**For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only**

# TREND XR
## (Divalproex Sodium Prolonged Release Tablets I.P.)

## COMPOSITION

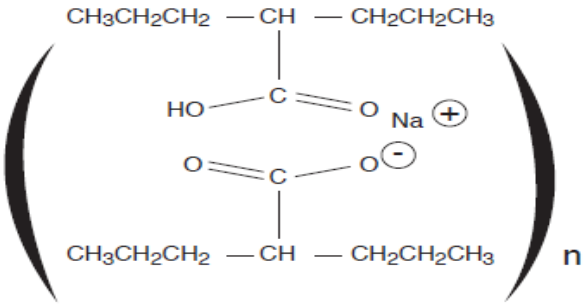
### TREND XR 250
Each film coated prolonged release tablet contains:
Divalproex Sodium I.P. equivalent to Valproic acid 250 mg
Excipients q.s.
Colors: Black Oxide of Iron & Titanium Dioxide I.P.

### TREND XR 500
Each film coated prolonged release tablet contains:
Divalproex Sodium I.P. equivalent to Valproic acid 500 mg
Excipients q.s.
Colors: Black Oxide of Iron & Titanium Dioxide I.P.

### TREND XR 750
Each film coated prolonged release tablet contains:
Divalproex Sodium I.P. equivalent to Valproic acid 750 mg
Excipients q.s.
Colors: Yellow Oxide of Iron & Titanium Dioxide I.P.

### TREND XR 1000
Each film coated prolonged release tablet contains:
Divalproex Sodium I.P. equivalent to Valproic acid 1000 mg
Excipients q.s.
Colors: Black Oxide of Iron & Titanium Dioxide I.P.

## DESCRIPTION
Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis (2-propylvalerate) oligomer. Divalproex sodium has the following structure:



## CLINICAL PHARMACOLOGY

### Mechanism of action

Divalproex sodium 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).

### Pharmacokinetics

#### *Absorption*

The absolute bioavailability of extended release divalproex sodium tablets administered as a single dose after a meal was approximately 90% relative to intravenous infusion. In multiple dose bioavailability studies when extended release divalproex sodium administered under fasting and nonfasting conditions, an average bioavailability of 89% relative to an equal total daily dose of divalproex sodium given BID, TID, or QID. The median time to maximum plasma valproate concentrations ($C_{max}$) after Divalproex Sodium ER administration ranged from 4 to 17 hours. After multiple once-daily dosing of Divalproex Sodium ER, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular divalproex sodium given BID, TID, or QID.Concomitant antiepilepsy drugs (topiramate, phenobarbital, carbamazepine, phenytoin, and lamotrigine were evaluated) that induce the cytochrome P450 isozyme system did not significantly alter valproate bioavailability when converting between divalproex sodium and extended release divalproex sodium.

#### *Distribution*

Protein Binding: The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 μg/mL to 18.5% at 130 μg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin).

#### *CNS Distribution*

A valproate concentration in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma.

#### *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 is 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.

**Special Populations**

***Pediatric***

Once-daily administration of divalproex extended release (ER) in pediatric patients (10-17 years) produced plasma Valproic acid concentration-time profiles similar to those that have been observed in adults.

***Elderly***

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

***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).

***Disease***

***Liver Disease***

Liver disease impairs the capacity to eliminate valproate. A study has been reported that 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.

***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.

## INDICATIONS AND USAGE

**Epilepsy:** Trend XR is indicated as monotherapy and adjunctive therapy in the treatment of adults and children 10 years of age or older with complex partial seizures that occur either isolation or in association with other types of seizures. Divalproex Sodium ER is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that include absence seizures.

**Mania:** Trend XR is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

**Migraine:** Trend XR is indicated for prophylaxis of migraine in adults.

## DOSAGE AND ADMINISTRATION

Trend XR is an extended-release product intended for once-a-day oral administration. Trend XR should be swallowed whole and should not be crushed or chewed.

### Mania

Trend XR are administered orally. The recommended initial dose is 25 mg/kg/day given once daily. 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 .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 Trend XR 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 Trend XR in such longer-term.

