For Use of Registered Medical Practitioner (Neurologist and Psychiatrist Only)

1. GENERIC NAME AND BRAND NAME

Divalproex Sodium Oral Solution
VALANCE® SOLUTION 250/ 500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Valance 250:
Each 5 ml contains:
Divalproex Sodium I.P. equivalent to
Valproic acid……250 mg
Flavoured syrupy base…..q.s.
Colour**:** Quinolone Yellow

Valance 500:
Each 5 ml Contains
Divalproex Sodium I.P. equivalent to
Valproic Acid…….500 mg
Flavoured Syrupy base…… q.s.

3.0 DOSAGE FORM AND STRENGTH

Kindly refer section 1 & 2

4.0 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION:

-As a monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures for adult patients only.
-Manic episodes associated with bipolar disorder.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Female children and women of childbearing potential
Divalproex must be initiated and supervised preferably by a specialist experienced in the management of epilepsy, mania or prophylaxis of migraine. Valproic Acid should not be used in female children, women of childbearing potential unless other treatments are ineffective or not tolerated.

Divalproex is prescribed and dispensed in accordance to the measures for prevention of pregnancy.

After the treating physician determines the suitability of the patient (according to section 4.2), Divalproex should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Usual requirements are as follows:

Adults

Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg

Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg

20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly

Although the pharmacokinetics of Sodium Divalproex are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency

It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Divalproex sodium/Valproate /Valproic acid is dialysable (see section 4.9) Dosing should be modified according to the clinical monitoring of the patient.

In patients with hepatic insufficiency

Salicylates should not be used concomitantly with Sodium Divalproex since they employ the same metabolic pathway.

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid.

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition, in conjunction with Sodium Divalproex, concomitant use in children under 3 years can increase the risk of liver toxicity.

Combined Therapy
When starting Sodium Divalproex in patients already on other anticonvulsants, these should be tapered slowly: initiation of Sodium Divalproex therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases, it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Sodium Divalproex. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.
Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected

4.3 CONTRAINDICATIONS

Valproic acid should not be administered to patients Patients with hepatic disease or significant dysfunction.
Valproic Acid is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ (POLG; e.g. Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder.
Valproic acid is contraindicated in patients with known hypersensitivity to the drug.
Valproic acid is contraindicated in patients with known urea cycle disorders. Valproic Acid is contraindicated in patients Patients with porphyria. Valproic Acid is contraindicated in the following situation:
Treatment of epilepsy
• in pregnancy unless there is no suitable alternative treatment
• in women of childbearing potential, unless the measures for prevention of pregnancy
Treatment of mania and prophylaxis of migraine attacks
• in pregnancy
• in women of childbearing potential, unless the measures for prevention of pregnancy
Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia

4.4 SPECIAL WARNING AND PRECAUTIONS

Hepatotoxicity
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 / Valproic Acid products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations, 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 three years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When Divalproex / Valproic Acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy (seizure control) 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 nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms.

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 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 4.3).

Patients with known or suspected mitochondrial disease
Divalproex 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 4.3).

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.

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

/ valproic acid 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. 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 challenge with Divalproex. 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 should be warned that abdominal pain, nausea, vomiting, and/or anorexia could be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, Divalproex 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. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Anyone considering prescribing valproic acid 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, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or 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 4.5 – Carbapenem Antibiotics).

Thrombocytopenia (see section 4.4- General)

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

Divalproex / Valproic Acid has a high teratogenic potential and children exposed in utero to Divalproex / Valproic Acid have a high risk for congenital malformations and neurodevelopmental disorders.

Divalproex / Valproic Acid is contraindicated in the following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).

- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned below are met.

Treatment of mania and prophylaxis of migraine attacks

- in pregnancy (see section 4.4 and 4.6).

The treating physician must ensure that

- in women of childbearing potential, unless the measures for prevention of pregnancy as mentioned below and in sections 4.3 and 4.6 are met.

- 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 / Valproic Acid in utero.

- 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 / Valproic Acid.

- 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.

