HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Stavzor safely and effectively. See full prescribing information for Stavzor.
Stavzor (valproic acid) Delayed Release Capsules
Initial U.S Approval: 2008

WARNING: LIFE THREATENING ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

- **Hepatotoxicity, including fatalities, usually during first 6 months of treatment. Children under the age of 2 years are at considerably higher risk of fatal hepatotoxicity. Monitor patients closely, and perform liver function tests prior to therapy and at frequent intervals thereafter (5.1)**
- **Fetal Risk, particularly neural tube defects and other major malformations (5.2, 5.3)**
- **Pancreatitis, including fatal hemorrhagic cases (5.4)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions
Use in Women of Childbearing Potential (5.2) 1/2013
Birth Defects and Neurobehavioral Adverse Effects (5.3) 1/2013
Use in Specific Populations,
Pregnancy (8.1) 1/2013
Patient Counseling Information,
Birth Defects and Neurobehavioral Development Adverse Effects (17.3) 1/2013

---------- INDICATIONS AND USAGE----------

Stavzor is indicated for:

- Acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features (1.1)
- Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures (1.2)
- Prophylaxis of migraine headaches (1.3)

----------DOSAGE AND ADMINISTRATION-------

- Safety of doses above 60 mg/kg/day is not established; divide daily dosage above 250 mg in separate doses (2.1, 2.2, 2.3)
- Bipolar Disorder, Mania: Start at 750 mg daily, in divided doses, increasing rapidly to achieve lowest therapeutic dose or desired plasma level (2.1)
- Complex Partial Seizures: Start at 10 to 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/day to achieve optimal clinical response; if response is not satisfactory, check valproate plasma level; see full prescribing information for conversion to monotherapy (2.2)
- Absence Seizures: Start at 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/day until seizure control or limiting side effects (2.2)
- Migraine: 250 mg twice daily (2.3)

----------DOSAGE FORMS AND STRENGTHS------

Delayed Release Capsules: 125 mg, 250 mg, 500 mg (3)

----------CONTRAINDICATIONS----------

- Hepatic disease or significant hepatic dysfunction (4, 5.1)
- Known hypersensitivity to the drug (4, 5.11)
- Urea cycle disorders (4, 5.5)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity; monitor liver function tests (5.1)
- Women of Childbearing Potential: weigh Stavzor benefits of use during pregnancy against risk to the fetus (5.2)
- Birth Defects: Stavzor can cause fetal harm when taken during pregnancy (5.3)
- Pancreatitis; Stavzor should ordinarily be discontinued (5.4)
- Suicidal Behavior and Ideation: Antiepileptic drugs, including Stavzor, increase the risk of suicidal thoughts or behavior (5.6)
- Thrombocytopenia; monitor platelet counts and coagulation tests (5.7)
- Hyperammonemia and hyperammonemic encephalopathy; measure ammonia level if unexplained lethargy and vomiting or changes in mental status (5.8, 5.9)
- Hypothermia; Hypothermia has been reported during valproate therapy with or without associated hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate (5.10)
- Multi-organ hypersensitivity reaction; discontinue Stavzor (5.11)
- Somnolence in the elderly can occur. Stavzor dosage should be increased slowly and with regular monitoring for fluid and nutritional intake (5.13)

----------ADVERSE REACTIONS----------

Most common adverse reactions (reported >5%) are nausea, somnolence, dizziness, vomiting, asthenia, abdominal pain, dyspepsia, rash, diarrhea, increased appetite, tremor, weight gain, back pain, alopecia, headache, fever, anorexia, constipation, diplopia, amblyopia/blurred vision, ataxia, nystagmus, emotional lability, thinking abnormal, amnesia, flu syndrome, infection, bronchitis, rhinitis, ecchymosis, peripheral edema, insomnia, nervousness, depression, pharyngitis, dyspnea, tinnitus (6.1, 6.2, 6.3, 6.4)

To report SUSPECTED ADVERSE REACTIONS, contact Noven Therapeutics, LLC at 1-800-455-8070 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Hepatic enzyme-inducing drugs (e.g. phenytoin, carbamazepine, phenobarbital, rifampin) can increase valproate clearance, while enzyme inhibitors (e.g. felbamate) can decrease valproate clearance. Monitor valproate and concomitant drug concentrations whenever enzyme-inducing or inhibiting drugs are introduced or withdrawn (7.1)
- Aspirin, carbapenem antibiotics: Monitoring of valproate concentrations is recommended (5.12, 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)
- Dosage adjustment of amitryptyline/nortryptyline, warfarin, and zidovudine may be necessary if used concomitantly with Stavzor (7.2)
- Topiramate: Hyperammonemia and encephalopathy (5.9, 7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Stavzor can cause congenital malformations including neural tube defects. Pregnancy registry available (5.2, 8.1)
- Pediatric: Children under the age of 2 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 (5.13, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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*Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING ADVERSE REACTIONS

Hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of 2 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 Stavzor 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.

These incidents usually have occurred during the first 6 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 6 months *[see Warnings and Precautions (5.1)]*.

Fetal Risk
Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). Valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using valproate *[see Warnings and Precautions (5.2, 5.3)]*.

A Medication Guide describing the risks of valproate is available for patients. *[see Patient Counseling Information (17)]*.

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 *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Mania

Stavzor® is indicated for the treatment of the manic episodes associated with bipolar disorder. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility.

The efficacy of valproate was established in 3-week trials with patients meeting DSM-III-R criteria for bipolar disorder who were hospitalized for acute mania *[see Clinical Studies (14.1)]*.

The safety and effectiveness of valproate for long-term use in mania, i.e., more than 3 weeks, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use Stavzor for extended periods should continually reevaluate the long-term usefulness of the drug for the individual patient.

1.2 Epilepsy

Stavzor is indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. Stavzor is also 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.

