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

TREND XR

1. Generic Name:

Divalproex Sodium Prolonged Release Tablets I.P.

2. Qualitative and quantitative composition:

TREND XR 250

Each film coated prolonged release tablet contains:

Divalproex sodiumI.P.

Equivalent to Valproic acid 250 mg

Excipients……. q.s.

Colors: Black Oxide of Iron & Titanium Dioxide I.P.

Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide black

TREND XR 500

Each film coated prolonged release tablet contains:

Divalproex sodiumI.P.

Equivalent to Valproic acid 500 mg

Excipients……. q.s.

Colors: Black Oxide of Iron & Titanium Dioxide I.P.

Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide black

TREND XR 750

Each film coated prolonged release tablet contains:

Divalproex sodiumI.P.

Equivalent to Valproic acid 750 mg

Excipients……. q.s.

Colors: Yellow Oxide of Iron & Titanium Dioxide I.P.

Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide yellow

TREND XR 1000

Each film coated prolonged release tablet contains:

Divalproex sodiumI.P.

Equivalent to Valproic acid 1000 mg

Excipients…… q.s.

Colors: Black Oxide of Iron & Titanium Dioxide I.P.

Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide black

3. Dosage form and strength:

Dosage form: Film coated prolonged release tablet

Strength: Divalproex sodium (Equivalent to Valproic acid 250/500/750/1000 mg)

4. Clinical particulars:

4.1 Therapeutic indication:

Prophylaxis of migraine headache in adults with warning -not for women who are pregnant or planning for pregnancy.

As monotherapy or adjunctive therapy in the treatment of patients with complex partial seizure and manic episodes associated with bipolar disorder.

4.2 Posology and method of 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.

4.3 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

4.4 Special warnings and precautions for use:

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 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 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 POLGrelated 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. 94101]) 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: shows absolute and relative risk by indication for all evaluated AEDs and 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.

4.5 Drug-Interaction:

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 halflives 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 ifTREND XRER 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/m2 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/m2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m2 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/m2 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.

4.6 Use in special populations(Pregnency, Fertility and Breast feeding)

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 a fibrinogenemia 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.

4.7 Effects on ability to drive and use machines:

You may feel sleepy when takingTREND XR. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

4.8 Undesirable effects:

The following CIOMS frequency rating is used, when applicable: very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

SOC	Very Common	Common	Uncommon	Rare	Very rare
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Myelodysplastic syndrome	
Blood and lymphatic system disorders		Anaemia Thrombocytopenia	Pancytopenia Leucopenia	Bone marrow failure[1]	
Endocrine disorders			Syndrome of Inappropriate Secretion of ADH (SIADH) Hyperandrogenism[2]	Hypothyroidism	
Metabolism and nutrition disorders		Hyponatraemia Weight increased		Hyperammonaemia Obesity	
Psychiatric disorders		Confusional state Hallucinations Aggression Agitation Disturbance in attention		Abnormal behaviour Psychomotor hyperactivity Learning disorder	
Nervous system disorders	Tremor	Extrapyramidal disorder Stupor Somnolence Convulsion	Coma Encephalopathy Lethargy Reversible parkinsonism Ataxia	Reversible dementia associated with reversible	

		Memory impairment Headache Nystagmus	Paraesthesia Aggravated convulsions	cerebral atrophy Cognitive disorder	
Eye disorders				Diplopia	
Ear and labyrinth disorders		Deafness			
Vascular disorders		Haemorrhage	Vasculitis		
Respiratory, thoracic and mediastinal disorders			Pleural effusion		
Gastrointestinal disorders	Nausea	Vomiting Gingival disorder (mainly gingival hyperplasia) Stomatitis Gastralgia Diarrhoea	Pancreatitis (sometimes fatal)		
Hepatobiliary disorders	Liver injury	Increased liver enzymes			Hepatic failure, sometimes fatal
Skin and subcutaneous tissue disorders		Hypersensitivity Transient and/or dose related alopecia Nail and nail bed disorders.	Angioedema Rash Hair disorder[3]	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Drug Rash with Eosinophilia and	

