DEPAKOTE ER
Divalproex Sodium Extended – Release Tablets

WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity

General Population: **Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months *[see Warnings and Precautions (5.1)]*.**

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 Depakote ER 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). Depakote ER 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 Contraindications (4)]*. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakote ER should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakote ER 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 *[see Warnings and Precautions (5.1)]*.**

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 *[see Contraindications (4)].* 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 *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

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

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated *[see Warnings and Precautions (5.5)]*.

NAME OF THE MEDICINAL PRODUCT

Divalproex Sodium Extended-Release Tablets:
250 mg, extended-release tablets
500 mg, extended-release tablets

Trademark is authorized as
Depakote ER

QUALITATIVE AND QUANTITATIVE COMPOSITION

Divalproex sodium extended-release tablets contain divalproex sodium in a once-a-day extended release formulation equivalent to 250 and 500 mg of valproic acid.

For the full list of excipients, see section List of Excipients.

Excipients with known effect:

Depakote 250 mg extended-release tablets:
The coating of the tablet contains Lactose.

Depakote 500 mg extended-release tablets:
This medicine contains Lactose.

PHARMACEUTICAL FORM

Depakote 250 mg, extended-release tablets:
White to off white ovaloid tablets with the embossed of Abbott logo on one side of the tablet.

Depakote 500 mg, extended-release tablets:
Gray ovaloid tablets with the embossed of Abbott logo on one side of the tablet.

CLINICAL PARTICULARS

Therapeutic indications

Mania

Divalproex sodium extended-release tablets 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 judgement, 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 efficacy of divalproex sodium extended-release tablets is based in part on studies of divalproex sodium delayed release tablets in this indication, and was confirmed in a 3-week trial with patients meeting DSM-IV TR criteria for bipolar I disorder, manic or mixed type, who were hospitalized for acute mania (see section **PHARMACODYNAMIC PROPERTIES** - *Clinical Studies*).

The effectiveness of divalproex sodium extended-release tablets for long-term use in mania, i.e., more than 3 weeks, has not been demonstrated in controlled clinical trials. Therefore, physicians who elect to use divalproex sodium extended-release tablets for extended periods should continually reevaluate the long-term risk and benefits of the drug for the individual patient.

Epilepsy

Divalproex sodium extended-release tablets are indicated as monotherapy and adjunctive therapy in the treatment of adults and children 10 years of age or older with complex partial seizures that occur either in isolation or in association with other types of seizure.

Divalproex sodium extended-release 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

Divalproex sodium extended-release is indicated for prophylaxis of migraine headaches in adults. There is no evidence that divalproex sodium extended-release is useful in the acute treatment of migraine headaches. Because valproic acid may be a hazard to the fetus, divalproex sodium extended-release should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patients and weighed against the potential benfits of treatment. (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE –** Women of Childbearing Potential*).*

See section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** for statement regarding fatal hepatic dysfunction.

Posology and method of administration

General

Divalproex sodium extended-release tablet is an extended-release product intended for once-a-day administration.

Divalproex sodium extended-release tablets should be swallowed whole and should not be crushed or chewed. A divalproex sodium extended-release tablet is an extended-release product intended or once-a-day administration.

Mania

Divalproex sodium extended-release 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 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 evidence available from controlled trials to guide a clinician in the longer term management of a patient who improves during divalproex sodium extended-release tablets 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 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 indicated as monotherapy and adjunctive therapy in complex partial seizures, and in simple and complex absence seizures in dults and pediatric patients 10 years of age or older. As the divalproex sodium extended-release tablets dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see DRUG INTERACTIONS).

Complex Partial Seizures (CPS)

For adults and children ten years of age or older.

Monotherapy (Initial Therapy)

Divalproex sodium has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL).

No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.
The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - Thrombocytopenia).

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 to 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 two weeks. This reduction may be started at initiation of divalproex sodium therapy, or delayed by one to two 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 extended-release tablets 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 to100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium extended-release tablets, no adjustment of carbamazepine or phenytoin dosage was needed (see **PHARMACODYNAMIC PROPERTIES** - *Clinical Studies*). 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 **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Simple and Complex Absence Seizures
For adults and children 10 years of age and 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.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, a therapeutic valproate serum concentration 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 (see section PHARMACODYNAMIC PROPERTIES - Clinical Studies).

As the divalproex sodium extended-release tablets dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see section PHARMACOLOGICAL PROPERTIES).

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 Prophylaxis

The recommended starting dose is 500 mg once daily for one week, thereafter increasing to 1,000 mg once daily. Although doses other than 1,000 mg once daily of divalproex sodium extended-release have not been evaluated in patients with migraine, the effective dose range of divalproex sodium enteric-coated tablets in these patients is 500 to 1,000 mg/day. As with other valproate products, doses of divalproex sodium extended-release should be individualized and dose adjustment may be necessary. Divalproex sodium extended-release tablets are not bioequivalent to divalproex sodium enteric-coated tablets (see section **PHARMACODYNAMIC PROPERTIES** - *Clinical Studies*). If a patient requires smaller dose adjustments than that available with divalproex sodium extended-release, divalproex sodium enteric-coated tablets should be used instead.

Conversion to Divalproex Sodium Extended-Release

In adult patients and pediatric patients 10 years of age or older with epilepsy previously receiving divalproex sodium, the divalproex sodium ER tablet should be administered once-daily using 8 to 20% higher than the total daily dose of divalproex sodium (see Table 1). For patients whose divalproex sodium total daily dose can not be directly converted to divalproex sodium ER tablet, consideration may be given at the clinician's discretions to increase the patient's divalproex sodium total daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium ER tablet. There is insufficient data to allow a conversion factor recommendation for patients with divalproex sodium doses above 3,125 mg/day.

