SUMMARY OF PRODUCT CHARACTERISTICS

DICORATE ER 500

(Divalproex Sodium Extended-Release Tablets 500 mg)

1. NAME OF THE MEDICINAL PRODUCT

DICORATE ER 500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DICORATE ER 500

Each Film-Coated extended release tablet contains
Divalproex Sodium USP equivalent to Valproic Acid 500 mg

For the full list of excipients, see section 6.1.

The product contains lactose.

3. Pharmaceutical form

Extended-release tablet

Product description:

Dicorate ER 500: Grey colour, oval, biconvex coated tablet plain on both sides.

The distribution category of the product i.e. 'Prescription only medicine'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mania
DICORATE ER tablets (divalproex sodium) are indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility. A mixed episode is characterized by the criteria for

a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The safety and effectiveness of divalproex sodium for long-term use in mania, i.e., more than 3 weeks, has not been reported in controlled clinical studies. Therefore, healthcare providers who elect to use divalproex sodium for extended periods should continually re-evaluate the long-term usefulness of the drug for the individual patient.

Epilepsy
DICORATE ER tablets (divalproex sodium) are indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. **DICORATE ER tablets** are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

Migraine
DICORATE ER tablets (divalproex sodium) are indicated for prophylaxis of migraine headaches. There is no reported evidence that divalproex sodium is useful in the acute treatment of migraine headaches.

Important Limitations
Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, neural tube defects, and other major congenital malformations, which may occur very early in pregnancy, valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable (see section 4.4 and 4.6).

For prophylaxis of migraine headaches, divalproex sodium is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception (see section 4.3).

4.2 Posology and method of administration

DICORATE ER tablets (divalproex sodium) are available in the strength 250 and 500 mg extended release tablets and may not be suitable for all dose recommendations given

below. In such case other suitable/available dose forms or strengths of divalproex sodium should be used.

Mania

DICORATE ER tablets 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. In a reported placebo-controlled clinical trial of acute mania or mixed type, patients were dosed to a clinical response with a trough plasma concentration between 85 and 125 mcg/mL. The maximum recommended dosage is 60 mg/kg/day.

There is no body of reported evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during divalproex sodium 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 reported data to support the benefits of divalproex sodium extended-release tablets in such longer-term treatment (i.e., beyond 3 weeks).

Epilepsy

Divalproex sodium extended-release tablets are administered orally, and must be swallowed whole. As divalproex sodium dosage is titrated upward, concentrations of clonazepam, diazepam, ethosuximide, lamotrigine, tolbutamide, phenobarbital, carbamazepine, and/or phenytoin may be affected (see section 4.5)

Complex Partial Seizures
For adults and children 10 years of age or older.

Monotherapy (Initial Therapy)
Divalproex sodium has not been reported to be systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The

benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium 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

Divalproex sodium may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

In a reported study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to valproate, no adjustment of carbamazepine or phenytoin dosage was needed. However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs, periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see section 4.5).

Simple and Complex Absence Seizures

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.

A good correlation has not been reported between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients

with absence seizures is considered to range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations.

As the divalproex sodium dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see section 4.5).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Migraine
DICORATE ER tablets are indicated for prophylaxis of migraine headaches in adults.

The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1,000 mg once daily. Although doses other than 1,000 mg once daily of divalproex sodium have not been evaluated in patients with migraine, the effective dose range of divalproex sodium delayed-release tablets in these patients is 500-1,000 mg/day. As with other valproate products, doses of divalproex sodium should be individualized and dose adjustment may be necessary. If a patient requires smaller dose adjustments than that available with divalproex sodium extended release, divalproex sodium delayed release tablets should be used instead.

Conversion from divalproex sodium delayed release to divalproex sodium extended release

In adult patients and pediatric patients 10 years of age or older with epilepsy previously receiving divalproex sodium delayed release, divalproex sodium extended release should be administered once-daily using a dose 8 to 20% higher than the total daily dose of divalproex sodium delayed release (Table). For patients whose divalproex sodium delayed release total daily dose cannot be directly converted to divalproex sodium extended release, consideration may be given at the clinician's discretion to increase the patient's divalproex sodium delayed release total daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium extended release.

