription medicine used alone or with other medicines, to treat:

- complex partial seizures in adults and children 10 years of age and older
- simple and complex absence seizures, with or without other seizure types

Who should not take valproic acid oral solution?

Do not take valproic acid oral solution if you:

- have liver problems
- have or think you have a genetic liver problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)
- are allergic to valproic acid, or any of the ingredients in valproic acid oral solution. See the end of this leaflet for a complete list of ingredients in valproic acid oral solution.

- have a genetic problem called urea cycle disorder
- are taking it to prevent migraine headaches and are either pregnant or may become pregnant because you are not using effective birth control (contraception)

What should I tell my healthcare provider before taking valproic acid oral solution?

Before you take valproic acid oral solution, tell your healthcare provider if you:
- have a genetic liver problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)
- drink alcohol
- are pregnant or breastfeeding. Valproic acid can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take valproic acid oral solution.
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, herbal supplements and medicines that you take for a short period of time.

Taking valproic acid oral solution with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist each time you get a new medicine.

How should I take valproic acid oral solution?
- Take valproic acid oral solution exactly as your healthcare provider tells you. Your healthcare provider will tell you how much valproic acid oral solution to take and when to take it.
- Your healthcare provider may change your dose.
- Do not change your dose of valproic acid oral solution without talking to your healthcare provider.
- **Do not stop taking valproic acid oral solution without first talking to your healthcare provider**. Stopping valproic acid oral solution suddenly can cause serious problems.
- If you take too much valproic acid oral solution, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking valproic acid oral solution?
- Valproic acid oral solution can cause drowsiness and dizziness. Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking valproic acid oral solution, until you talk with your doctor. Taking valproic acid oral solution with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive a car or operate dangerous machinery until you know how valproic acid oral solution affects you. Valproic acid oral solution can slow your thinking and motor skills.

What are the possible side effects of valproic acid oral solution?
- See **"What is the most important information I should know about valproic acid oral solution?"**

Valproic acid oral solution can cause serious side effects including:
- **Bleeding problems**: red or purple spots on your skin, bruising, pain and swelling into your joints due to bleeding or bleeding from your mouth or nose.
- **High ammonia levels in your blood**: feeling tired, vomiting, changes in mental status.

- **Low body temperature (hypothermia)**: drop in your body temperature to less than 95°F, feeling tired, confusion, coma.
- **Allergic (hypersensitivity) reactions**: fever, skin rash, hives, sores in your mouth, blistering and peeling of your skin, swelling of your lymph nodes, swelling of your face, eyes, lips, tongue, or throat, trouble swallowing or breathing.
- **Drowsiness or sleepiness in the elderly.**This extreme drowsiness may cause you to eat or drink less than you normally would. Tell your doctor if you are not able to eat or drink as you normally do. Your doctor may start you at a lower dose of valproic acid oral solution.

Call your healthcare provider right away, if you have any of the symptoms listed above.

The common side effects of valproic acid oral solution include:
- nausea
- headache
- sleepiness
- vomiting
- weakness
- tremor
- dizziness
- stomach pain
- blurry vision
- double vision
- diarrhea
- increased appetite
- weight gain
- hair loss
- loss of appetite
- problems with walking or coordination

These are not all of the possible side effects of **valproic acid oral solution**. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store valproic acid oral solution?
- Store valproic acid oral solution at 68° to 77°F (20° to 25°C).

Keep valproic acid oral solution and all medicines out of the reach of children.

General information about the safe and effective use of valproic acid oral solution

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use valproic acid oral solution for a condition for which it was not prescribed. Do not give valproic acid oral solution to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about valproic acid oral solution. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about valproic acid oral solution that is written for health professionals.

What are the ingredients in valproic acid oral solution?

Active ingredient: valproic acid

Inactive ingredients: alchohol (less than 0.05%), artificial cherry flavor, artificial wild

cherry flavor, corn syrup solids, FD&C Red No. 40, glycerin, hydrochloric acid, liquid sugar, methylparaben, potassium phosphate dibasic, propylene glycol, purified water, sodium benzoate and sodium hydroxide

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rx Only

Product No.: 4021

Manufactured By:

Xttrium Laboratories, Inc.

Mount Prospect, IL 60056

4021VALINST

REV. 06-25

Product No.: 4021

Manufactured By:

Xttrium Laboratories, Inc.