Table 1
Dose Conversion

Divalproex Sodium Total Daily Dose (mg)	**Divalproex Sodium Extended-Release Tablet (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 cannot be directly converted to an 8 to 20% higher total daily dose of divalproex sodium ER tablet because the required dosing strengths of divalproex sodium ER tablet are not available. Consideration may be given at the clinician's discretions to increase the patient's divalproex daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium ER tablet.	

Plasma valproate Cmin concentrations for divalproex sodium ER tablet are equivalent to divalproex sodium, but may vary across patients after conversion. If satisfactory clinical response has not been achieved, plasma levels should be measure to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL).

General Dosage Advice

Dosing in Elderly Patients

Due to a decrease in clearance of unbound 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 other divalproex sodium formulations. 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 (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Somnolence in the Elderly* and **PHARMACOLOGIC PROPERTIES** - *Geriatric*).

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 mcg/mL (females) or ≥ 135 mcg/mL (males) (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Thrombocytopenia). 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 divalproex sodium enteric-coated tablets.

Compliance

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

Contraindications

Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic dysfunction (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - Hepatotoxicity).

Divalproex sodium 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.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - Multi-Organ Hypersensitivity Reactions).

Divalproex sodium is contraindicated in patients with known urea cycle disorders (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** – Hyperammonemia- Urea Cycle Disorders).

Divalproex sodium is contraindicated in the following situation:
Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **PREGNANCY AND LACTATION**).
- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned in section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **PREGNANCY AND LACTATION** are met.

Treatment of mania and prophylaxis of migraine attacks

- in pregnancy (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **PREGNANCY AND LACTATION**).
- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned in section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **PREGNANCY AND LACTATION**).

Divalproex sodium is contraindicated in patients with porphyria.

Special warnings and precautions for use

Hepatotoxicity/ Hepatic dysfunction
Conditions of occurrence: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment.

Caution should be observed when administering divalproex sodium 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 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 this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Suggestive signs: 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.

Detection: Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

The use of divalproex sodium extended-release in children is not recommended for the prophylaxis of migraine headaches (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Pediatric Use*).
The drug should be discontinued immediately in the presence of significant hepatic dysfunction,suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug (see section **CONTRAINDICATIONS**).

Patiens 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 than those without these syndromes (see section **CONTRAINDICATIONS**).

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 testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such 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 liver function test monitoring.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving Divalproex sodium. 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 re-challenge with valproate. In clinical trials, there were two cases of pancreatitis without alternative etiology in 2,416 patients, representing 1,044 patient-years experience. Patients and guardians experiencing abdominal pain, nausea, vomiting, and/or anorexia should be warned that these could 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.

Suicidal Behavior and Ideation

An increase in the risk of suicidal thoughts or behavior in patients taking antiepileptic drugs (AEDs) for any indication has been reported. 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. 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 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 associated with morbidity and an increase risk of suicidal thoughts and behavior. Should suicidal thoughts and behaviors 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 (and caregivers of patients) 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 thought about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Interaction with Carbapenem Antibiotics

The concomitant use of INN and carbapenem agents is not recommended (*see section* **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** – *Carbapenem Antibiotics).*

Thrombocytopenia - (*see section* ***SPECIAL WARNINGS AND PRECAUTIONS FOR USE - General)***

Female children/Female adolescents/Women of childbearing potential/Pregnancy:

Divalproex sodium has a high teratogenic potential and children exposed in utero to Divalproex sodium have a high risk for congenital malformations and neurodevelopmental disorders (see section *PREGNANCY AND LACTATION*).

Divalproex sodium is contraindicated in the following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see section *see section* ***SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** and ***PREGNANCY AND LACTATION***).
- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned below and in sections **CONTRAINDICATIONS** and **PREGNANCY AND LACTATION** are met.

Treatment of mania and prophylaxis of migraine attacks

- in pregnancy (see section ***SPECIAL WARNINGS AND PRECAUTIONS FOR USE*** and ***PREGNANCY AND LACTATION***).

- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned below and in sections **CONTRAINDICATIONS** and **PREGNANCY AND LACTATION** are met.

The treating physician must ensure that

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to Divalproex Sodium
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with Divalproex Sodium.
- the patient understands the need for regular (at least annual) review of treatment by the treating physician, preferably by a specialist experienced in the management of epilepsy, or mania or prophylaxis of migraine.
- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the hazards and necessary precautions associated with Divalproex sodium use and the need to urgently consult her physician in case of pregnancy.
- the patient has received the patient guide.

These conditions also concern women who are not currently sexually active unless the treating physician considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

- The treating physician must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using Divalproex sodium experiences menarche.

The treating physician must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to Divalproex sodium in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for Divalproex sodium therapy annually and consider alternative treatment options. If Divalproex sodium is the only suitable treatment, the need for using effective contraception and all other measures as described in section **CONTRAINDICATIONS, SPECIAL WARNINGS AND PRECAUTIONS FOR USE,** and **PREGNANCY AND LACTATION** should be discussed. Every effort should be made by

the specialist to switch the female children to alternative treatment before they reach child bearing potential.

Pregnancy must be excluded before start of treatment with Divalproex sodium.

Contraception

Women of childbearing potential who are prescribed Divalproex sodium must use effective contraception, without interruption during the entire duration of treatment with Divalproex sodium. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews preferably by a specialist

The treating physician should at least annually review whether Divalproex sodium is the most suitable treatment for the patient.