1.3 Migraine

Stavzor is indicated for prophylaxis of migraine headaches. There is no evidence that Stavzor is useful in the acute treatment of migraine headaches. Because it may be a hazard to the fetus, Stavzor should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patient and weighed against the potential benefits of treatment *[see Warnings and Precautions (5.2), Patient Counseling Information (17.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Mania

Stavzor (valproic acid) delayed release capsules are administered orally, and must be swallowed whole. The recommended initial dose is 750 mg daily in divided doses. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. In placebo-controlled clinical trials of acute mania, patients were dosed to a clinical response with a trough plasma concentration between 50 and 125 mcg/mL. Maximum concentrations were generally achieved within 14 days. The maximum recommended dosage is 60 mg/kg/day.

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during Stavzor treatment of an acute manic episode. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the benefits of Stavzor in such longer-term treatment. Although there are no efficacy data that specifically address longer-term antimanic treatment with Stavzor, the safety of Stavzor in long-term use is supported by data from record reviews involving approximately 360 patients treated with valproate for greater than 3 months.

2.2 Epilepsy

Stavzor (valproic acid) delayed release capsules are administered orally, and must be swallowed whole. As Stavzor dosage is titrated upward, concentrations of clonazepam, diazepam, ethosuximide, lamotrigine, tolbutamide, phenobarbital, carbamazepine, and/or phenytoin may be affected *[see Drug Interactions (7.2)]*.

Complex Partial Seizures

For adults and children 10 years of age or older.

Monotherapy (Initial Therapy)

Valproate 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.

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 2 weeks. This reduction may be started at initiation of Stavzor therapy, or delayed by 1 to 2 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

Stavzor 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 2 to 3 doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to valproate, no adjustment of carbamazepine or phenytoin dosage was needed *[see Clinical Studies (14.3)]*. 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 Drug Interactions (7)]*.

Simple and Complex Absence Seizures

The recommended initial dose is 15 mg/kg/day, increasing at 1-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 2 to 3 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 are considered to range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations *[see Clinical Pharmacology (12.3)]*.

As Stavzor dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected *[see Drug Interactions (7.2)]*.

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.

In epileptic patients previously receiving Depakene (valproic acid) therapy, Stavzor should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on Stavzor, a dosing schedule of 2 or 3 times a day may be elected in selected patients.

2.3 Migraine

Stavzor (valproic acid) delayed release capsules are administered orally, and must be swallowed whole. The recommended starting dose is 250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day. In clinical trials, there was no evidence that higher doses led to greater efficacy.

2.4 General Dosing Advice

Dosing in Elderly Patients

Due to a decrease in unbound clearance of 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 reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response *[see Warnings and Precautions (5.13)]*.

Dose-Related Adverse Reactions

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 Warnings and Precautions (5.7)]*. The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

G.I. Irritation

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

3 DOSAGE FORMS AND STRENGTHS

- 125-mg orange-colored, oval-shaped capsules with NVN in black print
- 250-mg orange-colored, oval-shaped capsules with NVN1 in black print
- 500-mg orange-colored, oval-shaped capsules with NVN2 in black print

4 CONTRAINDICATIONS

- Stavzor should not be administered to patients with hepatic disease or significant hepatic dysfunction *[see Warnings and Precautions (5.1)]*.
- Stavzor is contraindicated in patients with known hypersensitivity to the drug *[see Warnings and Precautions (5.11)]*
- Stavzor is contraindicated in patients with known urea cycle disorders *[see Warnings and Precautions (5.5)]*

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first 6 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. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 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 products 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 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When Stavzor 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 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 Boxed Warning and Contraindications (4)]*.

5.2 Use in Women of Childbearing Potential

Because of the risk to the fetus of neural tube defects and other major congenital malformations which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using valproate. Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of valproate use during pregnancy, and alternative therapeutic options should be considered for these patients. *[see Boxed Warning and Use in Specific Populations (8.1)]*.

To prevent major seizures, Stavzor 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.

5.3 Birth Defects and Neurobehavioral Adverse Effects

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 (e.g., craniofacial defects, cardiovascular malformations and malformations involving various body systems). 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.

Several published epidemiological studies have indicated that children exposed to valproate *in utero* have lower cognitive test scores than children exposed to either another antiepileptic drug *in utero* or to no antiepileptic drugs in utero. The largest of these studies is a prospective cohort study conducted in the United States and United Kingdom that found that children with prenatal exposure to valproate had lower Differential Ability Scale (D.A.S) scores at age 3 (92 [95% C.I. 88-97]) than children with prenatal exposure to the other antiepileptic drug monotherapy treatments evaluated: lamotrigine (101 [95% C.I. 98-104]), carbamazepine (98 [95% C.I. 95-102]) and phenytoin (99 [95% C.I. 94 - 104]). The D.A.S., which has a mean score of 100 (SD = 15), is a battery of cognitive tests designed for children ages 2.5 to 17 years. The D.A.S. is a measure of neurobehavioral development performed when children are too young to undergo IQ testing and generally correlates with IQ scores later in childhood.

Although all of the available studies have methodological limitations, the weight of the evidence supports the conclusion that valproate exposure *in utero* causes subsequent adverse effects on cognitive development.

In animal studies, valproate-exposed offspring had malformations similar to those seen in humans and demonstrated behavioral deficits. [*see Use in Specific Populations (8.1)*]

5.4 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. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. 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, Stavzor should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated *[see Boxed Warning]*.

5.5 Urea Cycle Disorders

Stavzor is contraindicated in patients with known urea cycle disorders (UCD). Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with UCD, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of Stavzor 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 blood urea nitrogen (BUN), or 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 UCD *[see Contraindications (4)* and *Warnings and Precautions (5.8,5.9)]*.

5.6 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Stavzor, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated

patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

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. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.
Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Stavzor or any other AED must balance the risk of suicidal thoughts and behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.7 Thrombocytopenia

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose related. In a clinical trial of valproate as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤75 x 109/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, 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.

Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (eg, low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving Stavzor be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of valproate as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤75 x 10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥110 mcg/mL (females) or ≥135 mcg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

5.8 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 who present with hypothermia *[see Warnings and Precautions (5.10)]*

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* Contraindications and *Warnings and Precautions (4, 5.5)]*.

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.

5.9 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 Warnings and Precautions (5.10)]*.

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. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured *[see Contraindications (4)* and *Warnings and Precautions (5.8)]*.

5.10 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 Drug Interactions (7.3)]*. 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.