Mount Prospect, IL 60056

4021VALINST

REV. 06-25

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0116-4021-16

VALPROIC ACID ORAL SOLUTION, USP

250 mg/5 mL

Alcohol less than 0.05%

Each 5mL (teaspoonful) contains the equivalent of 250 mg Valproic Acid, USP (as the sodium salt) and less than 0.05% alcohol contributed by flavorings.

PHARMACIST: PLEASE DISPENSE THE ACCOMPANYING MEDICATION GUIDE TO EACH PATIENT.

Rx Only

NET: 1 Pint (480 mL)

USUAL DOSAGE: See accompanying package insert for full prescribing information.

WARNINGS: KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN. In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

Store at 20° - 25°C (68° - 77°F). [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with child-resistant closure.

Manufactured by:

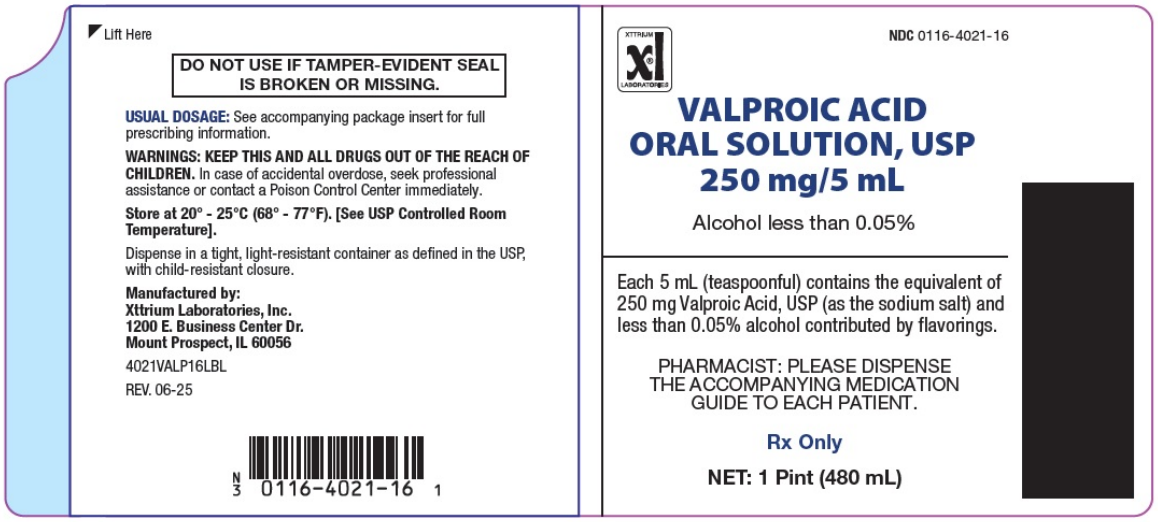
Xttrium Laboratories, Inc.

1200 E. Business Center Dr.

Mount Prospect, IL 60056

4021VALP16LBL

REV. 06-25



UNIT DOSE

Delivers 5 mL

NDC 0116-4021-05

Valproic Acid

Oral Solution USP,

250 mg/5 mL

Rx Only

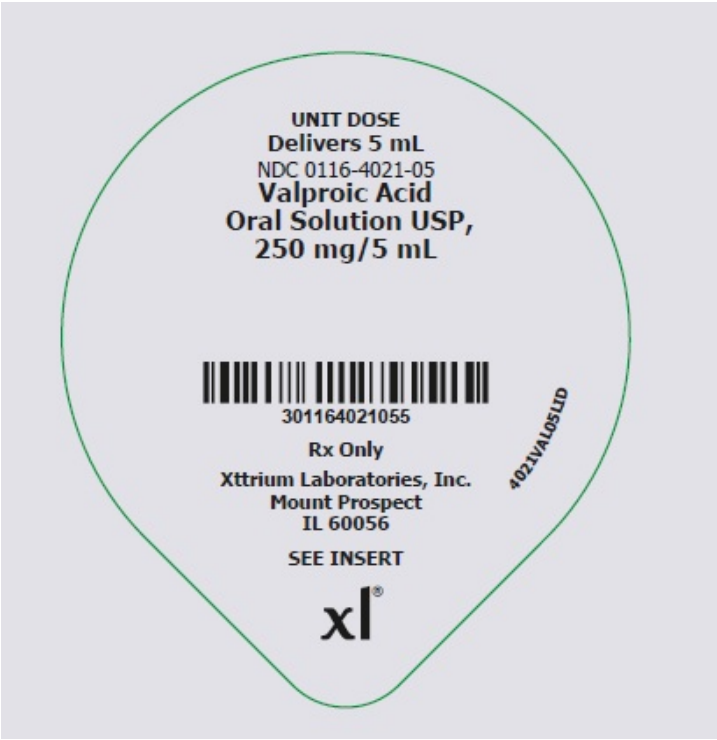
Xttrium Laboratories, Inc.