The treating physician should ensure the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to Divalproex sodium in utero.

Pregnancy planning.

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess Divalproex sodium therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section PREGNANCY AND LACTATION). If switching is not possible, the woman should receive further counselling regarding the Divalproex sodium risks for the unborn child to support her informed decision making regarding family planning.

For the indications mania and prophylaxis of migraine, if a woman is planning to become pregnant a specialist experienced in the management of mania and prophylaxis of migraine must be consulted and treatment with Valproic Acid should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy

In case of pregnancy, the patient should immediately contact a specialist/ physician to re-evaluate treatment and consider alternative options.

Pharmacist must ensure that

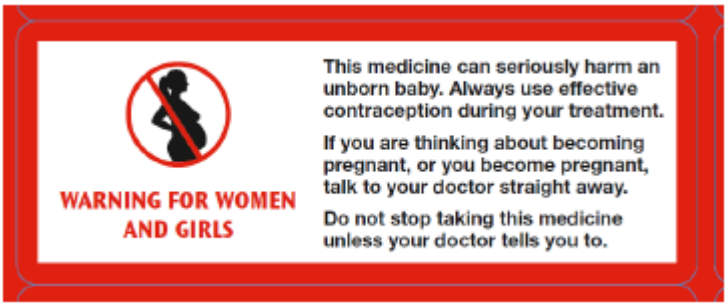
- the patients are advised not to stop Divalproex sodium medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to Divalproex sodium during pregnancy, the Marketing Authorization Holder has provided educational materials like a physician guide to reinforce the warnings and provide guidance regarding use of Divalproex sodium in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide should be provided to all women of childbearing potential using Divalproex sodium.

Visual reminder

In order to inform and remind patients about avoiding exposure to Divalproex sodium during pregnancy, the Marketing Authorization Holder has added a pictogram and warning to its outer packaging



Hyperammonemia

Hyperammonemia has been reported in association with divalproex sodium 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 measured. Hyperammonemia should also be considered in patients who present with hypothermia (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hypothermia*). If ammonia is increased, divalproex sodium 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 **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE)**

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.

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 initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with 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, 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 **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use*).

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hypothermia*). 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 (see section **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Urea Cycle Disorders* and *Hyperammonemia*).

Hypothermia

Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with divalproex sodium 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 **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** - *Topiramate* and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use*, and *Hyperammonemia*). 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.

Brain Atrophy

There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use valproate products; in some cases, patients recovered with permanent sequelae (see section **UNDESIRABLE EFFECTS**). The motor and cognitive functions of patients on valproate should be routinely monitored and drug should be discontinued in the presence of suspected or apparent signs of brain atrophy.

Reports of cerebral atrophy with various forms of neurological problems including developmental delays and psychomotor impairment have also been reported in children who were exposed in-utero to valproate products (see section **PREGNANCY AND LACTATION**).

General

Laboratory test: Because of reports of thrombocytopenia (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Thrombocytopenia*), inhibition of the secondary phase of platelet

aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. Prior to planned surgery it is recommended that patients receiving divalproex sodium be monitored for platelet count and coagulation parameters. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since divalproex sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Divalproex sodium is partially eliminated in the urine as a keto-metabolite that 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.

Recommendations:
Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.
Since divalproex sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

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.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The therapeutic benefit that may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Multi-Organ Hypersensitivity Reactions
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multi-organ hypersensitivity reactions have been rarely reported in close temporal association after the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported.

Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, hepato-renal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs not noted here may occur. If this reaction is suspected, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Information for Patients

Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia could be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.

Patients and guardians should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hyperammonemia*) and should be told to inform the prescriber if any of these symptoms occur.

Information for Female Patients

Since divalproex sodium has been associated with certain types of birth defects and developmental risk, female patients of childbearing age considering the use of divalproex sodium should be advised of the risks associated with the use of divalproex sodium during pregnancy (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Usage in Pregnancy and* **PREGNANCY AND LACTATION**).

Medication residue in the stool

There have been rare reports of medication residue in the stool, some of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In some reports, medication residues have occurred 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

Experience 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 (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hepatotoxicity*). Above the age of two years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

The safety and effectiveness of divalproex sodium extended release tablets for the prophylaxis of migraine headaches has not been established in patients below the age of 18 years.

The safety and effectiveness of divalproex sodium extended-release tablets for the treatment of complex partial seizures, simple and complex absence seizures, and multiple seizures types that include absence seizures has not been established in pediatric patients under the age of ten years.

Geriatric Use

Safety and effectiveness of divalproex sodium extended-release in the prophylaxis of migraine patients over 65 have not been established.

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

Somnolence in the elderly: 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 (see section **POSOLOGY AND METHOD OF ADMINISTRATION**).
In elderly patients, 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 (see section **POSOLOGY AND METHOD OF ADMINISTRATION**).

Information related to excipients

Depakote 250 and 500mg Extended Release Tablets:

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

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 betaoxidation.

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.

Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased four-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Divalproex sodium extended-release is not indicated for use in children (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** – *Pediatric Use*). Whether or not the interaction observed in this study applies to adults is unknown, but 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 (ertapenem, imipenem, meropenem) 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.

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, preferably during on-off intervals of the hormonal contraceptive cycle.

Felbamate - A study involving the co-administration of 1,200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentrations by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2,400

mg/day increased the mean valproate peak concentrations to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

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

Protease inhibitors- Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma level when co administered.
Cholestyramine- Cholestyramine may lead to a decrease in plasma level of valproate when coadministered.