- 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 / Valproic Acid 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.

- The treating physician must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using Divalproex / Valproic Acid 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 / Valproic Acid in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for Divalproex / Valproic Acid therapy annually and consider alternative treatment options. If Divalproex / Valproic Acid is the only suitable treatment, the need for using effective contraception and all other measures as described in section 4.3, 4.4 and 4.6 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 / Valproic acid.

Contraception

Women of childbearing potential who are prescribed Divalproex / Valproic Acid must use effective contraception, without interruption during the entire duration of treatment with Divalproex / Valproic Acid. 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 / Valproic Acid 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 / Valproic Acid 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 / Valproic Acid 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 4.6). If switching is not possible, the woman should receive further counselling regarding the Divalproex / Valproic Acid risks for the unborn child to support her informed decision-making regarding family planning.

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

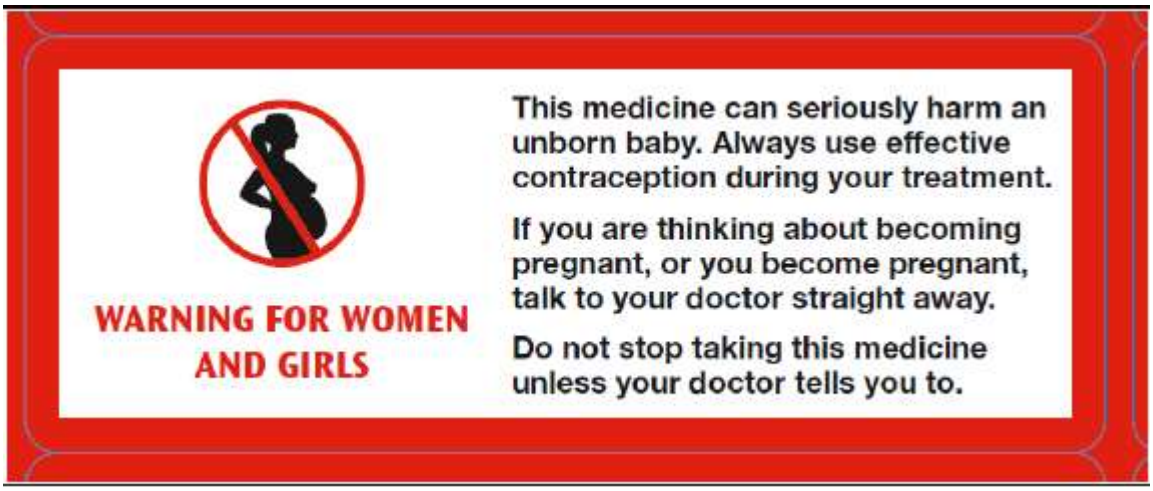
- the patients are advised not to stop Divalproex / Valproic Acid medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to Divalproex / Valproic Acid 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 / Valproic Acid 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 / Valproic Acid.

Visual Reminder on outer packaging

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



Use in male patients of reproductive potential

A retrospective observational study suggests an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared with the risk in those born to men treated with lamotrigine or levetiracetam (see section Pregnancy).

Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk and consider whether valproate remains the most appropriate treatment.

The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment.

The study did not evaluate the risk of neurodevelopmental disorders in children born to fathers who stopped using valproate more than 3 months before conception.

The male patient should be advised:
- not to donate sperm during treatment and for 3 months after stopping the treatment,
- of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,
- that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception.

The treatment in male patient should be initiated and supervised by a specialist in the management of epilepsy, bipolar disorder, or migraine.

There is the need for regular reviews by physician to assess if valproate remains the most appropriate treatment for the patient and discuss suitable treatment alternatives with the patient. This is particularly important if the male patient is planning to conceive a child and, in this case, before discontinuing contraception.

The Marketing Authorization Holder provides educational materials to healthcare professionals. A patient guide should be provided to all men of reproductive potential using valproate.