5.11 Multi-Organ Hypersensitivity Reactions

Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days: range 1 to 40 days). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, hepatorenal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

5.12 Interaction with Carbapenem Antibiotics

Carbapenem antibiotics (for example, ertapenem, imipenem, meropenem; this is not a complete list) 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 Drug Interactions (7.1)]*.

5.13 Somnolence in the Elderly

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), 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 reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence *[see Dosage and Administration (2.4)]*.

5.14 Monitoring: Drug Plasma Concentration

Since valproic acid 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 *[see Drug Interactions (7)]*.

5.15 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.

5.16 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.

6. ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Mania

The incidence of adverse reactions has been ascertained based on combined data from 2 placebo-controlled clinical trials of valproate in the treatment of manic episodes associated with bipolar disorder. The adverse reactions were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, valproate, and lithium carbonate. A total of 4%, 8% and 11% of patients discontinued therapy due to intolerance in the placebo, valproate, and lithium carbonate groups, respectively.

Table 2 summarizes those adverse reactions reported for patients in these trials where the incidence rate in the valproate -treated group was greater than 5% and greater than the placebo incidence, or where the incidence in the valproate -treated group was statistically significantly greater than the placebo group. Vomiting was the only event that was reported by significantly ($p \leq 0.05$) more patients receiving valproate compared to placebo.

Table 2. Adverse Reactions Reported by >5% of Valproate-Treated Patients During Placebo-Controlled Trials of Acute Mania[a]

Adverse Event	Valproate (n=89)	Placebo (n=97)
Nausea	22%	15%
Somnolence	19%	12%
Dizziness	12%	4%
Vomiting	12%	3%
Asthenia	10%	7%
Abdominal Pain	9%	8%
Dyspepsia	9%	8%
Rash	6%	3%

a. The following adverse reactions occurred at an equal or greater incidence for placebo than for valproate: back pain, headache, constipation, diarrhea, tremor, and pharyngitis.

The following additional adverse reactions were reported by greater than 1% but not more than 5% of the 89 valproate-treated patients in controlled clinical trials:

Body as a Whole: Chest pain, chills, chills and fever, fever, neck pain, neck rigidity.

Cardiovascular System: Hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation.

Digestive System: Anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess.

Hemic and Lymphatic System: Ecchymosis.

Metabolic and Nutritional Disorders: Edema, peripheral edema.

Musculoskeletal System: Arthralgia, arthrosis, leg cramps, twitching.

Nervous System: Abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo.

Respiratory System: Dyspnea, rhinitis.

Skin and Appendages: Alopecia, discoid lupus erythematosus, dry skin, furunculosis, maculopapular rash, seborrhea.

Special Senses: Amblyopia, conjunctivitis, deafness, dry eyes, ear pain, eye pain, tinnitus.

Urogenital System: Dysmenorrhea, dysuria, urinary incontinence.

6.2 Epilepsy

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, valproate was generally well tolerated with most adverse reactions rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the valproate -treated patients (6%), compared to 1% of placebo-treated patients.

Table 3 lists treatment-emergent adverse reactions which were reported by ≥5% of valproate -treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to valproate alone, or the combination of valproate and other antiepilepsy drugs.

Table 3. Adverse Reactions Reported by > 5% of Patients Treated with Valproate During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/Event	Valproate (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
Respiratory System		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0

Table 4 lists treatment-emergent adverse reactions which were reported by ≥ 5% of patients in the high dose valproate group, and for which the incidence was greater than in the low dose group, in a controlled trial of valproate monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse reactions can be ascribed to valproate alone, or the combination of valproate and other antiepilepsy drugs.

Table 4. Adverse Reactions Reported by >5% of Patients in the High-Dose Group in the Controlled Trial of Valproate Monotherapy for Complex Partial Seizures[a]

Body System/Event	High Dose (%) (n = 131)	Low Dose (%) (n = 134)
Body as a Whole		
Asthenia	21	10
Digestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18
Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

a. Headache was the only adverse event that occurred in ≥5% of patients in the high-dose group and at an equal or greater incidence in the low-dose group.

The following additional adverse reactions were reported by greater than 1% but less than 5% of the 358 patients treated with valproate in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.

Cardiovascular System: Tachycardia, hypertension, palpitation.

Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.

Hemic and Lymphatic System: Petechia.

Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.

Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.

Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.

Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.

Skin and Appendages: Rash, pruritus, dry skin.

Special Senses: Taste perversion, abnormal vision, deafness, otitis media.

Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

6.3 Migraine

Based on 2 placebo-controlled clinical trials and their long-term extension, valproate was generally well tolerated with most adverse reactions rated as mild to moderate in severity. Of the 202 patients exposed to valproate in the placebo-controlled trials, 17% discontinued for intolerance. This is compared to a rate of 5% for the 81 placebo patients. Including the long-term extension study, the adverse reactions reported as the primary reason for discontinuation by ≥1% of 248 valproate-treated patients were alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

Table 5 includes those adverse reactions reported for patients in the placebo-controlled trials where the incidence rate in the valproate-treated group was greater than 5% and was greater than that for placebo patients.

Table 5. Adverse Reactions Reported by >5% of Valproate-Treated Patients During Migraine Placebo-Controlled Trials With a Greater Incidence Than Patients Taking Placebo[a]

Body System Event	Valproate (n=202)	Placebo (n=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal pain	9%	4%
Increased appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%
Tremor	9%	0%
Other		
Weight gain	8%	2%
Back pain	8%	6%
Alopecia	7%	1%

The following additional adverse reactions were reported by greater than 1% but not more than 5% of the 202 valproate-treated patients in the controlled clinical trials:

Body as a Whole: Chest pain, chills, face edema, fever and malaise.

Cardiovascular System: Vasodilatation.

Digestive System: Anorexia, constipation, dry mouth, flatulence, gastrointestinal disorder (unspecified), and stomatitis.

Hemic and Lymphatic System: Ecchymosis.

Metabolic and Nutritional Disorders: Peripheral edema, SGOT increase, and SGPT increase.

Musculoskeletal System: Leg cramps and myalgia.

Nervous System: Abnormal dreams, amnesia, confusion, depression, emotional lability, insomnia, nervousness, paresthesia, speech disorder, thinking abnormalities, and vertigo.