				Systemic Symptoms (DRESS) syndrome	
Musculoskeletal and connective tissue disorders			Bone mineral density decreased Osteopenia Osteoporosis Fractures	Systemic lupus erythematosus Rhabdomyolysis	
Renal and urinary disorders		Urinary incontinence	Renal failure	Enuresis Tubulointerstitial nephritis Reversible Fanconi syndrome (glycosuria, aminoaciduria, phosphaturia, and uricosuria)	
Reproductive system and breast disorders		Dysmenorrhea	Amenorrhea	Male infertility Polycystic ovaries	Gynaecomastia
Congenital malformations and developmental disorders					
General disorders and administration site conditions			Hypothermia Peripheral oedema		

Investigations				Coagulation factors decreased abnormal coagulation tests[4]	

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 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.

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 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.

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

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.

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, Gum Hyperplasia.
- 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%).

It 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.

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

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, Gum Hyperplasia.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose:

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.

5. Pharmacological properties:

5.1 Mechanism of Action:

Divalproex sodiumdissociates 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).

5.2 Pharmacodynamic properties:

Sodium valproate and valproic acid are anticonvulsants.

The most likely mode of action for sodium valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain in-vitro studies it was reported that sodium valproate could stimulate HIV replication, but studies on peripheral blood mononuclear cells from HIV- infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed, the effect of sodium valproate on HIV replication ex- vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.3 Pharmacokinetic properties:

Absorption

The absolute bioavailability of extended release TREND XR tablets administered as a single dose after a meal was approximately 90% relative to intravenous infusion. In multiple dose bioavailability studies when extended release TREND XR administered under fasting and nonfasting conditions, an average bioavailability of 89% relative to an equal total daily dose of TREND XR given BID, TID, or QID. The median time to maximum plasma valproate concentrations (C_{max}) after TREND XR administration ranged from 4 to 17 hours. After multiple once-daily dosing of TREND XR, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular TREND XR 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 TREND XRand 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 enzymeinducing 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 (1017 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

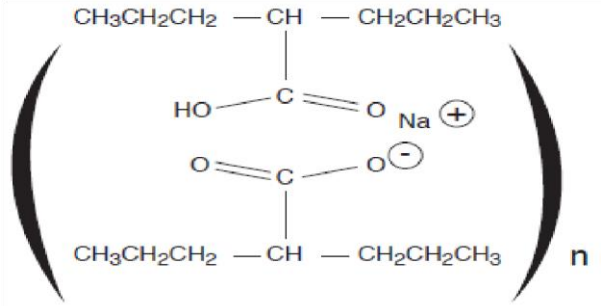
A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (Creatinine clearance <10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with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

6. Nonclinical properties:

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

7. Description:

Divalproex sodiumis 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.TREND XRhas the following structure:



Product Description:

TREND XR 250

Grey colored round shaped biconvex, film coated tablets plain on both sides.

TREND XR 500

Grey colored capsule shaped, film coated tablets plain on both sides

TREND XR 750

Yellow colored oval shaped, film coated tablets plain on both sides

TREND XR 1000

Light Grey colored capsule shaped, film coated tablets plain on both sides

8. Pharmaceutical particulars:

8.1 Incompatibilities:

Not applicable.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

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

8.4 Storage and handing instructions:

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

9. Patient Counselling Information

Package leaflet: Information for the user

TREND XR

Divalproex sodiumProlonged Release Tablets I.P.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What TREND XR is and what it is used for

The name of your medicine is TREND XR 200, 300 and 500mg prolong release tablets. "Prolonged-release" means that the active ingredient sodium valproate is slowly released from the tablets over a period of time TREND XR contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down TREND XR is used to treat epilepsy (fits) in adults and children.