Hyperammonemia
Hyperammonemia has been reported in association with Divalproex / Valproic Acid 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 4.4– Hypothermia). If ammonia is increased, Divalproex / Valproic Acid therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see section 4.3 and 4.4).
Asymptomatic elevations of ammonia are more common and, when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of Divalproex therapy should be considered (see section 4.3 and 4.4).

Urea Cycle Disorders (UCD) hyperammonemia: Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of Divalproex therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to initiation of Divalproex 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 Divalproex therapy should receive prompt treatment (including discontinuation of Divalproex therapy) and be evaluated for underlying urea cycle disorders (see section 4.3 and 4.4- Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use, Patients at risk of hypocarnitinemia and Hepatotoxicity/ Hepatic dysfunction).

Patients at risk of hypocarnitinemia
Valproate administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in

patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also Warnings on Patients with known or suspected mitochondrial disease and urea cycle disorders and risk of hyperammonemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics. Patients should be warned to report immediately any signs of hyperammonemia such as ataxia, impaired consciousness, vomiting for further investigation. Carnitine supplementation should be considered when symptoms of hypocarnitinemia are observed. Patients with known systemic primary carnitine deficiency and corrected for hypocarnitinemia should be treated with valproate only if the benefits of valproate treatment outweigh the risks in these patients and there is no suitable therapeutic alternative. In these patients, close monitoring for recurrence of hypocarnitinemia should be implemented. Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. Carnitine supplementation should be considered in these patients

Hyperammonemia and Encephalopathy associated with Concomitant Topiramate use

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 4.4– 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 4.3 and 4.4).

Hypothermia

Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has been reported in association with Divalproex / Valproic Acid therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with Divalproex after starting topiramate treatment or after increasing the daily dose of topiramate (see section 4.5- Topiramate and 4.4- Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use and Hyperammonemia).Consideration should be given to stopping Divalproex 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 post marketing reports of reversible and irreversible cerebral and cerebellar atrophy temporally associated with the use Divalproex products; in some cases, patients recovered with permanent sequelae (see section 4.8). The motor and cognitive functions of patients on Divalproex 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 Divalproex products (see section 4.6).

General

Laboratory tests:

Because of reports of thrombocytopenia (see 4.4- 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. It is recommended that patients receiving Divalproex / Valproic Acid be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since Divalproex / Valproic Acid may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of Divalproex and concomitant drugs are recommended during the early course of therapy (see section 4.5).

Divalproex / Valproic Acid 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 Divalproex. 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 / Valproic Acid/Divalproex sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of Divalproex and concomitant drugs are recommended during the early course of therapy (see section 4.5).

There are in vitro studies that suggest Divalproex 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 Divalproex or when following CMV infected patients clinically.

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.

It seems prudent not to use Divalproex sodium in patients with acute head trauma for the prophylaxis of post-traumatic seizures until further information is available.

Severe Cutaneous Adverse Reactions and Angioedema

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

Information for Female Patients
Since Divalproex / Valproic Acid has been associated with certain types of birth defects, female patients of childbearing age considering the use of Divalproex / valproic acid should be advised of the risks associated with the use of Divalproex / Valproic Acid during pregnancy.

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.

4.5 DRUG INTERACTIONS

Effects of Co-Administered Drugs on Divalproex clearance
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of Divalproex. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of Divalproex. 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 Divalproex clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in Divalproex clearance, monitoring of Divalproex 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 Divalproex pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which potentially important interaction has been observed
Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with Divalproex to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of Divalproex. Divalproex free fraction was increased four-fold in the presence of aspirin compared to Divalproex alone. The β-oxidation pathway consisting of 2-Evalproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on Divalproex alone to 8.3% in the presence of aspirin. Caution should be observed if Divalproex 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.

Cholestyramine- Cholestyramine may lead to a decrease in plasma level of valproate when coadministered.

Estrogen-Containing Hormonal contraceptives: Estrogen-containing hormonal contraceptives may increase the clearance of Divalproex, which may result in decreased concentration of Divalproex and potentially increased seizure frequency. Prescribers should monitor serum Divalproex concentrations and clinical response when adding or discontinuing estrogen containing products, preferably during on-off intervals of the hormonal contraceptive cycle. (see Section 4.4)

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

Metamizole - Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate

Methotrexate -Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate

Protease inhibitors- Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma level when co-administered.