Drugs For Which Either No Interaction or a Likely Clinically Unimportant Interaction Has Been Observed

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

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

Haloperidol - A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg b.i.d.) 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. The following list provides information about the potential for an influence of valproate coadministration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported

Drugs For Which a Potentially Important Valproate Interaction Has Been Observed

Amitriptyline/Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (ten males and five females) who received valproate (500 mg b.i.d.) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking

valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortripytline in the presence of valproate.

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

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

Diazepam -Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1,500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide - Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1,600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

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

Phenobarbital - Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg b.i.d. for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate. There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone - Primidone is metabolized into a barbiturate and therefore, may also be involved in a similar interaction with valproate as phenobarbital.

Propofol - A clinically significant interaction between valproate and propofol may occur leading to an increased blood level of propofol. Therefore, when co-administered with valproate, the dose of propofol should be reduced.

Phenytoin - Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg t.i.d.) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate.
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.
Valproic acid serum levels may be increased in case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia.
Nimodipine - Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50 %.

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.

Topiramate – **and acetazolamide** Concomitant administration of valproate and topiramate or acetazolamide has been associated with hyperammonemia with and without encephalopathy.
Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.
Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. Blood ammonia levels should be measured in patients with reported onset of hypothermia (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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

Zidovudine - In six patients, who were seropositive for HIV, the clearance of zidovudine (100 mg every eight hours) was decreased by 38% after administration of valproate (250 or 500 mg every eight hours); the half-life of zidovudine was unaffected.

Quetiapine - Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.

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.

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

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

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

Olanzapine - Valproic acid may decrease the olanzapine plasma concentration.

Rufinamide - Valproic acid may lead to an increase in plasma level of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

Oral Contraceptive Steroids - Administration of a single-dose of ethinyloestradiol (50 mcg) / levonorgestrel (250 mcg) to six women on valproate (200 mg b.i.d.) therapy for two months did not reveal any pharmacokinetic interaction.

Fertility, Pregnancy and Lactation

Divalproex sodium is contraindicated as treatment for mania and prophylaxis of migraine during pregnancy. Divalproex sodium is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Divalproex sodium is contraindicated for use in women of childbearing potential unless the measures for prevention of pregnancy as mentioned in sections **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** are met.

Valproate was shown to cross the placental barrier both in animal species and in humans (see section Pharmacokinetic Properties).

Pregnancy Exposure Risk related to Divalproex sodium

Both valproate monotherapy and Divalproex sodium polytherapy are frequently associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including Divalproex sodium is associated with a greater risk of congenital malformations than Divalproex sodium monotherapy.

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to Divalproex sodium monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established based on available data. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

In utero exposure to valproate may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function.
Cases describe both unilateral and bilateral deafness or hearing impairment. Monitoring of signs and symptoms of ototoxicity is recommended.

Developmental disorders

Data have shown that exposure to Divalproex sodium in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to Divalproex sodium show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems, possibly indicating neurodevelopmental defects. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of Divalproex sodium exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics.

Although the role of confounding factors cannot be excluded, there is evidence in children exposed to Divalproex sodium that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes. Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.
Available data suggest that children exposed to valproate *in utero* are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the general population.

Female children, female adolescents and woman of childbearing potential

If a Woman wants to plan a Pregnancy

- *For epilepsy indication*: During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
- *For epilepsy and/ or mania/bipolar disorder indication:* In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed
- *For epilepsy and/ or mania/bipolar disorder indication:* If a woman plans a pregnancy or becomes pregnant, valproate therapy should be stopped.
- *For epilepsy and/ or mania/bipolar disorder indication:* In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

If a woman plans a pregnancy

For the indication epilepsy, if a woman is planning to become pregnant, a specialist (preferably) experienced in the management of epilepsy, must reassess Divalproex sodium therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If switching is not possible, the woman should receive further counselling regarding the Divalproex sodium risks for the unborn child to support her informed decision making regarding family planning.

For the indication(s) mania and prophylaxis of migraine, if a woman is planning to become pregnant, preferably a specialist experienced in the management of mania or prophylaxis of migraine must be consulted and treatment with Divalproex sodium/Valproate sodium/ Valproic Acid should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

Pregnant women

Divalproex sodium as treatment for mania and prophylaxis of migraine attacks is contraindicated for use during pregnancy. Divalproex sodium as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections CONTRAINDICATIONS and SPECIAL WARNINGS AND PRECAUTIONS FOR USE), as evaluated and decided by the treating physician.

If a woman using Divalproex sodium becomes pregnant, she must be immediately referred to a specialist (preferably) to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of Divalproex sodium in pregnancy and after careful consideration of alternative treatment preferably by the specialist, in exceptional circumstances a pregnant woman must receive Divalproex sodium/Valproate sodium/ Valproic Acid for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of Divalproex sodium into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section POSOLOGY AND METHOD OF ADMINISTRATION).

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 exposures

All patients with a Divalproex sodium exposed pregnancy and their partners should consider specialized prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.

The available evidence does not suggest that folate supplementation before the pregnancy may prevent the risk of neural tube defects which may occur in all pregnancies.

Risk in the neonate

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken Divalproex sodium during pregnancy.

This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

- Cases of hypoglycaemia have been reported in neonates whose mothers have taken Divalproex sodium during the third trimester of their pregnancy.

- Cases of hypothyroidism have been reported in neonates whose mothers have taken Divalproex sodium during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Divalproex sodium is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section Undesirable effect). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from divalproex sodium therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using Divalproex sodium (see section Undesirable effect). Divalproex sodium administration may also impair fertility in men (see section Undesirable effect). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation

Effects on ability to drive and use machines
Since divalproex sodium may produce CNS depression, especially when combined with another CNS depressant (e.g. alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Undesirable effects

Mania
The incidence of treatment-emergent events has been ascertained based on combined data from two three-week placebo-controlled clinical trials of divalproex sodium extended-release tablets in the treatment of manic episodes associated with bipolar disorder.