Table: Dose Conversion	
Divalproex sodium delayed release	**Divalproex sodium extended release**
Total Daily Dose (mg)	**(mg)**
500*-625	750
750*-875	1,000

1,000*-1,125	1,250
1,250-1,375	1,500
1,500-1,625	1,750
1,750	2,000
1,875-2,000	2,250
2,125-2,250	2,500
2,375	2,750
2,500-2,750	3,000
2,875	3,250
3,000-3,125	3,500

* These total daily doses of divalproex sodium delayed release cannot be directly converted to an 8 to 20% higher total daily dose of divalproex sodium extended release because the required dosing strengths of divalproex sodium extended release are not available. Consideration may be given at the clinician's discretion to increase the patient's divalproex sodium delayed release total daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium extended release.

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 divalproex sodium delayed release. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response

Dose-Related Adverse Reactions

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

G.I. Irritation

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

Compliance

Patients should be informed to take divalproex sodium tablets 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.

Dosing in Patients Taking Rufinamide

Patients stabilized on rufinamide before being prescribed valproate should begin valproate therapy at a low dose, and titrate to a clinically effective dose (see section 4.5).

Method of administration

DICORATE ER tablet is an extended-release product intended for once-a-day oral administration

DICORATE ER tablets should be swallowed whole and should not be crushed or chewed.

4.3 Contraindications

DICORATE ER tablets (divalproex sodium) are contraindicated in:

- patients with hepatic disease or significant hepatic dysfunction
- patients with 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
- patients with known hypersensitivity to the drug or to any of the excipients listed in section 6.1.
- patients with known urea cycle disorders
- For use in prophylaxis of migraine headaches: Divalproex sodium is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

BOXED WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity

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

Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When divalproex sodium 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 has been reported to be decreased 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). Divalproex sodium 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, divalproex sodium should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with divalproex sodium for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice.**

Fetal Risk

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

Valproate is therefore contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception. Valproate should not be used to treat women with epilepsy

Hepatotoxicity

General Information on Hepatotoxicity

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

Caution should be observed when administering valproate products to patients with a prior history of hepatic disease. 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. See below, "Patients with Known or Suspected Mitochondrial Disease."

Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When divalproex sodium 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

Divalproex sodium 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 (see section 4.3). 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 than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been reported 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, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice

for the diagnostic evaluation of such disorders. The A467T and W748S mutations were reported to be present in few patients with autosomal recessive POLG-related disorders.

In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, divalproex sodium should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with divalproex sodium 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.

Structural Birth Defects
Valproate can cause fetal harm when administered to a pregnant woman. Reported pregnancy data showed that maternal valproate use can cause neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations). 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. Reported 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. It has been reported 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. It was concluded from reported studies that, valproate exposure *in utero* can cause decreased IQ in children.

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

Use in Women of Childbearing Potential
Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death such as prophylaxis of migraine headaches (see section 4.3). Women should use effective contraception while using valproate.

Women of childbearing potential should be counseled regularly regarding the relative risks and benefits of valproate use during pregnancy. This is especially important for women planning a pregnancy and for girls at the onset of puberty; alternative therapeutic options should be considered for these patients.

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

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

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been reported as hemorrhagic with rapid progression from initial symptoms to death. Some cases have been reported 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. 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, divalproex sodium should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Urea Cycle Disorders

Divalproex sodium 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 urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of divalproex sodium 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 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 urea cycle disorders (see section 4.3).

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including divalproex sodium, 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.

The increased risk of suicidal thoughts or behavior with AEDs has been to be reported as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. The risk of suicidal thoughts or behavior beyond 24 weeks cannot be reported. The absolute risk differences were reported to be similar for both epilepsy and psychiatric indications.

Anyone considering prescribing divalproex sodium 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 reported to be 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.

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

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. Behaviours of concern should be reported immediately to healthcare providers.

Bleeding and Other Hematopoietic Disorders

Valproate is reported to be associated with dose-related thrombocytopenia. In the reported clinical trials of valproate as monotherapy in patients with epilepsy, 27% patients receiving approximately 50 mg/kg/day on average, had been reported to have at least one value of platelets $\leq 75 \times 10^9$/L. Platelet counts have been reported to be returns to normal upon discontinuation of the treatment. 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 reported study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥

110 mcg/mL (females) or ≥ 135 mcg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects. Valproate use has also been reported to be associated with decrease 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 sodium 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 (see section 4.3).