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

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

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

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

Haloperidol - A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving Divalproex (200 mg b.i.d.) revealed no significant changes in Divalproex trough plasma levels.

Cimetidine and Ranitidine - Cimetidine and ranitidine do not affect the clearance of Divalproex.

Effects of Divalproex on Other Drugs
Divalproex has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyl transferases.

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

Drugs for which a potentially important Divalproex 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 Divalproex (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 post-marketing reports of concurrent use of Divalproex and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of Divalproex and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking Divalproex concomitantly with amitriptyline.

Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of Divalproex.

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

Ethosuximide - Divalproex inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with Divalproex (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving Divalproex 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 Divalproex co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with Divalproex. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and Divalproex administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant Divalproex administration.

Phenobarbital - Divalproex was found to inhibit the metabolism of phenobarbital. Co-administration of Divalproex (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 Divalproex.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or Divalproex 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 Divalproex as phenobarbital.

Phenytoin - Divalproex displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of Divalproex (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 Divalproex. In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of Divalproex 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.

Pivalate-conjugated medicines- Concomitant administration of valproate and pivalate-conjugated medicines that decrease carnitine levels (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) may trigger occurrence of hypocarnitinemia (see Section 4.45 Patients at risk of hypocarnitinemia). Concomitant administration of these medicines with valproate is not recommended. Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinemia

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

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 Divalproex. The clinical relevance of this displacement is unknown.

Cannabidiol - In patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19% of patients. Drug Interaction between valproate and cannabidiol may result in an increased risk of elevation of liver transaminases (see section 4.4). Appropriate liver monitoring should be exercised when valproate is used with

cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters.

Topiramate and acetazolamide – Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without 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.

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

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

Lithium - Co-administration of Divalproex (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 Divalproex (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.

4.6 USE IN SPECIAL POPULATIONS

Fertility, Pregnancy and Lactation

Treatment of epilepsy
• Divalproex sodium/Valproate / Valproic Acid is contraindicated during pregnancy, unless there is no suitable alternative treatment.
• Divalproex sodium/Valproate / Valproic Acid is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions).
Treatment of mania and prophylaxis of migraine attacks
• Divalproex sodium/Valproate / Valproic Acid is contraindicated during pregnancy.
• Divalproex sodium/Valproate / Valproic Acid is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions

Teratogenicity and Developmental Effects from female and male exposure

Pregnancy Exposure Risk related to valproate
Divalproex was shown to cross the placental barrier both in animal species and in humans (see section 5.2).

Pregnancy Exposure Risk related to Divalproex
In females, both Divalproex monotherapy and Divalproex sodium/ Divalproex/valproic acid polytherapy are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both Divalproex sodium as monotherapy and polytherapy (concomitantly with other antiepileptic drugs) compared to the population not exposed to Divalproex sodium.

Risk to children of fathers treated with valproate/Divalproex sodium/Valproate/Valproic Acid
Data from 2 countries in a retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate at time of conception compared to those treated with lamotrigine or levetiracetam. Data from the third country are currently under analysis. Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs.

The study data on male patients had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times. The study did not investigate the risk in children born to men who stopped using valproate more than 3 months before conception.

The data showed that around 5 out of 100 children had a neurodevelopmental disorder when born to fathers treated with valproate compared with around 3 out of 100 when born to fathers treated with lamotrigine or levetiracetam.

The possible risk in children born to men treated with valproate in the 3 months before conception is lower than the previously confirmed risk in children born to women treated with valproate during pregnancy.
Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential regularly (see section Warnings and Precautions).