Respiratory System: Cough increased, dyspnea, rhinitis, and sinusitis.

Skin and Appendages: Pruritus and rash.

Special Senses: Conjunctivitis, ear disorder, taste perversion, and tinnitus.

Urogenital System: Cystitis, metrorrhagia, and vaginal hemorrhage.

6.4 Other Patient Populations

Adverse reactions that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources 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 valproic acid capsules 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, hypesthesia, vertigo, incoordination, 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 Warnings and Precautions (5.5)]*.

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

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 Drug Interactions (7)]*.

Psychiatric

Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal

Weakness.

Hematologic

Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage *[see Warnings and Precautions (5.7)* and *Drug Interactions (7)]*. 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 (eg, 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 Warnings and Precautions (5.1)]*.

Endocrine

Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests *[see Warnings and Precautions (5.15)]*.

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 Warnings and Precautions (5.4)]*.

Metabolic: Hyperammonemia *[see Warnings and Precautions (5.8)*, 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.

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

There have been reports of developmental delay, autism and/or autism spectrum disorder in the offspring of women exposed to valproate during pregnancy.

7. DRUG INTERACTIONS

7.1 Effects of Co-Administered Drugs on Valproate Clearance

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed

Aspirin

A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate-free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Carbapenem antibiotics

A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics (for example, ertapenem, imipenem, meropenem; this is not a complete list) and may result in loss of seizure control. The mechanism of this interaction in 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 Warnings and Precautions (5.12)]*.

Felbamate

A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin

A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Alcohol

An in vitro study evaluating dissolution of valproic acid showed earlier dissolution in the presence of ethanol than in the absence of ethanol. This has not been studied in humans. However, there is a potential for an earlier T_{max} and therefore a higher C_{max} when valproic acid is given with alcohol. Caution is advised if valproic acid is taken with alcohol.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed

Antacids

A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine

A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol

A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine

Cimetidine and ranitidine do not affect the clearance of valproate.

7.2 Effects of Valproate on Other Drugs

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronosyltransferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed

Amitriptyline/Nortriptyline

Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/Carbamazepine-10,11-Epoxide

Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide

Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine

In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital

Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin

Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

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

From in vitro experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin

In an in vitro study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproic acid therapy is instituted in patients taking anticoagulants.

Zidovudine

In 6 patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); 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 3 epileptic patients.

Clozapine

In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium

Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam

Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids

Administration of a single-dose of ethinyloestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

7.3 Topiramate

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy *[see Warnings and Precautions (5.5), (5.8) and (5.9)]*. Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported [*see Warnings and Precautions (5.8, 5.10)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category D. *[see Warnings and Precautions (5.3)]*

Pregnancy Registry

To collect information on the effects of *in utero* exposure to Stavzor, physicians should encourage pregnant patients taking Stavzor to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling toll free 1-888-233-2334, and must be done by the patients themselves. Information on the registry can be found at the website, http://www.aedpregnancyregistry.org/.

Fetal Risk Summary

All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about 15%), or other adverse outcomes regardless of drug exposure. Maternal valproate use during pregnancy for any indication increases the risk of congenital malformations, particularly neural tube defects, but also malformations involving other body systems (e.g., craniofacial defects, cardiovascular malformations). The risk of major structural abnormalities is greatest during the first trimester; however, other serious developmental effects can occur with valproate use throughout pregnancy. The rate of congenital malformations among babies born to epileptic mothers who used valproate during pregnancy has been shown to be about four times higher than the rate among babies born to epileptic mothers who used other anti-seizure monotherapies.

Several published epidemiological studies have indicated that children exposed to valproate *in utero* have lower cognitive test scores than children exposed to either another antiepileptic drug *in utero* or to no antiepileptic drugs *in utero*. *[see Warnings and Precautions (5.3)]*.

In animal studies, offspring had structural malformations similar to those seen in humans and demonstrated behavioral deficits.

Clinical Considerations

- Neural tube defects are the congenital malformation most strongly associated with maternal valproate use. The risk of spina bifida following *in utero* valproate exposure is generally estimated as 1-2%, compared to an estimated general population risk for spina bifida of about 0.06 to 0.07% (6 to 7 in 10,000 births).
- To prevent major seizures, women with epilepsy should not discontinue Stavzor abruptly, as this can precipitate status epilepticus with resulting maternal and fetal hypoxia and threat to life. Even minor seizures may pose some hazard to the developing embryo or fetus. However, discontinuation of the drug may be considered prior to and during pregnancy in individual cases if the seizure disorder severity and frequency do not pose a serious threat to the patient.
- Available prenatal diagnostic testing to detect neural tube and other defects should be offered to pregnant women using valproate.
- 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 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.
- Patients taking valproate may develop clotting abnormalities *[see Warnings and Precautions (5.7)]*. A patient who had low fibrinogen when taking multiple anticonvulsants including valproate gave birth to an infant with afibrinogenemia who subsequently died of hemorrhage. If valproate is used in pregnancy, the clotting parameters should be monitored carefully.
- Patients taking valproate may develop hepatic failure (see Warnings and Box Warnings). Fatal cases of hepatic failure in infants exposed to valproate *in utero* have also been reported following maternal use of valproate during pregnancy.

Data

Human

There is an extensive body of evidence demonstrating that exposure to valproate *in utero* increases the risk of neural tube defects and other structural abnormalities. Based on published data from the CDC's National Birth Defects Prevention Network, the risk of spina bifida in the general population is about 0.06 to 0.07%. The risk of spina bifida following *in utero* valproate exposure has been estimated to be approximately 1 to 2%.

In one study using NAAED Pregnancy Registry data, 16 cases of major malformations following prenatal valproate exposure were reported among offspring of 149 enrolled women who used valproate during pregnancy. Three of the 16 cases were neural tube defects; the remaining cases included craniofacial defects, cardiovascular malformations and malformations of varying severity involving other body systems. The NAAED Pregnancy Registry has reported a major malformation rate of 10.7% (95% C.I. 6.3% – 16.9%) in the offspring of women exposed to an average of 1,000 mg/day of valproate monotherapy during pregnancy (dose range 500 – 2000 mg/day). The major malformation rate among the internal comparison group of 1,048 epileptic women who received any other antiepileptic drug monotherapy during pregnancy was 2.9% (95% CI 2.0% to 4.1%). These data show a four-fold increased risk for any major malformation (Odds Ratio 4.0; 95% CI 2.1 to 7.4) following valproate exposure *in utero* compared to the risk following exposure *in utero* to any other antiepileptic drug monotherapy.