Table 2 summarizes those adverse events reported for patients in these trials where the incidence rate in the divalproex sodium extended-release tablet-treated group was greater than 5% and greater than the placebo incidence.

Table 2
Adverse Events Reported by > 5% of Divalproex Sodium Extended-Release Tablets - Treated Patients During Placebo-Controlled Trials of Acute Mania [1]

Adverse Event	Divalproex Sodium Extended-Release Tablets (n = 338)	Placebo (n = 263)
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 event occurred at an equal or greater incidence for placebo than for Divalproex sodium extended-release tablets: headache		

The following additional adverse events were reported by greater than 1% but not more than 5% of the divalproex sodium extended-release tablet-treated patients in controlled clinical trials:

Body as a Whole: Back pain, flu syndrome, infection, infection fungal
Cardiovascular System: Hypertension
Digestive System: Constipation, dry mouth, flatulence
Hemic and Lymphatic System: Ecchymosis
Metabolic and Nutritional Disorders: Peripheral edema
Musculoskeletal System: Myalgia
Nervous System: Abnormal gait, hypertonia, tremor
Respiratory System: Rhinitis
Skin and Appendages: Pruritus, rash
Special Senses: Conjunctivitis
Urogenital System: Urinary tract infection, vaginitis

Epilepsy

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

Table 3 lists treatment-emergent adverse events that were reported by ≥ 5% of divalproex sodiumtreated patients and for which the incidence was greater than in the placebo group, in the placebocontrolled 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 events can be ascribed to divalproex sodium alone, or the combination of divalproex sodium and other antiepilepsy drugs.

Table 3
Adverse Events Reported by ≥ 5% of Patients Treated with Divalproex Sodium During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

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

Table 4 lists treatment-emergent adverse events that were reported by ≥ 5% of patients in the high dose divalproex sodium group, and for which the incidence was greater than in the low dose group, in a controlled trial of 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 events can be ascribed to divalproex sodium alone, or the combination of divalproex sodium and other antiepilepsy drugs.

Table 4
Adverse Events Reported by ≥ 5% of Patients in the High Dose Group in the Controlled Trial of Divalproex Sodium Monotherapy for Complex Partial Seizures[1]

Body System / Adverse 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
[1] 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 events were reported by greater than 1% but less than 5% of the 358 patients treated with divalproex sodium in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.
Cardiovascular System: Tachycardia, hypertension, palpitation.

Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System: Petechia.
Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.
Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System: Anxiety, confusion, speech disorder, 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, ear disorder, deafness, otitis media.
Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Migraine Prophylaxis

Based on the results of one multicenter, randomized, double-blind, placebo-controlled clinical trial, divalproex sodium extended-release was well tolerated in the prophylactic treatment of migraine headache. Of the 122 patients exposed to divalproex sodium extended-release in the placebocontrolled study, 8% discontinued for adverse events, compared to 9% for the 115 placebo patients.

Table 5 includes those adverse events reported for patients in the placebo-controlled trial where the incidence rate in the divalproex extended-release-treated group was greater than 5% and was greater than that for placebo patients.

Table 5
Adverse Events Reported by >5% of Divalproex Sodium Extended-Release-Treated Patients During the Migraine Placebo-Controlled Trial With a Greater Incidence Than Patients Taking Placebo [1]

Body System	Adverse Event	Divalproex Sodium Extended-Release (n = 122)	Placebo (n = 115)
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%	15%

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

The following additional adverse events were reported by greater than I% but not more than 5% of divalproex sodium extended-release-treated patients and with a greater incidence than placebo in the placebo-controlled clinical 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.

Based on two placebo-controlled clinical trials and their long-term extension, divalproex sodium enteric-coated tablets were generally well tolerated with most adverse events rated as mild to moderate in severity. Of the 202 patients exposed to divalproex sodium enteric-coated tablets 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 events reported as the primary reason for discontinuation by ≥1% of 248 divalproex sodium enteric coated-treated patients were alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

Table 6 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in the divalproex sodium enteric coated-treated group was greater than 5% and was greater than that for placebo patients.

Table 6
Adverse Reports Reported by >5% Of Divalproex Sodium Enteric-Coated-Treated Patients During the Migraine Placebo-Controlled Trial With a Greater Incidence Than Patients Taking Placebo [2]

Body System	Adverse Event	Divalproex Sodium Enteric-Coated (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%
[2] The following adverse events occurred in greater than 5% of divalproex sodium enteric-coatedtreated Patients and at a greater incidence for placebo than for divalproex sodium enteric-coated: Flu syndrome and pharyngitis.			