Congenital malformations from in utero exposure
Data derived from a meta-analysis (including registries and cohort studies) showed that about 11 of children of epileptic women exposed to Divalproex sodium monotherapy during pregnancy had major congenital malformations

This is a greater than the risk of major malformations than for in the general population , for whom the risk is (about 2-3%). The risk of major congenital malformations in children after in utero exposure to anti-epileptic polytherapy including Divalproex sodium/Valproate/Valproic Acid is higher than that of anti-epileptic drugs polytherapy not including Divalproex sodium. This risk is dose- dependent in Divalproex sodium/Valproate/Valproic Acid monotherapy, and available data suggest it is dose-dependent in Divalproex sodium/Valproate/Valproic Acid polytherapy. However, 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 Divalproex sodium/Valproate/Valproic Acid may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

In utero exposure to Divalproex 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.

Neuro - Developmental disorders from in utero exposure
Data have shown that exposure to Divalproex sodium/ Divalproex/Valproic acid in utero can have adverse effects on mental and physical development of the exposed children. The risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when Divalproex sodium/Valproate/Valproic Acid is used in monotherapy 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. When Divalproex sodium/Valproate/Valproic Acid is administered in monotherapy, studies in preschool children exposed in utero to Divalproex 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 disorders.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of Divalproex sodium/Valproate/Valproic Acid of Divalproex 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 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 Divalproex 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 Divalproex sodium/Valproate/Valproic Acid 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 Divalproex sodium/Valproate/Valproic Acid 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//prophylaxis of migraine indication: In women planning to become pregnant or who are pregnant, Divalproex sodium/Valproate/Valproic Acid valproate therapy should be reassessed
- For epilepsy and/ or mania/bipolar disorder/prophylaxis of migraine indication: If a woman plans a pregnancy or becomes pregnant, Divalproex sodium/Valproate/Valproic Acid valproate therapy should be stopped.
- For epilepsy and/ or mania/bipolar disorder/prophylaxis of migraine indication: In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

• During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
• In women planning to become pregnant or who are pregnant, Divalproex therapy should be reassessed

• If a woman plans a pregnancy or becomes pregnant, Divalproex therapy should be stopped.
• In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.
Divalproex therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with Divalproex for the patient by a physician experienced in the management of epilepsy or Mania.

If based on a careful evaluation of the risks and the benefits Divalproex treatment is continued during the pregnancy, it is recommended to:
- Use the lowest effective dose and divide the daily dose Divalproex 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.
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to Divalproex exposure.
- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Pregnant women
Valproic Acid as treatment for mania and prophylaxis of migraine attacks is contraindicated for use during pregnancy. Valproic Acid as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment, as evaluated and decided by the treating physician.
If a woman using Valproic Acid 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 Valproic Acid in pregnancy and after careful consideration of alternative treatment preferably by the specialist, in exceptional circumstances a pregnant woman must receive Divalproex sodium/Divalproex sodium/ Valproic Acid for epilepsy, it is recommended to:
• Use the lowest effective dose and divide the daily dose of Valproic Acid 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.
All patients with a Valproic Acid 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 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 during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken Divalproex 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 Divalproex during the last trimester of their pregnancy.

Breastfeeding
Divalproex 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. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sodium Divalproex 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. Divalproex administration may also impair fertility in men. Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation

Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using Divalproex sodium/Divalproex / Valproic Acid (see section 4.8). Divalproex sodium/Divalproex / Valproic Acid administration may also impair fertility in men (see section 4.8).
In the few cases in which Divalproex was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed.

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. When valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups. Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

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

The basic toxicology and pathologic manifestations of Divalproex 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 an mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on an mg/m^2 basis.

Geriatric Use
No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. The discontinuation of Divalproex 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.
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.
No unique safety concerns were identified in the 19 patients > 65 years of age receiving Divalproex sodium in clinical trials.

Aggravated convulsions
As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with Divalproex. In case of aggravated convulsions, the patients should be advised to consult their physician immediately.

4.7 EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Since valproic acid 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.