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 valproate has been reported to be 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 reaction is not reported due to a pharmacokinetic interaction. 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 valproate may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured (see section 4.3).

Hypothermia

Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with valproate therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproate after starting topiramate treatment or after increasing the daily dose of topiramate (see section 4.5). 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 valproate concentrations to sub-therapeutic levels, resulting in loss of seizure control. Serum valproate concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproate concentrations drop significantly or seizure control deteriorates.

Somnolence in the Elderly

A significant higher proportion of elderly patients with dementia were reported for somnolence upon receiving an increased dose of valproate by 125 mg/day to a target dose of 20 mg/kg/day. Discontinuation for somnolence have also been reported. In some patients with somnolence, reduced nutritional intake and weight loss have also been reported. 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 valproate may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy.

Effect on Ketone and Thyroid Function Tests
Valproate is reported to be 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
Valproate stimulates the replication of the HIV and CMV viruses under certain reported *in vitro* experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these reported findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these reported 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.

Medication Residue in the Stool
There have been rare reports of medication residue in the stool. Some patients have had anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In some reports, medication residues have been reported in the context of diarrhea. It is recommended that plasma valproate levels be checked in patients who experience medication residue in the stool, and patients' clinical condition should be monitored. If clinically indicated, alternative treatment may be considered.

Pediatric Use
Pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When divalproex sodium is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproate concentrations. Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that reportedly approximate those of adults.

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
A higher percentage of patients above 65 years of age were reported for accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally reported to be associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from pre-existing medical illness and concomitant medication use among these patients.

The starting dose should be reduced in elderly patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see section 4.2).

There is insufficient information available to discern the safety and effectiveness of valproate for the prophylaxis of migraines in patients over 65.

Excipient
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product

4.5 Interaction with other medicinal products and other forms of 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 (such as ritonavir), may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450

microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

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

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

Drugs for which a potentially important interaction has been reported

Aspirin
Co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients have been reported to decrease protein binding and an inhibition of metabolism of valproate. Valproate free fraction has been reported to increase 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OHvalproic acid, and 3-keto valproic acid was reported to be decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Carbapenem Antibiotics
A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics (for example, ertapenem, imipenem, meropenem; this is not a complete list) and may result in loss of seizure control. The mechanism of this interaction is not well understood. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates (see section 4.5).

Estrogen-Containing Hormonal Contraceptives
Estrogen-containing hormonal contraceptives may increase the clearance of valproate, which may result in decreased concentration of valproate and potentially increased seizure frequency. Prescribers should monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products.

Felbamate
An increase in mean valproate peak concentration by 35% have been reported when co-administered with felbamate (1,200 mg/day). On increasing the dose of felbamate to 2,400 mg/day the mean valproate peak concentration was reported to be increased by another 16%.
A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

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

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

Antacids
Co-administration of valproate 500 mg with commonly administered antacids did not report any effect on the extent of absorption of valproate.

Chlorpromazine
A 15% increase in trough plasma levels of valproate (200 mg BID) have been reported in schizophrenic patients, upon administration of chlorpromazine (100 to 300 mg/day).

Haloperidol
No significant changes in valproate (200 mg BID) trough plasma levels in schizophrenic patients have been reported, upon administration of 6 to 10 mg/day of haloperidol.

Cimetidine and Ranitidine
Cimetidine and ranitidine have not been reported to affect the clearance of valproate.

Effects of Valproate on Other Drugs
Valproate has been reported to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronosyltransferases.

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

Drugs for which a potentially important valproate interaction has been reported

Amitriptyline/Nortriptyline
A 21% decrease in plasma clearance of single dose amitriptyline (50 mg) and a 34% decrease in the net clearance of nortriptyline have been reported upon administration of valproate (500 mg BID).

Concurrent use of valproate and amitriptyline have been reported to increase amitriptyline level. Concurrent use of valproate and amitriptyline has rarely been associated with

toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/carbamazepine-10, 11-Epoxide
Upon co-administration of valproate and carbamazepine to epileptic patients, a decrease of 17% for carbamazepine and an increase of 45% for carbamazepine-10, 11 epoxide in serum levels.