### Migraine

Trend XR is indicated for prophylaxis of migraine headaches in adults.
The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1000 mg once daily. As with other valproate products, doses of Trend XR should be individualized and dose adjustment may be necessary.

### Epilepsy

Trend XR is indicated as monotherapy and adjunctive therapy for complex partial seizures, and for simple and complex absence seizures in adult patients and pediatric patients 10 years of age or older. As the Trend XR dosage is titrated upward, concentrations of phenobarbital, Clonazepam, diazepam, ethosuximide, Lamotrigine carbamazepine, and/or phenytoin may be affected.

**Complex partial seizures for adult patients and children 10 years of age or older:**
Monotherapy (Initial Therapy): Trend XR 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. No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

Conversion to Monotherapy: Concomitant antiepileptic drugs (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of Trend XR 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: Trend XR 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.

**Simple and complex absence seizures for adult patients and children 10 years of age or older:** The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day.

**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. Starting doses in the elderly lower than 250 mg can only be achieved by the use of Trend XR. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response.

Dose-Related Adverse Events - The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 mg/mL (females) or ≥ 135 mg/mL (males). 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 initiating therapy with a lower dose of Trend XR.

Compliance - Patients should be informed to take Trend XR every day as prescribed. If a dose is missed it should be taken as soon as possible, unless it is almost time for the next dose. If a dose is skipped, the patient should not double the next dose.

## CONTRAINDICATIONS

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

## WARNINGS AND PRECAUTIONS

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

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

**Patients with Mitochondrial Disease:** There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g. Alpers Huttenlocher Syndrome) Valproic acid is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Valproic acid should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Valproic acid for the development of acute liver injury with regular clinical assessments

and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice. 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.

**Fetal Risk**
Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following in utero exposure. Valproate is therefore contraindicated in pregnant women treated for prophylaxis of migraine. Valproate should only be used to treat pregnant women with epilepsy or bipolar disorder if other medications have failed to control their symptoms or are otherwise unacceptable.

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.

**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.

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

Caution should be observed when administering 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 two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When Valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. In progressively older patient groups experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably.

**Patients with Known or Suspected Mitochondrial Disease**
Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate then those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testingshould be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations, are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders. Valproic acid is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Valproic acid should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Valproic acid for the development of acute liver injury with regular clinical assessments and serum liver test monitoring.

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.

**Birth Defects**
Valproate can cause fetal harm when administered to a pregnant woman. Pregnancy registry data show that maternal valproate use can cause neural tube defects and other structural abnormalities (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.

**Decreased IQ following in utero exposure**

Valproate can cause decreased IQ scores following in utero exposure. Published epidemiological studies have indicated that children exposed to valproate in utero have lower cognitive test scores than children exposed in utero to either another antiepileptic drug or to no antiepileptic drugs. The largest of these studies 1 is a prospective cohort study conducted in the United States and United Kingdom that found that children with prenatal exposure to valproate (N=62) had lower IQ scores at age 6 (97 [95% C.I. 94-101]) than children with prenatal exposure to the other antiepileptic drug monotherapy treatments evaluated: lamotrigine (108 [95% C.I. 105–110]), carbamazepine (105 [95% C.I. 102–108]), and phenytoin (108 [95% C.I. 104–112]). Because the women in this study were exposed to antiepileptic drugs throughout pregnancy, whether the risk for decreased IQ was related to a particular time period during pregnancy could not be assessed. Although all of the available studies have methodological limitations, the weight of the evidence supports the conclusion that valproate exposure in utero causes decreased IQ in children.

In animal studies, offspring with prenatal exposure to valproate had malformations similar to those seen in humans and demonstrated neurobehavioral deficits.

Valproate use is contraindicated during pregnancy in women being treated for prophylaxis of migraine headaches. Women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant should not be treated with valproate unless other treatments have failed to provide adequate symptom control or are otherwise unacceptable. In such women, the benefits of treatment with valproate during pregnancy may still outweigh the risks.

**Use in Women of Childbearing Potential**

Because of the risk to the fetus of decreased IQ and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless 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.