4.8 UNDESIRABLE EFFECTS

System organ class	Frequency	Adverse reaction

Congenital, familial and genetic disorders	Congenital malformations and developmental disorders (see section 4.4 and 4.6)	
	Unknown	Porphyria acute
Blood and lymphatic system disorders	Common	Thrombocytopenia
	Uncommon	Anemia, Hypochromic anemia, Leukopenia, Thrombocytopenic purpura
	Unknown	Agranulocytosis, Anemia folate deficiency, Anemia macrocytic, Aplastic anemia, Bone marrow failure, Eosinophilia, Hypofibrinogenemia, Lymphocytosis, Macrocytosis, Pancytopenia, Platelet aggregation inhibition,
Investigations	Common	Weight decreased, Weight increased
	Uncommon	Alanine aminotransferase increased[1], Aspartate aminotransferase increased[1], Blood creatinine increased, Blood folate decreased, Blood lactate dehydrogenase increased, Blood urea increased, Drug level increased, Liver function test abnormal, Protein bound iodine increased, White blood cell count decreased,
	Unknown	Acquired Pelger-Huet morphology[13] Blood bilirubin increased[1], Carnitine decreased, Thyroid function test abnormal,
Nervous system disorders	Very Common	Somnolence, Tremor
	Common	Amnesia, Ataxia, Dizziness, Dysgeusia, Headache, Nystagmus, Paresthesia, Speech Disorder
	Uncommon	Aphasia, Coordination abnormal, Dysarthria, Dystonia, Encephalopathy[2], Hyperkinesia, Hyperreflexia, Hypertonia, Hypoesthesia, Hyporeflexia, Seizure[3], Stupor, Tardive dyskinesia, Visual field defect
	Unknown	Asterixis, Cerebellar atrophy[4], Cerebral Atrophy[4], Cognitive disorder, Coma, Extrapyramidal disorder, Disturbance in

		attention, Memory impairment, Parkinsonism, Psychomotor hyperactivity, Psychomotor skills impaired, Sedation[5]
Ear and labyrinth disorders	Common	Tinnitus
	Uncommon	Deafness[6], Ear disorder, Hyperacusis, Vertigo
	Unknown	Ear pain
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough, Dyspnoea, Dysphonia, Epistaxis
	Unknown	Pleural effusion
Gastrointestinal disorders	Very Common	Nausea[7]
	Common	Abdominal pain, Constipation, Diarrhoea, Dyspepsia[7], Flatulence, Vomiting
	Uncommon	Anal incontinence, Anorectal disorder, Breath odour, Dry mouth, Dysphagia, Eructation, Gingival bleeding, Glossitis, Hematemesis, Melena, Pancreatitis[8], Rectal tenesmus, Salivary hypersecretion
	Unknown	Gingival disorder, Gingival hypertrophy, Gingival hyperplasia.
Renal and urinary disorders	Uncommon	Haematuria, Micturition urgency, Pollakiuria, Urinary incontinence
	Unknown	Enuresis, Fanconi syndrome[9], Renal failure, Tubulointerstitial nephritis
Skin and tissue disorders	Common	Alopecia[10] , Ecchymosis, Pruritus, Rash
	Uncommon	Acne, Angioedema, Dermatitis exfoliative, Dry skin, Eczema, Erythema nodosum, Hyperhidrosis, Nail disorder, Petechiae, Seborrhoea
	Unknown	Cutaneous vasculitis, Drug Rash with Eosinophilia and Systemic Symptoms syndrome (DRESS) (see section 4.4), Erythema multiforme, Hair disorder, Hyperpigmentation, Nail bed disorder, Photosensitivity reaction, Stevens-Johnson syndrome, Toxic epidermal necrolysis
Musculoskeletal and	Uncommon	Muscle spasm, Muscle twitching, Muscular weakness