Several published epidemiological studies have indicated that children exposed to valproate *in utero* have lower cognitive test scores than children exposed to either another antiepileptic drug *in utero* or to no antiepileptic drugs *in utero*. The largest of these studies is a prospective cohort study conducted in the United States and United Kingdom that found that children with prenatal exposure to valproate had lower Differential Ability Scale (D.A.S.) scores at age 3 (92 [95% C.I. 88-97]) than children with prenatal exposure to the other anti-epileptic drug monotherapy treatments evaluated: lamotrigine (101 [95% C.I. 98-104]), carbamazepine (98 [95% C.I. 95-102]) and phenytoin (99 [95% C.I. 94-104]). The D.A.S., which has a mean score of 100 (SD = 15), is a battery of cognitive tests designed for children ages 2.5 to 17 years. The D.A.S. is a measure of neurobehavioral development performed when children are too young to undergo IQ testing and generally correlates with IQ scores later in childhood.

Although all of the available studies have methodological limitations, the weight of the evidence supports a causal association between valproate exposure *in utero* and subsequent adverse effects on cognitive development.

There are published case reports of fatal hepatic failure in offspring of women who used valproate during pregnancy.

Animal

In developmental toxicity studies conducted in mice, rats, rabbits, and monkeys, increased rates of fetal structural abnormalities, intrauterine growth retardation, and embryo-fetal death occurred following treatment of pregnant animals with valproate during organogenesis at clinically relevant doses

(calculated on a body surface area basis). Valproate induced malformations of multiple organ systems, including skeletal, cardiac, and urogenital defects. In mice, in addition to other malformations, fetal neural tube defects have been reported following valproate administration during critical periods of organogenesis, and the teratogenic response correlated with peak maternal drug levels. Behavioral abnormalities (including cognitive, locomotor, and social interaction deficits) and brain histopathological changes have also been reported in mice and rat offspring exposed prenatally to clinically relevant doses of valproate.

8.3 Nursing Mothers

Valproate is excreted in human milk. Caution should be exercised when valproate is administered to a nursing woman.

8.4 Pediatric Use

Experience has indicated that pediatric patients under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions *[see Boxed Warning, Warning and Precautions (5.1)]*. 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.

Valproate has not been established to be safe and effective for the treatment of partial seizures in children under the age of 10 years.

Pediatric Clinical Trials

Valproate was studied in seven pediatric clinical trials.

A double-blind placebo-controlled trial evaluated the efficacy of valproate for the treatment of mania in 150 patients aged 10 to 17 years, 76 of whom were on valproate. Efficacy was not established.

A double-blind placebo-controlled trial evaluated the efficacy of valproate for the treatment of migraine in 304 patients aged 12 to 17 years, 231 of whom were on valproate. Efficacy was not established. Based on the results of this study, it is not expected that valproate would be effective in patients with migraine below the age of 12.

The remaining five trials were long term safety studies. Two six-month pediatric studies were conducted to evaluate the long-term safety of valproate for the indication of mania (292 patients aged 10 to 17 years). Two twelve-month pediatric studies were conducted to evaluate the long-term safety of valproate for the indication of migraine (353 patients aged 12 to 17 years). One twelve-month study was conducted to evaluate the safety of valproate in the indication of partial seizures (169 patients aged 3 to 10 years). The safety and tolerability of valproate in pediatric patients were shown to be comparable to those in adults *[see Adverse Reactions (6)]*.

Nonclinical Developmental Toxicology

In studies of valproate in immature animals, toxic effects not observed in adult animals included retinal dysplasia in rats treated during the neonatal period (from postnatal day 4) and nephrotoxicity in rats treated during the neonatal and juvenile (from postnatal day 14) periods. The no-effect dose for these findings was less than the maximum recommended human dose on a mg/m^2 basis.

8.5 Geriatric Use

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor.

Discontinuation of valproate was occasionally associated with the latter 2 events. 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.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence *[see Warnings and Precautions (5.13)]*. The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence *[see Dosage and Administration (2.4)]*.

There is insufficient information available to discern the safety and effectiveness of valproic acid for the prophylaxis of migraines in patients over 65. 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) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

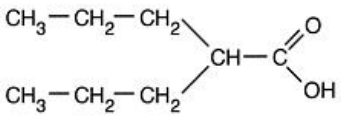
Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2120 mcg/mL.

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. 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 (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 has the following structure



Stavzor (valproic acid) delayed release capsules are for oral administration and are provided as orange-colored, oval- shaped capsules in 3 dosage strengths: 125 mg, 250 mg, 500 mg of valproic acid.

Inactive Ingredients

Stavzor (valproic acid) delayed release capsules also contain ammonium hydroxide, gelatin, glycerin, methacrylic acid

copolymer, triethyl citrate, water, and FD&C Yellow No. 6 as the colorant. Each capsule is printed with Opacode WB as the black printing ink.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

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).

12.3 Pharmacokinetics

Absorption/Bioavailability

A single-dose randomized crossover study compared Stavzor 500-mg strength capsules to 500-mg Depakote delayed-release tablets. These studies demonstrated that the 2 products had similar plasma concentration-time profiles under fasted conditions in terms of valproic acid, although the median T_{max} occurred earlier with STAVZOR (2.0 hrs versus 3.5 hrs). Co-administration with food increased the T_{max} of Stavzor (2.0 hrs without food and approximately 4.8 hours with food), and resulted in a 23% decrease in C_{max} of valproic acid, although there was no change in systemic exposure (AUC).