9.2 What you need to know before you take TREND XR

Do not take TREND XR and tell your doctor if:

- You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of TREND XR. Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You have liver problems or you or your family have a history of liver problems.
- You have a rare illness called porphyria.
- You have a known metabolic disorder, i.e. a urea cycle disorder.
- You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).
- You are pregnant, unless nothing else works for you (see 'Pregnancy, breast-feeding and fertility – Important advice for women' below).

If you are a woman able to have a baby you must not take TREND XR unless you use an effective method of birth control (contraception) at all times during your treatment with TREND XR.

Do not stop taking TREND XR or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see below under 'Pregnancy, breast-feeding and fertility – Important advice for women').

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking TREND XR.

Warnings and precautions

- A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- As with other anti-epileptic drugs, convulsions may become worse or happen more frequently whilst taking this medicine.

If this happens contact your doctor immediately.

Talk to your doctor or pharmacist before taking TREND XR if:

- You have diabetes. This medicine may affect the results of urine tests.
- You have a carnitine palmitoy ltransferase type II deficiency.
- You have kidney problems. Your doctor may give you a lower dose.
- You have a brain disease or a metabolic condition affecting your brain.
- You have a 'urea cycle disorder' where too much ammonia builds up in the body.
- You have an illness called 'systemic lupus erythematosus (SLE)' a disease of the immune system which affects skin, bones, joints and internal organs.
- You know that there is a genetic problem caused by mitochondrial disorder in your family.

If you are not sure if any of the above apply to you, **talk to your doctor or pharmacist** before taking TREND XR.

- Weight gain
- Taking TREND XR may make you put on weight
- Talk to your doctor about how this will affect you
- Blood tests
- Your doctor may wish to do blood tests before you start taking TREND XR and during your treatment

Other medicines and TREND XR

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because TREND XR can affect the way some other medicines work.

Also some medicines can affect the way TREND XR works.

The following medicines, when taken with TREND XR, can increase the chance of you getting side effects:

- Some medicines used for pain and inflammation (salicylates) such as aspirin.
- Some other medicines used to treat fits (epilepsy), 'Patients taking other medicines for fits'. This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate.

Divalproex sodium may increase the effect of the following medicines:

- Medicines used for thinning the blood (such as warfarin).
- Zidovudine used to treat HIV infection.
- Temozolomide used to treat cancer.
- Medicines for depression.
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid.
- Medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine.

- Nimodipine.
- Propofol – used for anaesthesia.
- The following medicines can affect the way TREND XR works:
- Oestrogen-containing products (including some birth control pills).
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine.
- Cimetidine used for stomach ulcers.
- Protease inhibitors such as lopinavir and ritonavir – used for HIV infection and AIDS.
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin.

The combination of TREND XR and carbapenems should be avoided because it may decrease the effect of your medicine.

• Cholestyramine used to lower blood fat (cholesterol) levels.

Taking TREND XR with food and drink

Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

Important advice for women

- You must not use TREND XR if you are pregnant, unless nothing else works for you.
- If you are a woman able to have a baby, you must not take TREND XR unless you use an effective method of birth control (contraception) during your entire treatment with TREND XR.
- Do not stop taking TREND XR or your birth control (contraception), until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy

- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations;
- limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child

you should not stop taking your medicine or your method of birth control (contraception) until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact their doctor once your child experiences their first period (menarche).
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose the situations which apply to you and read the descriptions below:

• I AM STARTING TREATMENT WITHTREND XR

• I AM TAKINGTREND XR AND NOT PLANNING TO HAVE A BABY

• I AM TAKINGTREND XR AND PLANNING TO HAVE A BABY

• I AM PREGNANT AND I AM TAKINGTREND XR

I AM STARTING TREATMENT WITHTREND XR

If this is the first time you have been prescribed TREND XR your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of birth control (contraception) without interruption throughout your treatment with TREND XR. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:

- Pregnancy must be excluded before start of treatment with TREND XR with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with TREND XR.
- You must discuss appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKINGTREND XR AND NOT PLANNING TO HAVE A BABY

If you are continuing treatment with TREND XR but you are not planning to have a baby, make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with TREND XR. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:

- You must use an effective method of birth control (contraception) during your entire treatment with TREND XR.
- You must discuss birth control (contraception) with your doctor.

Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).

- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKINGTREND XR AND PLANNING TO HAVE A BABY

- If you are planning to have a baby, first schedule an appointment with your doctor.
- Do not stop taking TREND XR or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further.
- Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development, which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.
- Your specialist may decide to change the dose of TREND XR, switch you to another medicine, or stop treatment with TREND XR a long time before you become pregnant – this is to make sure your illness is stable.
- Ask your doctor about taking folic acid when trying for a baby.
- Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop taking TREND XR unless your doctor tells you to.
- Do not stop using your birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine or stop treatment with TREND XR a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USINGTREND XR

Do not stop taking TREND XR unless your doctor tells you to as your condition may become worse.

Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. You will be referred to a specialist experienced in the management of epilepsy so that alternative treatment options can be evaluated.

In the exceptional circumstances when TREND XR is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition

and to check how your unborn child is developing. You and your partner should receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking TREND XR unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of epilepsy to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of TREND XR during pregnancy, including malformations and developmental effects in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.
- Make sure you read the Patient Guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it.
- You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.
- Newborn babies of mothers who took valproate during pregnancy may have:
- Blood clotting problems (such as blood not clotting very well).
- This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar).
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

Very little TREND XR gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You may feel sleepy when taking TREND XR. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

9.3 How to take TREND XR

Always take TREND XR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Divalproex sodium treatment must be started and supervised by a doctor specialised in the treatment of epilepsy.

Taking this medicine

- Your doctor will decide how much TREND XR to give you or your child depending on your or your child's body weight.
- Take this medicine by mouth.
- Take TREND XR with or after food. This will help to stop the feelings of sickness that may happen after taking TREND XR.
- Do not crush or chew the tablets. Swallow whole with a glass of water.

- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor.

How to take this medicine

This medicine can be taken once or twice daily.

How much to take

Adults (including the elderly)

- The starting dose is 600mg daily. Your doctor will gradually increase this dose by 200mg every 3 days depending on your condition.
- The usual dose is generally between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day.
- This may be increased to 2500mg each day depending on your illness.

Children over 20 kilograms

- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness.
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day.
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness.

Children under 20 kilograms

•TREND XR is not recommended in children that weigh less than 20 kilograms. Liquid formulations of sodium valproate are recommended instead.

Patients with kidney problems

- Your doctor may decide to adjust your or your child's dose. Patients taking other medicines for fits (epilepsy)
- You or your child may be taking other medicines for epilepsy at the same time as TREND XR. If so, your doctor should gradually initiate treatment depending on your or your child's condition.
- Your doctor may increase the dose of TREND XR by 5-10mg for each kilogram of body weight each day depending on which other medicines you are taking.

If you take more TREND XR than you should

- If you take more TREND XR than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.
- The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take TREND XR

- If you forget to take a dose, take it as soon as you remember.
- However, if it is nearly time for the next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking TREND XR

Keep taking TREND XR until your doctor tells you to stop. Do not stop taking TREND XR just because you feel better. If you stop your fits may come back.

Tests

Make sure you or your child keep your regular appointments for a check-up. They are very important as your or your child's dose may need to be changed. TREND XR can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking TREND XR.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, TREND XR can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- You have an allergic reaction. The signs include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking TREND XR. It includes feeling and being sick many times; being very tired, sleepy and weak; stomach pain including very bad upper stomach pain; jaundice (yellowing of the skin or whites of the eyes); loss of appetite; swelling (especially of the legs and feet but may include other parts of the body); worsening of your fits or a
- general feeling of being unwell. Your doctor may tell you to stop taking TREND XR immediately if you have these symptoms.
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'.
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'.
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills, and aching muscles. This may be something called 'Toxic epidermal necrolysis'.
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow
- depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason.
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma).
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism).
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion).