The following additional adverse events not referred to above were reported by greater than 1% but not more than 5% of divalproex sodium enteric-coated-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trials:

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

Other Patient Populations
The following adverse events not listed previously were reported by greater than 1% of divalproex sodium enteric-coated-treated patients and with a greater incidence than placebo in placebo-controlled trials of epilepsy or manic episodes associated with bipolar disorder:

Body as a Whole: Chills, chills and fever, drug level increased, fever, headache, malaise, neck pain, neck rigidity.
Cardiovascular System: Arrhythmia, hypertension, hypotension, palpitation, postural hypotension.
Digestive System: Anorexia, dysphagia, eructation, fecal incontinence, gastroenteritis, glossitis, gum hemorrhage, hematemesis, mouth ulceration, periodontal abscess.
Hemic and Lymphatic System: Anemia, bleeding time increased, leukopenia, petechia.
Metabolic and Nutritional Disorders: Hypoproteinemia, SGOT increased, SGPT increased, weight loss.
Musculoskeletal System: Arthralgia, arthrosis, twitching.
Nervous System: Agitation, amnesia, ataxia, catatonic reaction. depression, diplopia.dysarthria, emotional lability, hallucinations, hypokinesia, incoordination, nystagmus, psychosis, reflexes increased, sleep disorder, tardive dyskinesia.
Respiratory System: Bronchitis, hiccup, pneumonia.
Skin and Appendages: Discoid lupus erythematosis, dry skin, erythema nodosum, furunculosis, maculopapular rash, seborrhea, sweating, rash.
Special Senses: Amblyopia, conjunctivitis, deafness, dry eyes, eye disorder, eye pain, photophobia, taste perversion.

Urogenital System: Cystitis, dysmenorrhea, dysuria, menstrual disorder, urinary incontinence, vaginitis.

Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Since divalproex sodium has usually been used with other antiepilepsy drugs in the treatment of epilepsy, 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 drugs.

Gastrointestinal

The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Obesity has been as well reported in rare cases in the framework of the post marketing experience. Diarrhea, abdominal cramps, and gingival disorder (mainly gingival hyperplasia) constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. In some patients, many of who have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of divalproex sodium extended-release tablets in the stool.

CNS Effects

Sedative effects have been noted in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, memory impairment, cognitive disorder, and extrapyramidal disorders including parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Urea Cycle Disorders* and *Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use*, and *Hyperammonemia*). Additionally, there have been reports of encephalopathy in the absence of elevated ammonia levels.

There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use of valproate products. In some cases the patients recovered with permanent sequelae (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE –** *Brain Atrophy*). Cerebral atrophy seen in children exposed to valproate in utero led to various forms of neurological events, including developmental delays and psychomotor impairment Congenital malformations and developmental disorders have been as well reported (see section **PREGNANCY AND LACTATION –**).

Dermatologic

Transient hair loss, hair disorders (such as hair texture abnormal, hair colour changes, hair growth abnormal) skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a six-month-old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35-year-old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**- *Lamotrigine*). Nail and nail bed disorders have been as well reported in the framework of the post marketing experience.

Psychiatric

Emotional upset, depression, psychosis, aggression, psychomotor hyperactivity, hostility, agitation, disturbance in attention, abnormal behavior, learning disorder, and behavioral deterioration.

Musculoskeletal

Weakness.

Reports have been received of decreased bone mass, potentially leading to osteoporosis and osteopenia, during long-term therapy with anticonvulsant medications, including valproate. Some studies have indicated that supplemental calcium and vitamin D may be of benefit to patients who are on chronic valproate therapy.

Hematologic

Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and hemorrhage (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *General* and section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** - *Warfarin*). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

Hepatic

Minor elevations of transaminase (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hepatotoxicity*).

Endocrine

Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Hyperandrogenism (hirsutism, virilism, acnea, male pattern alopecia, and/or androgen increased). Abnormal thyroid function tests , including hypothyroidism (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *General*). There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic
Acute pancreatitis including fatalities (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Pancreatitis*).

Metabolic
Hyperammonemia (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - *Hyperammonemia*), hyponatremia, and inappropriate ADH secretion. There have been rare reports of Fanconi's syndrome occurring chiefly in children. Decreased carnitine concentrations have been reported although the clinical relevance is unknown. Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Insulin resistance and dyslipidemia have been as well reported in the framework of the post marketing experience.

Genitourinary
Enuresis, renal failure, tubulointerstitial nephritis and urinary tract infection.

Reproductive
Male infertility including azoospermia, abnormal semen analysis, decreased sperm count, spermatozoa morphology abnormal, aspermia, and decrease spermatozoa motility have been reported.

Special Senses
Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Myelodysplastic syndrome

Respiratory, thoracic and mediastinal disorders
Pleural effusion

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

Other patient population
Extrapyramidal disorders and encephalopathy in the absence of elevated ammonia levels have been reported in post-marketing data.

Overdose
Overdosage with valproate may result in somnolence, heart block, hypotension and circulatory collapse/shock, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2,120 mcg/mL. The presence of sodium content in the valproate

formulations may lead to hypernatremia when taken in overdose. 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group:
Anticonvulsant and mood-stabilizing drug
ATC-Code: N03AG01

Divalproex sodium is a stable coordination 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.
Divalproex sodium is chemically designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has a molecular weight of 310.41 and occurs as a white powder with a characteristic odor. Its empirical formula is C16H31Na04.

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

DESCRIPTION OF CLINICAL STUDIES

Mania
The effectiveness of divalproex sodium extended-release tablets for the treatment of acute mania is based in part on studies establishing the effectiveness of divalproex sodium delayed release tablets for this indication. Divalproex sodium extended-release tablets' effectiveness was confirmed in one randomized, double-blind, placebo-controlled, parallel group, 3-week, multicenter study. The study was designed to evaluate the safety and efficacy of divalproex sodium extended-release tablets in the treatment of bipolar I disorder, manic or mixed type, in adults. Adult male and female patients who had a current DSM-IV TR primary diagnosis of bipolar I disorder, manic or mixed type, and who were hospitalized for acute mania, were enrolled into this study. Divalproex sodium extended-release tablets were initiated at a dose of 25 mg/kg/day given once daily, increased by 500 mg/day on Day 3, then adjusted to achieve plasma valproate concentrations in the range of 85-125 µg/mL. Mean daily divalproex sodium extended-release tablets doses for observed cases were 2,362 mg (range: 500-4,000), 2,874 mg (range: 1,500-4,500), 2,993 mg (range: 1,500-4,500), 3,181 mg (range: 1,500-5,000), and 3,353 mg (range: 1,500-5,500) at Days 1, 5, 10, 15 and 21, respectively. Mean valproate

concentrations were 96.5 µg/mL, 102.1 µg/mL, 98.5 µg/mL, 89.5 µg/mL at Days 5, 10, 15 and 21, respectively. Patients were assessed on the Mania Rating Scale (MRS; score ranges from 0- 52).