Although the rate of valproate ion absorption may vary with the conditions of use (eg, fasting or postprandial), 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 an influence on the rate of absorption of the capsule (increase in T_{max} from 2.3 to 6.1 hours). While the absorption rate from the GI tract and fluctuation in valproate plasma concentrations vary with dosing regimen, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to 4-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicates 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 are inconsequential from a practical clinical standpoint. Whether or not rate of absorption influences the efficacy of valproate as an antimanic or antimigraine agent is unknown. Co-administration of oral valproate products with food should cause no clinical problems in the management of patients with epilepsy *[see Dosage and Administration (2.2)]*.

An in vitro study evaluating dissolution of valproic acid showed earlier dissolution in the presence of ethanol than in the absence of ethanol. This has not been studied in humans. However, there is a potential for an earlier T_{max} and therefore a higher C_{max} when valproic acid is given with alcohol.

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 (eg, aspirin). Conversely, valproate may displace certain protein-bound drugs (eg, phenytoin, carbamazepine, warfarin, and tolbutamide) [*See Drug Interactions (7)* 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 1000 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 2 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 (ie, between 3 months and 10 years) have 50% higher clearances expressed on weight (ie, 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). 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 (2.4)]*.

Effect of Gender

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), 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.

Plasma Levels 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.

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.

Mania

In placebo-controlled clinical trials of acute mania, patients were dosed to clinical response with trough plasma concentrations between 50 and 125 mcg/mL *[see Dosage and Administration (2.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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 human dose on a mg/m^2 basis) for 2 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. The significance of these findings for humans is unknown.

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. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.

Fertility

Chronic toxicity studies of valproate in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent 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 1.4 times the MRHD or greater 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. The effect of valproate on testicular development and on sperm production and fertility in humans is unknown.

14 CLINICAL STUDIES

14.1 Mania

The effectiveness of valproate for the treatment of acute mania was demonstrated in two 3-week, placebo controlled, parallel group studies.

(1) Study 1: The first study enrolled adult patients who met DSM-III-R criteria for bipolar disorder and who were hospitalized for acute mania. In addition, they had a history of failing to respond to or not tolerating previous lithium carbonate treatment. Valproate was initiated at a dose of 250 mg TID and adjusted to achieve serum valproate concentrations in a range of 50-100 mcg/mL by day 7. Mean valproate doses for completers in this study were 1118, 1525, and 2402 mg/day at Days 7, 14, and 21, respectively. Patients were assessed on the Young Mania Rating Scale (YMRS; score ranges from 0-60), an augmented Brief Psychiatric Rating Scale (BPRS-A), and the Global Assessment Scale (GAS). Baseline scores and change from baseline in the Week 3 endpoint (last-observation-carried-forward[LOCF]) analysis were as follows:

Study 1

YMRS Total Score			
Group	**Baseline[1]**	**BL to Wk3[2]**	**Difference[3]**
Placebo	28.8	+0.2	
Valproate	28.5	-9.5	9.7
BPRS–A Total Score			
Group	**Baseline[1]**	**BL to Wk3[2]**	**Difference[3]**
Placebo	76.2	+1.8	
Valproate	76.4	-17.0	18.8
GAS Score			
Group	**Baseline[1]**	**BL to Wk3[2]**	**Difference[3]**
Placebo	31.8	0.0	
Valproate	30.3	+18.1	18.1

1. Mean score at baseline
2. Change from baseline to Week 3 (LOCF)
3. Difference in change from baseline to Week 3 endpoint (LOCF) between valproate and placebo

Valproate was statistically significantly superior to placebo on all three measures of outcome.

(2) Study 2: The second study enrolled adult patients who met Research Diagnostic Criteria for manic disorder and who were hospitalized for acute mania. Valproate was initiated at a dose of 250 mg TID and adjusted within a dose range of 750-2500 mg/day to achieve serum valproate concentrations in a range of 40-150 mcg/mL. Mean valproate doses for completers in this study were 1116, 1683, and 2006 mg/day at Days 7, 14, and 21, respectively. Study 2 also included a lithium group for which lithium doses for completers were 1312, 1869, and 1984 mg/day at Days 7, 14, and 21, respectively. Patients were assessed on the Manic Rating Scale (MRS; score ranges from 11-63), and the primary outcome measures were the total MRS score, and scores for 2 subscales of the MRS, i.e., the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS). Baseline scores and change from baseline in the Week 3 endpoint (LOCF) analysis were as follows:

Study 2

MRS Total Score			
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	38.9	-4.4	
Lithium	37.9	-10.5	6.1
Valproate	38.1	-9.5	5.1
MSS Total Score			
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**

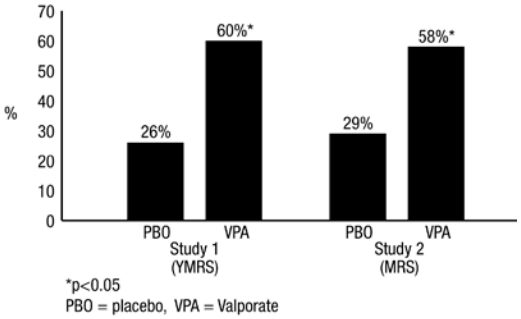
Placebo	18.9	-2.5	
Lithium	18.5	-6.2	3.7
Valproate	18.9	-6.0	3.5
BIS Total Score			
Group	**Baseline[1]**	**BL to Day 21[2]**	**Difference[3]**
Placebo	16.4	-1.4	
Lithium	16.0	-3.8	2.4
Valproate	15.7	-3.2	1.8

1. Mean score at baseline
2. Change from baseline to Day 21 (LOCF)
3. Difference in change from baseline to Day 21 endpoint (LOCF) between valproate and placebo and lithium and placebo

Valproate was statistically significantly superior to placebo on all three measures of outcome. An exploratory analysis for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or gender.

A comparison of the percentage of patients showing ≥30% reduction in the symptom score from baseline in each treatment group, separated by study, is shown in Figure 1.

Figure 1. Percentage of Patients Achieving ≥30% Reduction in Symptom Score From Baseline



14.2 Epilepsy

The efficacy of valproate in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in 2 controlled trials.

In one, multiclinic, placebo-controlled study employing an add-on design, (adjunctive therapy) 144 patients who continued to suffer 8 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 valproate or placebo. Randomized patients were to be followed for a total of 16 weeks. The following Table presents the findings.