Tell your doctor as soon as possible if you have any of the following side effects:

- Changes in behaviour including being very alert, and sometimes also aggressive, hyperactive and unusual or inappropriate behaviour. This is more likely if other medicines to treat fits such as phenobarbital and topiramate are taken at the same time or if the TREND XR starting dose is high or has been suddenly increased.
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert.
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements.
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits.
- Blisters with the skin flaking away.
- Rapid, uncontrollable movement of the eyes.
- An increase in the number and severity of convulsions.

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:

- Feeling sick (nausea), being sick (vomiting), stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food.
- Swelling of gums or sore mouth.
- Fainting.
- Hearing loss.
- Nail and nail bed disorders.
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine.

- Hair disorders (changes in texture, colour or growth), hair loss which is usually temporary. When It grows back it may be more curly than before.
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest, acne or thinning hair.
- Skin rash caused by narrow or blocked blood vessels (vasculitis).
- Changes in women's periods and increased hair growth in women.
- Breast enlargement in men.
- Swelling of the feet and legs (oedema).
- Obesity, weight gain – as your appetite may be increased.
- Kidney disease, kidney problems, blood in the urine, bedwetting or increased need to pass urine, urinary incontinence (unintentional passing of urine).
- Headache.
- Seeing or hearing things that are not there (hallucinations).
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder.
- Tingling or numbness in the hands and feet.
- Lowering of normal body temperature.
- Abnormal blood clotting factors.
- Muscle pain and weakness (rhabdomyolysis).
- Gum Hyperplasia.

Additional side effects in children

Some side effects of valproate occur more frequently in children or are more severe compared to adults. These include liver damage, inflammation of the pancreas (pancreatitis), bedwetting (enuresis), renal dysfunction (Fanconi Syndrome), overgrowth of gum tissue, aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity and learning disorder.

Bone disorders

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term anti-epileptic medication have a history of osteoporosis, or take steroids.

Tests

Divalproex sodium can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male fertility

Taking TREND XR can be a contributing factor in male infertility.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store TREND XR

- Keep out of the sight and reach of children.
- Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the last day of that month.
- Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Store in a dry place below 30°C.
- These measures help protect the tablets from moisture and light.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

9.6 Contents of the pack and other information

What TREND XR contains

TREND XR 250

Each film coated prolonged release tablet contains:

Divalproex sodiumI.P. (Equivalent to Valproic acid 250 mg)

The Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide black

Grey colored round shaped biconvex, film coated tablets plain on both sides.

TREND XR 500

Each film coated prolonged release tablet contains:

Divalproex sodiumI.P. (Equivalent to Valproic acid 500 mg)

The Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide black

Grey colored capsule shaped, film coated tablets plain on both sides

TREND XR 750

Each film coated prolonged release tablet contains:

Divalproex sodium I.P. (Equivalent to Valproic acid 750 mg)

The Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide yellow

Yellow colored oval shaped, film coated tablets plain on both sides

TREND XR 1000

Each film coated prolonged release tablet contains:

Divalproex sodium I.P. (Equivalent to Valproic acid 1000 mg)

The Other excipients used are ethyl cellulose, acetone, hydroxy propyl methyl celulose, silicon dioxide, magnesium stearate, talc, titanium dioxide, polyethylene glycol, iso propyl alcohol, ferric oxide black

Light Grey colored capsule shaped, film coated tablets plain on both sides

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

10. Details of manufacturer

Manufactured By

32 No. Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135

11. Details of permission or licence number with date

M/563/2010 issued on 26.04.2014

12. Date of revision

MAY 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TREND XR 250, 500, 750, 1000 mg/MAY-21/06/PI