Divalproex sodium extended-release tablets were significantly more effective than placebo in reduction of the MRS total score.

Epilepsy

Complex Partial Seizures (CPS)

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

In one, multiclinic, placebo controlled study employing an add-on design (adjunctive therapy), 144 patients who continued to experience eight or more CPS per eight weeks during an eight week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either divalproex sodium or placebo. Randomized patients were to be followed for a total of 16 weeks. Table 7 presents the findings.

Table 7
Adjunctive Therapy Study Median Incidence of CPS per 8 Weeks

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

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

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

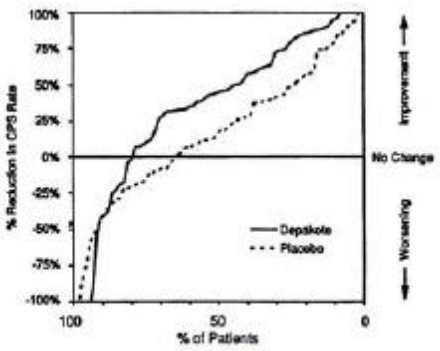


Figure 1

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

Table 8 presents the findings for all patients randomized who had at least one post-randomized assessment.

Table 8
Monotherapy Study
Median Incidence of CPS per 8 Weeks

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

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

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

divalproex sodium monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose divalproex sodium.

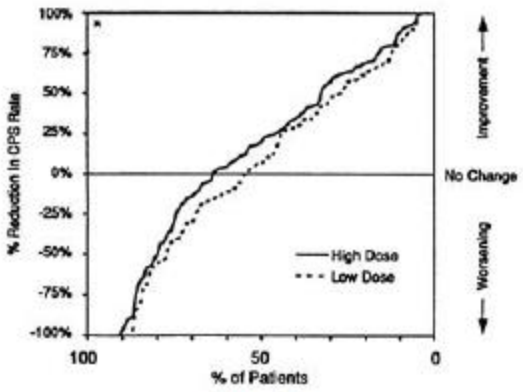


Figure 2

In a clinical trial of divalproex sodium as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 x 10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males).

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age was 83 years old), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration.

Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN.

Migraine

The results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial demonstrated the effectiveness of divalproex sodium extended-release in the prophylactic treatment of migraine headache. This trial recruited patients with a history of migraine headaches with or without aura occurring on average twice or more a month for the preceding three months. Patients with cluster or chronic daily headaches were excluded. Women of childbearing potential were allowed in the trial if they were deemed to be practicing an effective method of contraception.

Patients who experienced ≥ two migraine headaches in the four-week baseline period were randomized in a 1:1 ratio to divalproex sodium extended-release or placebo and treated for twelve weeks. Patients initiated treatment on 500 mg once daily for one week, and were then increased to 1,000 mg once daily with an option to permanently decrease the dose back to 500 mg once daily during the second week of treatment if intolerance occurred. Ninety-eight of 114 divalproex sodium extended-release-treated patients (86%) and 100 of 110 placebo-treated patients (91%) treated at least two weeks maintained the 1,000 mg once daily dose for the duration of their treatment periods.

Treatment outcome was assessed on the basis of reduction in four-week migraine headache rate in the treatment period compared to the baseline period.

Patients (50 male, 187 female) ranging in age from 16 to 69 were treated with divalproex sodium extended-release (n=122) or placebo (n=115). Four patients were below the age of 18 and three were above the age of 65. Two hundred and two patients (101 in each treatment group) completed the treatment period. The mean reduction in four-week migraine headache rate was 1.2 from a baseline mean of 4.4 in the divalproex sodium extended-release group, versus 0.6 from a baseline mean of 4.2 in the placebo group. The treatment difference was statistically significant (see Figure 3).

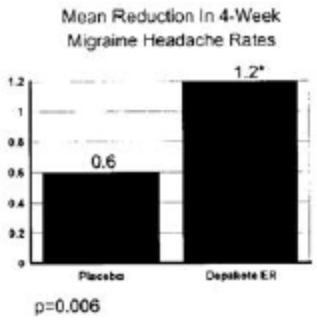


Figure 3

Pharmacokinetic properties

Absorption/Bioavailability

The absolute bioavailability of divalproex sodium extended-release (ER) 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 ER is less than that of divalproex sodium (divalproex sodium enteric-coated tablets). In five multiple-dose studies in healthy subjects (n=82) and in subjects with epilepsy (n=86), when administered under fasting and nonfasting conditions, divalproex sodium ER given once daily produced an average bioavailability of 89% relative to an equal total daily dose of divalproex sodium given b.i.d., t.i.d., or q.i.d. The median time to maximum plasma valproate concentrations (Cmax) after divalproex sodium ER administration ranged from 4 to 17 hours. After multiple once daily dosing of divalproex sodium ER, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular divalproex sodium given b.i.d., t.i.d., or q.i.d.