Mount Prospect

IL 60056

SEE INSERT

4021VAL05LID



UNIT DOSE

Delivers 10 mL

NDC 0116-4021-10

Valproic Acid Oral Solution USP,

500 mg/10 mL

Rx Only

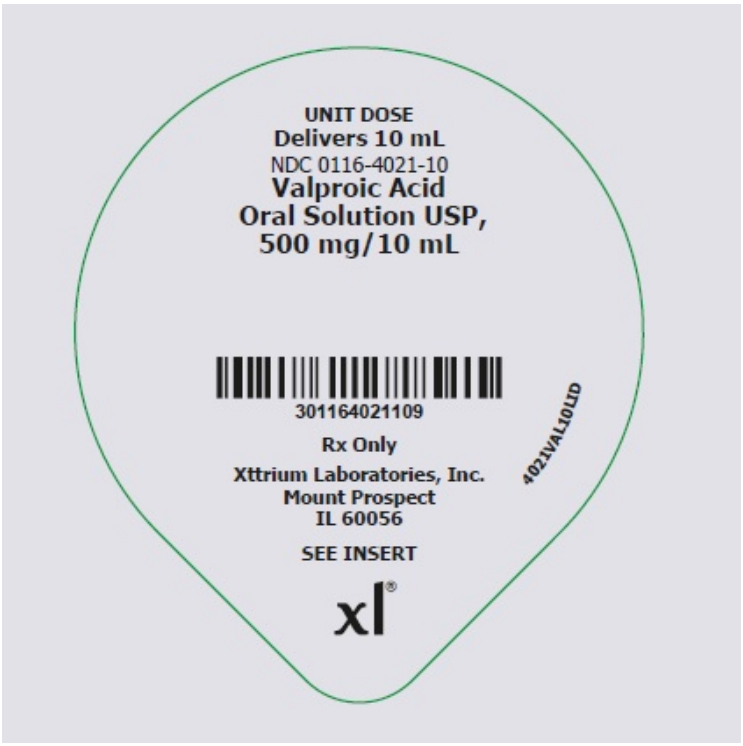
Xttrium Laboratories, Inc.

Mount Prospect

IL 60056

SEE INSERT

4021VAL10LID



VALPROIC ACID

valproic acid solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0116-4021
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
VALPROIC ACID (UNII: 614OI1Z5WI) (VALPROIC ACID - UNII:614OI1Z5WI)	VALPROIC ACID	250 mg in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
PRUNUS SEROTINA (WILD CHERRY) BARK (UNII: 5D48E975HA)	
GLYCERIN (UNII: PDC6A3C0OX)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
POTASSIUM PHOSPHATE, DIBASIC (UNII: CI71S98N1Z)	
CORN SYRUP (UNII: 9G5L16BK6N)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SUCROSE (UNII: C151H8M554)	
ALCOHOL (UNII: 3K9958V90M)	
CHERRY (UNII: BUC5I9595W)	

Product Characteristics			
Color	red (Red (Clear))	**Score**	

Shape		**Size**	
Flavor	CHERRY	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0116-4021-16	473 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	07/29/2025	
2	NDC:0116-4021-40	4 in 1 CASE	07/29/2025	
2		10 in 1 TRAY		
2	NDC:0116-4021-05	5 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product		
3	NDC:0116-4021-41	10 in 1 CASE	07/29/2025	
3		10 in 1 TRAY		
3	NDC:0116-4021-05	5 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product		
4	NDC:0116-4021-11	10 in 1 CASE	07/29/2025	
4		10 in 1 TRAY		
4	NDC:0116-4021-10	10 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070868	07/01/1986	

Labeler - Xttrium Laboratories Inc. (007470579)

Establishment

Name	Address	ID/FEI	Business Operations
Xttrium Laboratories Inc.		007470579	label(0116-4021) , manufacture(0116-4021) , pack(0116-4021)

Revised: 7/2025 Xttrium Laboratories Inc.