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

Diazepam
Valproate have been reported to displace diazepam from its plasma albumin binding sites and inhibits its metabolism.

Co-administration of valproate (1,500 mg daily) have been reported to increase the free fraction of diazepam (10 mg) by 90% in healthy volunteers. Plasma clearance and volume of distribution for free diazepam have been reported to reduce by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide
Valproate have been reported to inhibit the metabolism of ethosuximide. Upon administration of a single ethosuximide dose of 500 mg with valproate (800 to 1,600 mg/ day) to healthy volunteers, a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance have been reported, as compared to ethosuximide alone.
Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine
Elimination half-life of lamotrigine have been reported to be increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital

Valproate was reported to inhibit the metabolism of phenobarbital. A 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose) have been reported upon co-administration of valproate (250 mg BID for 14 days) to normal subjects. The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

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

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

Phenytoin
Valproate has been reported to displace phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. A 60% increase in the free fraction of phenytoin have been reported upon co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers. Total plasma clearance and apparent volume of distribution of phenytoin have been reported to be increased by 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reported to be reduced by 25%.

In patients with epilepsy, breakthrough seizures have been reported with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Propofol
The concomitant use of valproate and propofol may lead to increased blood levels of propofol. Reduce the dose of propofol when co-administering with valproate. Monitor patients closely for signs of increased sedation or cardiorespiratory depression.

Rufinamide
The clearance of rufinamide has been reported to be decreased by valproate. Rufinamide concentrations have been reported to be increased by <16% to 70%, dependent on concentration of valproate (with the large increase being reported in pediatric patients at high doses or concentrations of valproate). Patients stabilized on rufinamide before being prescribed valproate should begin valproate therapy at a low dose, and titrate to a clinically effective dose. Similarly, patients on valproate should begin at a rufinamide dose lower than 10 mg/kg per day (pediatric patients) or 400 mg per day (adults).

Tolbutamide

The unbound fraction of tolbutamide was reported to be increased from 20% to 50% when added to plasma samples taken from patients (*in vitro*) treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin
Valproate have been reported to increase the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproate therapy is instituted in patients taking anticoagulants.

Zidovudine
The clearance of zidovudine (100 mg q8h) was reported to be decreased by 38% after administration of valproate (250 or 500 mg q8h) in patients; the half-life of zidovudine was reported to be unaffected.

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

Acetaminophen
Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to epileptic patients.

Clozapine
In psychotic patients, no interaction was reported when valproate was co-administered with clozapine.

Lithium
No effect on the steady-state kinetics of lithium have been reported upon co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers.

Lorazepam
Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers was reported for a 17% decrease in the plasma clearance of lorazepam.

Olanzapine
No dose adjustment for olanzapine is necessary when olanzapine is administered concomitantly with valproate. Co-administration of valproate (500 mg BID) and olanzapine (5 mg) to healthy adults have been reported to cause 15% reduction in C_{max} and 35% reduction in AUC of olanzapine.

Oral Contraceptive Steroids

No pharmacokinetic interaction have been reported upon co-administration of a single-dose of ethinyloestradiol (50 mcg)/levonorgestrel (250 mcg) to women on valproate (200 mg BID) therapy for 2 months.

Topiramate
Concomitant administration of valproate and topiramate has been reported to be associated with hyperammonemia with and without encephalopathy (see section 4.3 and 4.4). Concomitant administration of topiramate with valproate has also been reported to be associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary
For use in prophylaxis of migraine headaches, valproate is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception (see section 4.3).

For use in epilepsy or bipolar disorder, valproate should not be used to treat women who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable (see section 4.4). Women with epilepsy who become pregnant while taking valproate should not discontinue valproate abruptly, as this can precipitate status epilepticus with resulting maternal and fetal hypoxia and threat to life.

Maternal valproate use during pregnancy for any indication have been reported to increase the risk of congenital malformations, particularly neural tube defects including spina bifida, but also malformations involving other body systems (e.g., craniofacial defects including oral clefts, cardiovascular malformations, hypospadias, limb malformations). This risk is dose-dependent; however, a threshold dose below which no risk exists cannot be established. Valproate polytherapy with other AEDs has been reported to be associated with an increased frequency of congenital malformations compared with AED monotherapy. 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 reported to be about four times higher than the rate among babies born to epileptic mothers who used other anti-seizure monotherapies.