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

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

**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, Valproic acid should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

**Urea Cycle Disorders**

Valproic acid 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 Valproic acid 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.

**Suicidal Behavior and Ideation**

Antiepileptic drugs (AEDs), including Valproic acid, 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 1,000 Patients** | **Drug Patients with Events per 1,000 Patients** | **Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients** | **Risk Difference: Additional Drug Patients with Events Per 1,000 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 divalproex or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and 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.

**Bleeding and other Hematopoietic Disorders**
Valproate is associated with dose-related thrombocytopenia. 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 $\leq 75 \times 10^9$/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 $\geq$ 110 mcg/mL (females) or $\geq$ 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. Valproate use has also been associated with decreases in other cell lines and myelodysplasia.

Because of reports of cytopenias, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen, coagulation factor deficiencies, acquired von Willebrand's disease), measurements of complete blood counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving divalproex be monitored for blood counts and coagulation parameters prior to planned surgery and during pregnancy. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

**Hyperammonemia**
Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. 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.

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.

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

**Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use** Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either

drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia.

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.

**Hypothermia**
Hypothermia, defined as an unintentional drop in body core temperature to < 35° C (95° F), has been reported in association with valproate therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproate after starting topiramate treatment or after increasing the daily dose of topiramate. Consideration should be given to stopping valproate in patients who develop hypothermia, 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.

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity Reactions**
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking valproate. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Valproate should be discontinued and not be resumed if an alternative etiology for the signs or symptoms cannot be established.

**Interaction with Carbapenem Antibiotics**
Carbapenem antibiotics (for example, ertapenem, imipenem, meropenem; this is not a complete list) may reduce serum 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.

**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 were 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.

**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.

**Effect on Ketone and Thyroid Function Tests**
Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

**Effect on HIV and CMV Viruses Replication**
There are in vitro studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these in vitro findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV-infected patients receiving valproate or when following CMV-infected patients clinically.

**DRUG INTERACTIONS**
***Effects of co-administered drugs on valproate clearance***
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, 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.

***Drugs for which a potentially important interaction has been observed***

Aspirin - Co-administration of aspirin with valproate inhibits the metabolism of valproate. Caution should be observed if valproate and aspirin are co-administered.

Felbamate - A study has been reported that 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.

Carbapenem Antibiotics - Carbapenem antibiotics (ertapenem, imipenem, meropenem) may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control.

Rifampin - A study has been reported that valproate administered with rifampin caused 40% increase in the oral clearance of valproate hence 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 Tmax and therefore a higher Cmax 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 clinical unimportant interaction has been observed***

Antacids - A study has been reported that the co-administration of valproate 500 mg with commonly administered antacids did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine - A study has been reported that 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 has been reported that 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.

***Effects of valproate on other drugs***
Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyltransferases.

**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.

***Drugs for Which Either no Interaction or a Likely Clinically Unimportant***
**Interaction has been observed**
**Acetaminophen**
Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

**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 six women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

***Drugs for which a potentially important valproate interaction has been observed***
*Amitriptyline/Nortriptyline* - Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patient 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 displaced diazepam from its plasma albumin binding sites and inhibit its metabolism. A study has been reported that 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 inhibit the metabolism of ethosuximide.

*Lamotrigine* - 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.

*Phenobarbital* - Valproate inhibit the metabolism of phenobarbital. The fraction of Phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

*Phenytoin* - Valproate displaced phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. 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.

*Topiramate* - Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy.

*Warfarin* - In an *in vitro* study, valproate increase the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if Divalproex Sodium ER therapy is instituted in patients taking anticoagulants.

## CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

### Carcinogenesis

The toxicity study was reported that valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a $mg/m^2$ basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibro-sarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

### Mutagenesis

Valproate has not been found mutagenic in an *in vitro* bacterial assay (Ames test), and has not produced dominant lethal effects in mice, and has 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.

### Fertility

Chronic toxicity studies have been reported in juvenile and adult rats and dogs and they have been 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 human daily dose on a $mg/m^2$ basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a $mg/m^2$ basis). Segment I fertility studies in rats have shown oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a $mg/m^2$ basis) for 60 days to have no effect on fertility. The effect of valproate on testicular development and on sperm production and fertility in humans is unknown.