connective tissue disorders	Unknown	Bone density decreased, Bone pain, Osteopenia, Osteoporosis, Rhabdomyolysis, Systemic lupus erythematosus
Endocrine disorders	Unknown	Hyperandrogenism[11], Hypothyroidism, Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Common	Decreased appetite, Increased appetite
	Uncommon	Hyperkalaemia, Hypernatremia, Hypoglycaemia, Hyponatremia, Hypoproteinaemia
	Unknown	Biotin deficiency, Dyslipidemia, Hyperammonemia, Hypocarnitinemia *(see section 4.3 and 4.4)*, Insulin resistance, Obesity
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Haemangioma of skin
	Unknown	Myelodysplastic syndrome
Vascular disorders	Uncommon	Orthostatic hypotension, Pallor, Peripheral vascular disorder, Vasodilatation
General disorders and administration site conditions	Very Common	Asthenia
	Common	Gait disturbance, Oedema peripheral
	Uncommon	Chest pain, Chills, Face oedema, Pyrexia
	Unknown	Hypothermia
Hepatobiliary disorders	Unknown	Hepatotoxicity
Reproductive system and breast disorders	Uncommon	Amenorrhea, Dysmenorrhea, Erectile dysfunction, Menorrhagia, Menstrual disorder, Metrorrhagia, Vaginal haemorrhage
	Unknown	Breast enlargement, Galactorrhea, Infertility Male[12], Menstruation irregular, Polycystic Ovaries
Psychiatric disorders	Common	Abnormal dreams, Affect lability, Confusional state, Depression, Insomnia, Nervousness, Thinking abnormal
	Uncommon	Agitation, Anxiety, Apathy, Catatonia, Delirium, Euphoric mood, Hallucination,

		Hostility, Personality disorder
	Unknown	Abnormal behaviour, Aggression, Emotional distress, Learning disorder, Psychotic disorder
Cardiac disorders	Uncommon	Bradycardia, Cardiac arrest, Cardiac failure congestive, Tachycardia
Eye disorders	Common	Amblyopia, Diplopia
	Uncommon	Chromatopsia, Dry eye, Eye disorder, Eye pain, Lacrimation disorder, Miosis, Photophobia, Visual impairment
Immune system disorders	Unknown	Anaphylactic reaction, Hypersensitivity
Infections and infestations	Common	Infection
	Uncommon	Bronchitis, Furuncle, Gastroenteritis, Herpes simplex, Influenza, Rhinitis, Sinusitis
	Unknown	Otitis media, Pneumonia, Urinary tract Infection
Injury, poisoning and procedural complications	Common	Injury

[1] may reflect potentially serious hepatotoxicity (see section 4.4)

[2] encephalopathy with or without fever has developed shortly after the introduction of Divalproex monotherapy without evidence of hepatic dysfunction or inappropriately high plasma Divalproex 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 4.4). Encephalopathy in the absence of elevated ammonia levels was also observed.

[3] here, consider aggravated seizure and reference to section 4.4

[4] reversible and irreversible. Cerebral atrophy seen in children exposed to Divalproex in utero led to various forms of neurological events, including developmental delays and psychomotor impairment (see section 4.4)

[5] noted in patients receiving Divalproex alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication

[6] either reversible or irreversible

[7] these effects are usually transient and rarely require discontinuation of therapy

[8] includes acute pancreatitis including fatalities

[9] occurring primarily in children

[10] reversible

[11] with events of hirsutism, virilism, acnea, male pattern alopecia, androgen increased

[12] including azoospermia, abnormal semen analysis, decreased sperm count, spermatozoa morphology abnormal, aspermia, and decrease spermatozoa motility.
[13] Isolated cases of acquired Pelger-Huet morphology.
Recognizing it is crucial for discontinuing valproates as discontinuation is the only treatment if drug induced and further avoiding unnecessary over-diagnosing neoplastic disorders such as myelodysplastic syndrome. This morphology anomaly may be associated with other cytopenias as well.

Pediatric population The safety profile of Divalproex in the pediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the pediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of three years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 5).

Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to webmasterindia@abbott.com

4.9 OVERDOSAGE

Overdosage with Divalproex may result in somnolence, heart block, hypotension and circulatory collapse/shock and deep coma. Fatalities have been reported; however, patients have recovered from Divalproex levels as high as 2,120 µg/ml.

The presence of sodium content in the Divalproex formulations may lead to hypernatremia when taken in overdose.