It has been reported that children exposed to valproate *in utero* have lower IQ scores and a higher risk of neurodevelopmental disorders compared to children exposed to either another AED *in utero* or to no AEDs *in utero*.

It was also reported that exposure to valproate products during pregnancy increases the risk of autism spectrum disorders.

In reported animal studies, valproate administration during pregnancy resulted in fetal structural malformations similar to those seen in humans and neurobehavioral deficits in the offspring at clinically relevant doses.

Hypoglycemia in neonates and fatal cases of hepatic failure in infants following maternal use of valproate during pregnancy have been reported.

Pregnant women taking valproate may develop hepatic failure or clotting abnormalities including thrombocytopenia, hypofibrinogenemia, and/or decrease in other coagulation factors, which may result in hemorrhagic complications in the neonate including death (see section 4.4).

Available prenatal diagnostic testing to detect neural tube and other defects should be offered to pregnant women using valproate.

Folic acid supplementation prior to conception and during the first trimester of pregnancy have been reported to decrease 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 (see section 4.4).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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.

Maternal adverse reactions

Pregnant women taking valproate may develop clotting abnormalities including thrombocytopenia, hypofibrinogenemia, and/or decrease in other coagulation factors,

which may result in hemorrhagic complications in the neonate including death. If valproate is used in pregnancy, the clotting parameters should be monitored carefully in the mother. If abnormal in the mother, then these parameters should also be monitored in the neonate.

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

Hypoglycemia has been reported in neonates whose mothers have taken valproate during pregnancy.

Lactation

Risk Summary

Valproate is reported to be excreted in human milk. Reported data describe the presence of valproate in human milk (range: 0.4 mcg/mL to 3.9 mcg/mL), corresponding to 1% to 10% of maternal serum levels. Children up to six years of age have not been reported for adverse developmental or cognitive effects following exposure to valproate *via* breast milk.

There are no reported data to assess the effects of divalproex sodium on milk production or excretion.

Clinical Considerations

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for divalproex sodium and any potential adverse effects on the breastfed child from divalproex sodium or from the underlying maternal condition.

Monitor the breastfed infant for signs of liver damage including jaundice and unusual bruising or bleeding. Hepatic failure and clotting abnormalities have been reported in offspring of women who used valproate during pregnancy.

Fertility

Women of childbearing potential should use effective contraception while taking valproate (see section 4.4). This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death such as prophylaxis of migraine headaches (see sections 4.3).

Male infertility coincident with valproate therapy have been reported.

In reported animal studies, oral administration of valproate at clinically relevant doses resulted in adverse reproductive effects in males.

4.7 Effects on ability to drive and use machines

Divalproex sodium can affect the ability to drive and use machines. Undesirable effects such as dizziness or drowsiness have been reported with the use of divalproex sodium. Divalproex sodium can slow thinking and motor skills. If affected, patients should not drive or use machines.

4.8 Undesirable effects

The following serious adverse reactions are described below and elsewhere in the document:

- Hepatic failure (see section 4.4)
- Birth defects (see section 4.4)
- Decreased IQ following *in utero* exposure (see section 4.4)
- Pancreatitis (see section 4.4)
- Hyperammonemic encephalopathy (see section 4.4)
- Suicidal behaviour and ideation (see section 4.4)
- Bleeding and other hematopoietic disorders (see section 4.4)
- Hypothermia (see section 4.4)
- Drug reaction with eosinophilia and systemic symptoms (dress)/multiorgan hypersensitivity reactions (see section 4.4)
- Somnolence in the elderly (see section 4.4)

Mania

The incidence of treatment-emergent events has been ascertained based on combined data from reported clinical trials of divalproex sodium in the treatment of manic episodes associated with bipolar disorder.