Conversion from divalproex sodium to divalproex sodium ER

When divalproex sodium ER is given in doses 8 to 20% higher than the total daily dose of divalproex sodium, the two formulations are bioequivalent. In two randomized, crossover studies, multiple daily doses of divalproex sodium were compared to 8 to 20% higher once-daily doses of divalproex sodium ER. In these two studies, divalproex sodium ER and divalproex sodium regimens were equivalent with respect to area under the curve (AUC; a measure of the extent of bioavailability). Additionally, valproate Cmax was lower, and Cmin was either higher or not different, for divalproex sodium ER relative to divalproex sodium regimens (see following table).

Bioavailability of divalproex sodium ER tablets relative to divalproex sodium when divalproex sodium ER dose is 8 to 20% higher				
Study	*Regimens*	*Relative Bioavailability*		
Population	divalproex sodium ER *vs.* divalproex sodium	AUC24	Cmax	Cmin
Healthy Volunteers (n=35)	1,000 & 1,500 mg divalproex sodium ER *vs.* 875 & 1,250 mg divalproex sodium	1.059	0.882	1.173
Patients with epilepsy on concomitant enzyme-inducing antiepilepsy drugs (n=64)	1,000 to 5,000 mg divalproex sodium ER *vs.* 875 to 4,250 mg divalproex sodium	1.008	0.899	1.022

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

Distribution

Protein Binding

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide) (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** for more detailed information on the pharmacokinetic interactions of valproate with other drugs).

CNS Distribution

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

Placental transfer (see section **FERTILITY, PREGNANCY, AND LACTATION**)

Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta, to a similar extent as in humans.

- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30 to 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 to 20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

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

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1,000 mg.

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

Special population

Children

(Note: Safety and effectiveness of divalproex sodium extended-release in the prophylaxis of migraine in pediatric patients have not been established. Therefore, the information below is applicable to the pediatric population when used for epilepsy indication only.)

The valproate pharmacokinetic profile following administration of divalproex sodium ER was characterized in a multiple-dose, non-fasting, open-label, multi-center study in children and adolescens. Divalproex sodium ER once-daily doses ranged from 250 to 1750 mg. Once-daily administration of divalproex sodium ER in pediatric patients (10 – 17 years) produced plasma valproic acid concentration-time profiles similar to those that have been observed in adults.

Elderly

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

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 m2, respectively).

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

Liver disease
(See CONTRAINDOCATIONS and CONTRAINDICATIONS and section SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hepatotoxicity).

Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in seven patients with cirrhosis and by 16% in four patients with acute hepatitis, compared to six 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 clearance of unbound valproate has been reported in patients with renal failure (cratinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

Plasma Levels and Clinical Effect
The relationship etween plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate that affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

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

Mania
In a placebo-controlled clinical trial of acute mania, patients were dosed to clinical response with through plasma concentrations between 85 and 125 µg/mL.

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.

Preclinical safety data

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

The 2-year carcinogenicity studies were conducted in mice and rats given oral valproate doses of approximately 80 and 160 mg/kg/day (which are the maximum tolerated doses in these species but less than the maximum recommended human dose based on body surface area). Subcutaneous fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to historical control data.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Valproate was not mutagenic in bacteria (Ames test) or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay) and did not induce DNA repair activity in primary culture of rat hepatocytes. It did not induce either chromosome aberrations in rat bone marrow or dominant lethal effects in mice after oral administration.

In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand-breaks, chromosomal aberrations or micronuclei) have been reported in rodents. However, the relevance of the results obtained with the intraperitoneal route of administration is unknown.

Statistically significant higher incidences of sisterchromatid exchange (SCE) have been observed in patients exposed to valproate as compared to healthy subjects not exposed to valproate. However, these data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with valproate versus untreated epileptic patients, provided contradictory results. The biological significance of an increase in SCE frequency is not known.

Impairment of Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to 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. Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits. In published literature, behavioral abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure to clinically relevant doses/exposures of valproate. In mice, behavioral changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute *in utero* exposure of the first generation. The relevance of these findings for humans is unknown.

PHARMACEUTICAL PARTICULARS

List of excipients

Divalproex sodium extended-release tablets include various inactive ingredients. Please consult your

approved International Manufacturing Formula for specific ingredients.

Depakote 250 mg, extended-release tablets:
Microcrystalline cellulose
Hypromellose
Silicon dioxide
Potassium sorbate
Opadry, White (Lactose monohydrate), Hypromellose, Titanium dioxide, Tricetin)
Opadry, Clear (Hypromellose, Macrogol)

Depakote 500 mg, extended-release tablets:
Microcrystalline cellulose
Lactose, Monohydrate
Hypromellose
Silicon dioxide
Opadry, Gray (Hypromellose, Titanium dioxide, Polydextrose, Triacetin, Macrogol, Black Iron oxide)
Potassium sorbate
Opadry, Clear (Hypromellose, Macrogol)

Incompatibilities
Not applicable.

Shelf life
The expiry date is indicated on the packaging.

HOW SUPPLIED

Depakote ER 250 mg is available as white ovaloid tablets with embossed of Abbott logo on one side of the tablet. Each divalproex sodium extended-release tablet contains divalproex sodium equivalent to 250 mg of valproic acid in bottles of 100 tablets.

Reg. No.: DKL1800206814B1

Depakote ER 500 mg is available as gray ovaloid tablets with embossed of Abbott logo on one side of the tablet. Each divalproex sodium extended-release tablet contains divalproex sodium equivalent to 500 mg of valproic acid in bottles of 100.

Reg. No.: DKL1700206814A1

HARUS DENGAN RESEP DOKTER

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