In case of valproate overdose resulting in hyperammonemia, carnitine can be given through IV route to attempt to normalize ammonia levels.

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. General supportive measures should be applied with attention to the maintenance of adequate urinary output.

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

3. PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION

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

5.2 PHARMACODYNAMIC PROPERTIES

Valproic acid is a carboxylic acid. Other chemical names for this compound are 2-propylpentanoic acid, 2-propylvaleric acid and n-dipropylacetic acid. Valproic acid (pKa 4.8) is a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/mL) and very soluble in organic solvents. Its empirical formula is C8H1602 and has a molecular weight of 144.

Divalproex sodium is the sodium salt of valproic acid and is chemically designated as sodium 2-propylpentanoate. Divalproex sodium has a molecular weight of 166.2. It occurs as an essentially white and odorless, crystalline, deliquescent powder

5.3 PHARMACOKINETIC PROPERTIES

The half-life of sodium Divalproex is usually reported to be within the range 8-20 hours. It is usually shorter in children.
In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.
The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/ litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.
The pharmacological (or therapeutic) effects of may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Placental transfer (see section 4.6) Divalproex crosses the placental barrier in animal species and in humans: - In animal species, Divalproex crosses the placenta, to a similar extent as in humans. - In humans, several publications assessed the concentration of Divalproex in the umbilical cord of neonates at delivery. Divalproex serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

6.0 NON-CLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Carcinogenesis

The 2-year carcinogenicity studies were conducted in mice and rats given oral Divalproex 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

Divalproex 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.

Divalproex 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 Divalproex, 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 sister-chromatid exchange (SCE) have been observed in patients exposed to Divalproex as compared to healthy subjects not exposed to Divalproex. However, these data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with Divalproex versus untreated epileptic patients, provided contradictory results

Impairment of Fertility and developmental toxicity

Divalproex 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 or greater than the maximum human daily dose on a mg/m2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m2 basis). Segment I fertility studies in rats have shown oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m2 basis) for 60 days to have no effect on fertility. 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 Divalproex. 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.

7.0 DESCRIPTION

Valance Solution 250: Yellow coloured, clear solution with Mango flavour. (The solution should be free from any suspended matter)

Valance Solution 500: Clear, colorless solution. A slight of tinge brown colour may appear on ageing.

8.0 PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
Not Applicable

8.2 SHELF-LIFE
Refer pack.

8.3 PACKAGING INFORMATION
Valance Solution 250: 100 ml & 60 ml bottle
Valance Solution 500: 100 ml & 200 ml bottle

8.4 STORAGE AND HANDLING
Store at a temperature not exceeding 30^0C. Protect from moisture.

9.0 PATIENT COUNSELLING INFORMATION

[Divalproex] is an effective medicine for epilepsy, mania and prophylaxis of migraine. [Divalproex] can seriously harm an unborn child when taken during pregnancy – it should not be taken by women and girls unless nothing else works. Whatever your condition never stop taking or reduce the dose of [Divalproex] before discussing with your doctor first. When taking [Divalproex] always use effective contraception that has been recommended by your doctor at all times during your treatment – so that you do not have an unplanned pregnancy. Make an urgent appointment with your doctor if you think you are pregnant. Consult your doctor if you are thinking about having a baby and do not stop using contraception until you and your doctor, preferably a specialist experienced in the management of epilepsy, or mania or prophylaxis of migraine agree on what to do with your treatment. Remember to visit your doctor regularly – at least once a year.

10.DETAILS OF MANUFACTURER
Manufactured By:
Abbott Healthcare Pvt. Ltd.
Village Bhatauli Khurd, P.O. Baddi - 173 205,
Dist. Solan, Himachal Pradesh, India.
® Regd. Trade Mark of Abbott Healthcare Pvt. Ltd.

11. DETAILS OF THE PERMISSION OR LICENSE NUMBER WITH DATE
MNB/06/295 dated 09th Oct 2020

12. DATE OF REVISION
Version 14.0 Dated 31st July 2024

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com

Source
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