Table: Adverse Reactions Reported by > 5% of Divalproex Sodium-Treated Patients of Acute Mania[1]

Adverse Event	Divalproex Sodium ER (%)	Placebo (%)
Somnolence	26	14
Dyspepsia	23	11
Nausea	19	13
Vomiting	13	5
Diarrhea	12	8

Dizziness	12	7
Pain	11	10
Abdominal Pain	10	5
Accidental Injury	6	5
Asthenia	6	5
Pharyngitis	6	5
[1] The following adverse reactions/event occurred at an equal or greater incidence for placebo than for divalproex Sodium extended release: headache		

The following additional adverse reactions were reported by greater than 1% of the divalproex sodium-treated patients in reported controlled clinical trials:

Body as a Whole: Back Pain, Chills, Chills and Fever, Drug level increased, Flu syndrome, Infection, Infection fungal, Neck rigidity.
Cardiovascular System: Arrhythmia, Hypertension, Hypotension, Postural Hypotension
Digestive System: Constipation, Dry Mouth, Dysphagia, Fecal Incontinence, Flatulence, Gastroenteritis, Glossitis, Gum Hemorrhage, Mouth Ulceration.
Hemic and Lymphatic System: Anemia, Bleeding Time Increased, Ecchymosis, Leucopenia.
Metabolic and Nutritional Disorders: Hypoproteinemia, Peripheral Edema.
Musculoskeletal System: Arthrosis, Myalgia.
Nervous System: Abnormal Gait, Agitation, Catatonic Reaction, Dysarthria, Hallucinations, Hypertonia, Hypokinesia, Psychosis, Reflexes Increased, Sleep Disorder, Tardive Dyskinesia, Tremor.
Respiratory System: Hiccup, Rhinitis.
Skin and Appendages: Discoid Lupus Erythematosus, Erythema Nodosum, Furunculosis, Maculopapular Rash, Pruritus, Rash, Seborrhea, Sweating, Vesiculobullous Rash.
Special Senses: Conjunctivitis, Dry Eyes, Eye Disorder, Eye Pain, Photophobia, Taste Perversion.
Urogenital System: Cystitis, Urinary Tract Infection, Menstrual Disorder, Vaginitis.

Epilepsy
Divalproex sodium was generally well tolerated with most adverse reactions rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the divalproex sodium-treated patients.

Table below lists treatment-emergent adverse reactions which were reported by ≥ 5% of divalproex sodium-treated patients 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 divalproex sodium alone, or the combination of divalproex sodium and other antiepilepsy drugs.

Table: Adverse Reactions Reported by ≥ 5% of Patients Treated with Valporate for Complex Partial Seizures

Body System/Reaction	**Divalproex Sodium (%)**	**Placebo (%)**
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

Body System/Reaction	Divalproex Sodium (%)	Placebo (%)
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0

Table below 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, with divalproex sodium 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 divalproex sodium alone, or the combination of valproate and other antiepilepsy drugs.

Table: Adverse Reactions Reported by ≥ 5% of Patients in the High Dose Group in the Controlled Trial of Valproate Monotherapy for Complex Partial Seizures[1]

Body System/Reaction	High Dose (%)	Low Dose (%)
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

Body System/Reaction	High Dose (%)	Low Dose (%)
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

[1]Headache was the only adverse reaction 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% in patients treated with valproate for complex partial seizures:
Body as a Whole: Back pain, chest pain, malaise.
Cardiovascular System: Tachycardia, hypertension, palpitation.
Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System: Petechia.
Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.
Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.

Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages: Rash, pruritus, dry skin.
Special Senses: Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Migraine
Valproate was generally well tolerated with most adverse reactions rated as mild to moderate in severity. The adverse reactions reported in long-term extension study as the primary reason for discontinuation by ≥ 1% of 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%).

Below table presents adverse reactions reported for patients, with incidence rate greater than 5% in divalproex sodium-treated group and greater than that for placebo patients.

Table: Adverse Reactions Reported by > 5% of Divalproex Sodium ER-Treated Patients during Migraine[1]

Body System Event	Divalproex Sodium ER (%)	Placebo (%)
Gastrointestinal System		
Nausea	15	9
Dyspepsia	7	4
Diarrhea	7	3
Vomiting	7	2
Abdominal Pain	7	5
Nervous System		
Somnolence	7	2
Other		
Infection	15	14

[1] The following adverse reactions occurred in greater than 5% of divalproex Sodium ER-treated patients and at a greater incidence for placebo than for divalproex Sodium ER: asthenia and flu syndrome.