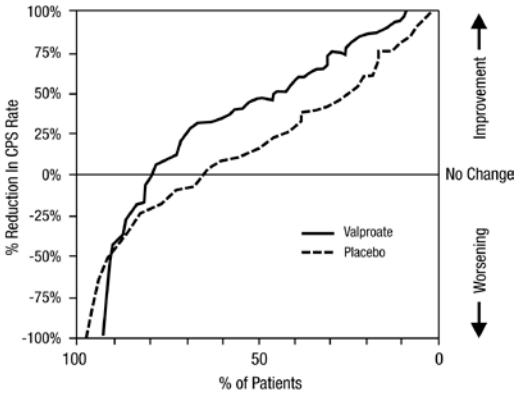
Adjunctive Therapy Study Median Incidence of CPS per 8 Weeks

Add-On Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
Valproate	75	16.0	8.9*
Placebo	69	14.5	11.5

*****Reduction from baseline statistically significantly greater for valproate than placebo 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 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 valproate than for placebo. For example, 45% of patients treated with valproate had a ≥50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 2.



The second study assessed the capacity of valproate 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- weeklong period of monotherapy with adequate doses of an AED (ie, phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a 2-week interval to valproate. 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 valproate 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.

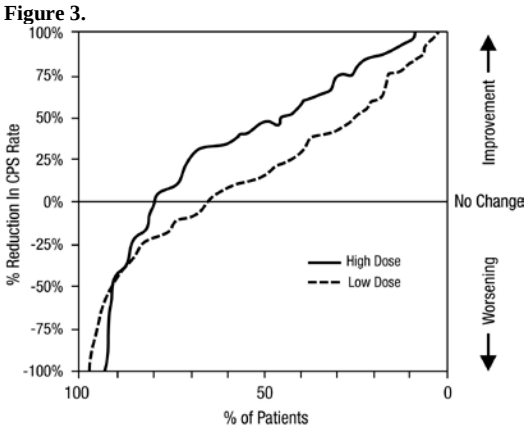
Monotherapy Study Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High-Dose Valproate	131	13.2	10.7*
Low-Dose Valproate	134	14.2	13.8

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

Figure 3 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 valproate than for low dose valproate. For example, when switching from carbamazepine, phenytoin, phenobarbital, or primidone monotherapy to high-dose valproate monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low-dose valproate.

Figure 3.



14.3 Migraine

The results of 2 multicenter, randomized, double-blind, placebo-controlled clinical trials established the effectiveness of valproate in the prophylactic treatment of migraine headache.

Both studies employed essentially identical designs and recruited patients with a history of migraine with or without aura (of at least 6 months in duration) who were experiencing at least 2 migraine headaches a month during the 3 months prior to enrollment. Patients with cluster headaches were excluded. Women of childbearing potential were excluded entirely from one study, but were permitted in the other if they were deemed to be practicing an effective method of contraception.

In each study following a 4-week single-blind placebo baseline period, patients were randomized, under double blind conditions, to valproate or placebo for a 12-week treatment phase, comprised of a 4-week dose titration period followed by an 8-week maintenance period. Treatment outcome was assessed on the basis of 4-week migraine headache rates during the treatment phase.

In the first study, a total of 107 patients (24 M, 83 F), ranging in age from 26 to 73 were randomized 2:1, valproate to placebo. Ninety patients completed the 8-week maintenance period. Drug dose titration, using 250-mg tablets, was individualized at the investigator's discretion. Adjustments were guided by actual/sham trough total serum valproate levels in order to maintain the study blind. In patients on valproate doses ranged from 500 to 2500 mg a day. Doses over 500 mg were given in 3 divided doses (TID). The mean dose during the treatment phase was 1087 mg/day resulting in a mean trough total valproate level of 72.5 mcg/mL, with a range of 31 to 133 mcg/mL.

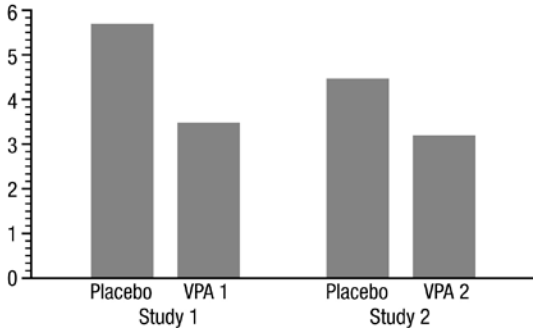
The mean 4-week migraine headache rate during the treatment phase was 5.7 in the placebo group compared to 3.5 in the valproate group (see Figure 2). These rates were significantly different.

In the second study, a total of 176 patients (19 males and 157 females), ranging in age from 17 to 76 years, were randomized equally to one of three valproate dose groups (500, 1000, or 1500 mg/day) or placebo. The treatments were given in 2 divided doses (BID). One hundred thirty-seven patients completed the 8-week maintenance period. Efficacy was to be determined by a comparison of the 4-week migraine headache rate in the combined 1000/1500 mg/day group and placebo group.

The initial dose was 250 mg daily. The regimen was advanced by 250 mg every 4 days (8 days for 500 mg/day group), until the randomized dose was achieved. The mean trough total valproate levels during the treatment phase were 39.6, 62.5, and 72.5 mcg/mL in the valproate 500, 1000, and 1500 mg/day groups, respectively.

The mean 4-week migraine headache rates during the treatment phase, adjusted for differences in baseline rates, were 4.5 in the placebo group, compared to 3.3, 3.0, and 3.3 in the valproate 500, 1000, and 1500 mg/day groups, respectively, based on intent-to-treat results (see Figure 4). Migraine headache rates in the combined valproate 1000/1500 mg group were significantly lower than in the placebo group.

Figure 4. Mean 4-Week Migraine Rates



16 HOW SUPPLIED/STORAGE AND HANDLING

Stavzor (valproic acid) delayed release capsules are supplied as:

- 125-mg orange-colored, oval-shaped capsules with NVN in black print:
  Bottles of 100 (NDC 68968-3125-1)
- 250-mg orange-colored, oval-shaped capsules with NVN1 in black print:
  Bottles of 100 (NDC 68968-3250-1)
- 500-mg orange-colored, oval-shaped capsules with NVN2 in black print:
  Bottles of 100 (NDC 68968-3500-1)

Store at 25° C (77° F); excursions permitted to 15°- 30° C (59°-86° F) [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

See FDA-Approved patient labeling (Medication Guide)

17.1 Hepatotoxicity

Patients and guardians should be warned that nausea, vomiting, abdominal pain, anorexia, diarrhea, asthenia, and/or jaundice can be symptoms of hepatotoxicity and, therefore, require further medical evaluation promptly.