**USE IN SPECIFIC POPULATIONS**
**Pregnancy**

**Pregnancy Category D** for epilepsy

*Pregnancy Registry*

*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 IQ scores than children exposed to either another antiepileptic drug *in utero* or to no antiepileptic drugs *in utero* .

A reported observational study has suggested that exposure to valproate products during pregnancy may increase the risk of autism spectrum disorders. In this study, children born to mothers who had used valproate products during pregnancy had 2.9 times the risk (95% confidence interval [CI]: 1.7-4.9) of developing autism spectrum disorders compared to children born to mothers not exposed to valproate products during pregnancy. The absolute risks for autism spectrum disorders were 4.4% (95% CI: 2.6%-7.5%) in valproate-exposed children and 1.5% (95% CI: 1.5%-1.6%) in children not exposed to valproate products. Because the study was observational in nature, conclusions regarding a causal association between *in utero* valproate exposure and an increased risk of autism spectrum disorder cannot be considered definitive.

In animal studies, offspring with prenatal exposure to valproate had structural malformations similar to those seen in humans and demonstrated neurobehavioral 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).*

*Valproate can cause decreased IQ scores in children whose mothers were treated with valproate during pregnancy.*

*Because of the risks of decreased IQ, neural tube defects, and other fetal adverse events, 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).

Valproate should not be used to treat women with epilepsy who are pregnant or who plan to become pregnant unless other treatments have failed to provide adequate symptom control or are otherwise unacceptable. In such women, the benefits of treatment with valproate during pregnancy may still outweigh the risks. When treating a pregnant woman or a woman of childbearing potential, carefully consider both the potential risks and benefits of treatment and provide appropriate counseling.

To prevent major seizures, women with epilepsy should not discontinue valproate 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 or decreased IQ in the offspring of women receiving valproate is reduced by folic acid supplementation. Dietary folic acid supplementation both prior to conception and during pregnancy should be routinely recommended for patients using valproate.

Patients taking valproate may develop clotting abnormalities. 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 . Fatal cases of hepatic failure in infants exposed to valproate *in utero* have also been reported following maternal use of valproate during pregnancy.

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

**Pediatric Use**
Experience with oral valproate has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions in warnings. The safety of Sodium valproate has not been studied in individuals below the age of 2 years. If a decision is made to use Sodium valproate in this age 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 valproate concentrations.
The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

**Geriatric Use**
In a reported 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 later two 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. The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence.

**ADVERSE REACTIONS**
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 1 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.

**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.

**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.

**Post-Marketing Experience**
The following adverse reactions have been identified during post approval use of Divalproex Sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Dermatologic:** Photosensitivity, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Psychiatric: Emotional upset, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

**Psychiatric:** Emotional upset, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

**Neurologic:** There have been several reports of acute or subacute cognitive decline and behavioral changes (apathy or irritability) with cerebral pseudoatrophy on imaging associated with valproate therapy; both the cognitive/behavioral changes and cerebral pseudoatrophy reversed partially or fully after valproate discontinuation.

**Musculoskeletal:** Fractures, decreased bone mineral density, osteopenia, osteoporosis, and weakness.

**Hematologic:** Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leucopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

**Endocrine:** Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, parotid gland swelling, polycystic ovary disease, decreased carnitine concentrations, hyponatremia, hyperglycinemia, and inappropriate ADH secretion.

**Genitourinary:** Enuresis and urinary tract infection.

**Special Senses:** Hearing loss.

**Other:** Allergic reaction, anaphylaxis, developmental delay, bone pain, bradycardia, and cutaneous vasculitis.

## 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.

**DIRECTION**
Tablets to be swallowed whole, not to be chewed.

**EXPIRY DATE**
Do not use after the date of expiry.

**STORAGE**
Store at a temperature not exceeding 30$^{o}$C, protected from light and moisture.

**PRESENTATION**
TREND XR 250, TREND XR 500, TREND XR 750 and TREND XR 1000 is available in strip of 10 tablets.

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.
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**TREN/JAN 2015/Ver 05**