The following additional adverse reactions were reported by greater than 1% but not more than 5% of divalproex sodium-treated patients and with a greater incidence than placebo in reported trial for migraine prophylaxis:

Body as a Whole: Accidental injury, viral infection.
Digestive System: Increased appetite, tooth disorder.
Metabolic and Nutritional Disorders: Edema, weight gain.
Nervous System: Abnormal gait, dizziness, hypertonia, insomnia, nervousness, tremor, vertigo.
Respiratory System: Pharyngitis, rhinitis.
Skin and Appendages: Rash.
Special Senses: Tinnitus.

Below table presents adverse reactions reported for patients, with incidence rate greater than 5% in valproate-treated group and greater than that for placebo patients.

Table: Adverse Reactions Reported by > 5% of Valproate-Treated Patients during Migraine[1]

Body System Reaction	**Divalproex sodium (%)**	**Placebo (%)**
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

[1] The following adverse reactions occurred in greater than 5% of divalproex sodium-treated patients and at a greater incidence for placebo than for divalproex Sodium: flu syndrome and pharyngitis.

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

Body as a Whole: Chest pain
Cardiovascular System: Vasodilatation.
Digestive System: Constipation, dry mouth, flatulence and stomatitis.
Hemic and Lymphatic System: Ecchymosis.
Metabolic and Nutritional Disorders: Peripheral edema
Musculoskeletal System: Leg cramps
Nervous System: Abnormal dreams, confusion, paresthesia, speech disorder and thinking abnormalities
Respiratory System: Dyspnea and sinusitis.
Skin and Appendages: Pruritus
Urogenital System: Metrorrhagia

Post-Marketing Experience

Dermatologic: Hair texture changes, hair color changes, photosensitivity, erythema multiforme, toxic epidermal necrolysis, nail and nail bed disorders, and Stevens-Johnson syndrome.

Psychiatric: Emotional upset, psychosis, aggression, psychomotor hyperactivity, hostility, disturbance in attention, learning disorder, and behavioral deterioration.
Neurologic: Paradoxical convulsion, parkinsonism

Acute or sub-acute cognitive decline and behavioral changes (apathy or irritability) with cerebral pseudoatrophy on imaging were reported to be associated with valproate therapy; both the cognitive/behavioral changes and cerebral pseudoatrophy have been reported to be reversed partially or fully after valproate discontinuation.

Acute or subacute encephalopathy have been reported in the absence of elevated ammonia levels, elevated valproate levels, or neuroimaging changes. The encephalopathy has been reported to be reversed partially or fully after valproate discontinuation.

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

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

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

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Metabolism and nutrition: Weight gain.

Reproductive: Aspermia, azoospermia, decreased sperm count, decreased spermatozoa motility, male infertility, and abnormal spermatozoa morphology.

Genitourinary: Enuresis and urinary tract infection.

Special Senses: Hearing loss.

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

4.9 Overdose

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

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticonvulsant, Antimanic, Antimigraine
ATC code: N03AG01

Mechanism of action:

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been reported to be established. It has been reported that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

PK/PD relationship

The relationship between plasma concentration and clinical response is not well reported. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

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

Epilepsy

The therapeutic range in epilepsy is commonly considered to be 50 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Mania

In reported studies of acute mania, patients were dosed to clinical response with trough plasma concentrations between 50 and 125 mcg/mL.

5.2 Pharmacokinetic properties

Absorption/Bioavailability

The absolute bioavailability of divalproex sodium extended release tablets administered as a single dose after a meal was approximately 90% relative to intravenous infusion.

When given in equal total daily doses, the bioavailability of divalproex sodium extended release tablets is less than that of divalproex sodium delayed-release tablets. In reported study the median time to maximum plasma valproate concentrations (C_{max}) after divalproex sodium extended release tablets administration ranged from 4 to 17 hours. After multiple once-daily dosing of divalproex sodium extended release tablets, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular divalproex sodium delayed-release tablets given BID, TID, or QID.

Conversion from divalproex sodium delayed-release tablets to divalproex sodium extended release tablets

When divalproex sodium extended-release tablets are given in doses 8 to 20% higher than the total daily dose of divalproex sodium delayed-release tablets, the two formulations are bioequivalent. In reported studies, divalproex sodium extended-release tablets and divalproex sodium delayed-release tablets regimens were equivalent with respect to area under the curve (AUC; a measure of the extent of bioavailability). Additionally, valproate C_{max} was lower, and C_{min} was either higher or not different, for divalproex sodium extended-release tablets relative to divalproex sodium delayed-release tablets regimens.