17.2 Pancreatitis

Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly *[see Warnings and Precautions (5.4)]*.

17.3 Birth Defects and Neurobehavioral Development Adverse Effects

Prescribers should inform pregnant women and women of childbearing potential that use of Stavzor during pregnancy increases the risk of birth defects and adverse effects on neurobehavioral development. Prescribers should advise women to use effective contraception while using valproate. Prescribers should 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 (e.g., migraine). Patients should read the Medication Guide, which appears as the last section of the labeling *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Patients should be encouraged to enroll in the 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 *[see Use in Specific Populations (8.1)]*.

17.4 Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including Stavzor, may increase the risk of suicidal thoughts and behavior and should be advised of the need 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. Behaviors of concern should be reported immediately to healthcare providers.

17.5 Hyperammonemia

Patients should be informed of the signs and symptoms associated with hyperammonemic encephalopathy and be told to inform the prescriber if any of these symptoms occur *[see Warnings and Precautions (5.8, 5.9)]*.

17.6 CNS Depression

Since valproate products may produce CNS depression, especially when combined with another CNS depressant (eg, 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.

17.7 Multi-organ Hypersensitivity Reaction

Patients should be instructed 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 (5.11)]*

Manufactured for:
Noven Therapeutics, LLC
Miami, FL 33186

Manufactured by:
Banner Pharmacaps, Inc.
High Point, NC 27265

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Depakene® and Depakote® are registered trademarks of Abbott Laboratories.

Medication Guide
STAVZOR® (STAV- ZOR)
(valproic acid)
Delayed Release Capsules

Read this Medication Guide before you start taking STAVZOR 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 STAVZOR?

Do not stop taking STAVZOR without first talking to your healthcare provider. Stopping STAVZOR suddenly can cause serious problems.

STAVZOR 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. **STAVZOR may harm your unborn baby.**
   - If you take STAVZOR during pregnancy for any medical condition, your baby is at risk for serious birth defects. The most common birth defects with STAVZOR 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 can 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 Stavzor during pregnancy for any medical condition, your child is at risk for having a lower IQ.
- There may be other medicines to treat your condition that have a lower chance of birth defects.
- **All women of child-bearing age should talk to their healthcare provider about using other possible treatments instead of STAVZOR. If the decision is made to use Stavzor, you should use effective birth control (contraception) unless you are planning to become pregnant.**
- Tell your healthcare provider right away if you become pregnant while taking STAVZOR. You and your healthcare provider should decide if you will continue to take STAVZOR while you are pregnant.
-
- **Pregnancy Registry:** If you become pregnant while taking STAVZOR, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic 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, STAVZOR 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 attention 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 symptoms.

Do not stop Stavzor without first talking to a healthcare provider. Stopping Stavzor suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy can cause seizures that do 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 STAVZOR?

STAVZOR is a prescription medicine used:

- to treat manic episodes associated with bipolar disorder.
- 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
- to prevent migraine headaches

Who should not take STAVZOR?

Do not take STAVZOR if you:

- have liver problems
- are allergic to valproic acid, divalproex sodium, sodium valproate, or any of the ingredients in STAVZOR. See the end of this leaflet for a complete list of ingredients in STAVZOR.
- have a genetic problem called a urea cycle disorder

What should I tell my healthcare provider before taking STAVZOR?

Before you take STAVZOR, tell your healthcare provider if you:

- drink alcohol
- are pregnant or breastfeeding. STAVZOR can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take STAVZOR.
- 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 STAVZOR 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 STAVZOR?

- Take STAVZOR exactly as your healthcare provider tells you. Your healthcare provider will tell you how much STAVZOR to take and when to take it.
- Your healthcare provider may change your dose.
- Do not change your dose of STAVZOR without talking to your healthcare provider.
- **Do not stop taking STAVZOR without first talking to your healthcare provider.** Stopping STAVZOR suddenly can cause serious problems.
- Swallow STAVZOR whole. Do not crush, chew, or break STAVZOR. Tell your healthcare provider if you can not swallow STAVZOR whole. You may need a different medicine.
- If you take too much STAVZOR, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking STAVZOR?

- STAVZOR can make you sleepy or dizzy. Do not drink alcohol or take other drugs that make you sleepy or dizzy while taking STAVZOR, until you talk to your doctor. Taking STAVZOR with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how STAVZOR affects you. STAVZOR can slow your thinking and motor skills.

What are the possible side effects of STAVZOR?

See "What is the most important information I should know about STAVZOR?".

STAVZOR may cause other serious side effects including:

- **Low blood count:** red or purple spots on your skin, bruising, bleeding from your mouth, teeth or nose.
- **High ammonia levels in your blood:** feeling tired, vomiting, changes in mental status.
- **Low body temperature (hypothermia):** drop in body temperature to less than 95^0F, 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 Stavzor.

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

The most common side effects of STAVZOR 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 STAVZOR. 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 STAVZOR?

- Store STAVZOR between 59°F to 86°F (15°C to 30°C)

Keep STAVZOR and all medicines out of the reach of children.

General Information about STAVZOR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use STAVZOR for a condition for which it was not prescribed. Do not give STAVZOR 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 STAVZOR. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about STAVZOR that is written for health professionals.

For more information, go to www.STAVZOR.com or call 1-800-455-8070

What are the ingredients in STAVZOR?

Active ingredient: valproic acid

Inactive ingredient: ammonium hydroxide, gelatin, glycerin, methacrylic acid copolymer, triethyl citrate, water, and FD&C Yellow No. 6 as the colorant

Manufactured for:
Noven Therapeutics, LLC
Miami, FL 33186

Manufactured by:
Banner Pharmacaps, Inc.
High Point, NC 27265

02/2013

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