Concomitant antiepilepsy drugs (topiramate, phenobarbital, carbamazepine, phenytoin, and lamotrigine were evaluated) that induce the cytochrome P450 isozyme system did not significantly alter valproate bioavailability when converting between divalproex sodium delayed-release tablets and divalproex sodium extended-release tablets.

Distribution

Protein Binding

The plasma protein binding of valproate is reported to be concentration dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Protein binding of valproate is reported to be reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide).

CNS Distribution

Valproate concentrations have been reported in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism

Valproate is reported to be metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose reportedly appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other reported major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is reported to be eliminated by other oxidative mechanisms. Less than 3% of an administered dose is reported to be excreted unchanged in urine.

The relationship between dose and total valproate concentration is reported to be nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are reported to be linear.

Excretion

Mean plasma clearance and volume of distribution for total valproate are reported to be 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 reported to be 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean

terminal half-life for valproate monotherapy have been reported to be ranged from 9 to 16 hours following oral dosing regimens of 250 to 1,000 mg.

The reported estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Pharmacokinetics in special populations

Effect of Age

Pediatric
The valproate pharmacokinetic profile following administration of divalproex sodium extended-release tablets was characterized in a reported study in children and adolescents. Divalproex sodium extended-release tablets once daily doses ranged from 250-1,750 mg. Once daily administration of divalproex sodium extended-release tablets in pediatric patients (10-17 years) produced plasma VPA concentration-time profiles similar to those that have been reported in adults.

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

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

Effect of Race
The effects of race on the kinetics of valproate have not been reported to be studied.

Effect of Disease

Liver Disease
Liver disease have been reported to impair the capacity to eliminate valproate. In a reported study, the clearance of free valproate was decreased by 50% in patients with cirrhosis and by 16% in patients with acute hepatitis, compared with healthy subjects. In that study, the half-life of valproate was reported to be increased from 12 to 18 hours. Liver disease is also reported to be 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 reported to be substantially reduced; thus, monitoring total concentrations may be misleading.

5.3 Preclinical safety data

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

Administration of valproate have been reported for testicular atrophy and reduced spermatogenesis at oral doses of 400 mg/kg/day or greater in rats (approximately equal to or greater than the maximum recommended human dose (MRHD) on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately equal to or greater than the MRHD on a mg/m^2 basis). No effect on fertility have been reported at oral doses of valproate up to 350 mg/kg/day (approximately equal to the MRHD on a mg/m^2 basis) for 60 days in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DICORATE ER 250

Hydrogenated Castor Oil, Anhydrous Lactose, Hypromellose 2208, Talc, Magnesium Stearate, Silicon Dioxide, Opadry 03F58739 White.

Opadry 03F58739 White contains: Hypromellose, Titanium Dioxide, Macrogol/PEG, Talc

DICORATE ER 500
Hydrogenated Castor Oil, Anhydrous Lactose, Hypromellose 2208, Talc, Magnesium Stearate, Silicon Dioxide, Opadry 03F57509 Gray.

Opadry 03F57509 Gray Contains: HPMC 2910/Hypromellose, Titanium Dioxide, Macrogol/PEG, Talc, Ferrosoferric Oxide (NF)/Black Iron Oxide, Iron Oxide Yellow, Iron Oxide Red.

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in original Package in order to protect from light.

6.5 Nature and contents of container

DICORATE ER 250/500 tablets are supplied in alu-alu blister packs further packed in to a carton along with package insert.

Each blisters contain s 10 tablets. 05 alu-alu blisters are pack in a carton.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited,Sun House, Plot No. 201 B/1 Western, Express Highway, Goregaon (East), Mumbai, - 400063 India.

MANUFACTURER:

Sun Pharmaceutical Industries Limited, Survey No. 214, Plot No. 20, G.I.A. Phase II, Piparia, Silvassa 396320, U.T. of Dadra and Nagar Haveli, India.

8. MARKET AUTHORIZATION NUMBER: TAN 21 HM 0190

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be provided

10. DATE OF REVISION OF THE TEXT

February 2021