Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

DIVALSCAN-ER 500

2. Qualitative and quantitative composition

Each film coated extended release Tablets contains: Divalproex Sodium

Eq. To Valproic acid 500mg. Excipiets q.s

Colour: Yellow Oxide of iron

Excipients of known effect: Lactose Monohydrate

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Film coated extended release tablet

Yellow coloured elongated shape biconvex one side break line extended release uncoated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Primary form of generalized epilepsy
- typical and atypical absences (petit mal)
- myoclonic seizures - tonic-clonic seizures (grand mal)
- mixed forns of tonic-clonic seizures and absences
- atonic seizures

May also be used for manifestations of epilepsy that do not adequately respond to other antiepileptic agents, such as:
Partial epilepsy
- both with elemental (focal) and complex (psychomotor) symptoms.
- Secondary forms of generalized epilepsy especially akinetic and atonic seizures.

Monotherapy is often possible in the primary form of generalized epilepsy. In partial epilepsy combined therapy will have to be instituted more frequently, likewise in the secondary form of generalized epilepsy and in mixed forms of primary generalized and partial epilepsy

Posology and method of administration

Posology Adults

Unless otherwise prescribed, the fallowing doses are recommended:

The effective dose and duration of this long-term therapy has to be determined individually with the aim beeing free from seizures with the minimum dosage, particularly during pregnancy. Monitoring of the patients is recommended during the period of dose adjustment.Although a good correlation between daily dose, plasma level and therapeutic effect has not been demonstrated, generally a plasma level between 40 and 100 micrograms per ml (300-700 micromol/l)

sodium valproate is attempted to be obtained. Nevertheless, favourable results with a lower or higher level have not been excluded, especially in children.

In cases of dosages of 35 mg sodium valproate/kg bodyweight per day or more, it is advisable to monitor the plasma level.

In some cases the full treatment response is achieved after 4-6 weeks. The daily doses should therefore not be increased too early beyond mean values.

A maximum daily dose of 60 mg sodium valproate/kg/day should not be exceeded.

When changing from pretreatment with (immediate release) pharmaceutical forms to Valproate chrono 300/500 mg prolonged-release tablets, it must be ensured, that adequate serum levels are maintained.

In general, the following dosage regimen may be used:

Monotherapy

Initial dose:

Adults and children

Initially 10 -15 mg sodium valproate/kg bodyweight per day is taken in two or more doses during meals; increase the dose weekly in steps of 5-10 mg sodium valproate/kg bodyweight per day until the desired therapeutic effect is achieved.

Maintenance dose:

As average 20-30 mg sodium valproate/kg bodyweight per day is taken ranging as follows:

Adults : 9-35 mg sodium valproate/kg bodyweight per day

Children : 15-60 mg sodium valproate/kg bodyweight per day

The optimal daily maintenance dose is usually divided into 1 to 2 doses during meals. Children under 20 kg bodyweight:

An alternative formulation of valproate should be used in this group of patients, due to the need for dose titration.

Elderly The pharmacokinetics of valproate may be altered in the elderly. Dosage should be determined by seizure control. (See section 5.2).

Use in renal impairment:
A dose reduction might be necessary in patients with renal impairment due to a possible increase in the level of free valproic acid in serum (see sections 4.4. and 5.2.). Exact calculation of the dosage in mg/kg bodyweight is not strictly necessary. In some patients on lower doses, the daily dose may even be given in one administration, provided that this is well tolerated.

Combined therapy

If Valproate chrono 300/500 mg prolonged-release tablets are administered in combination

with or as substitution therapy for previous medicinal products, it should be considered to reduce the dosage or the previously ordinated medicinal product (especially phenoparbitone) in order to avoid undesirable effects (see section 4.5) If the previous medicinal product is discontinued, this must be done gradually.

As the enzyme-inducing effect of other antiepileptics such as phenobarbitone, phenytoin, primidone and carbamazepine is reversible, the serum level of valproic acid should be measured approximately 4-6 weeks after the last intake of such an antiepileptic and the daily dose reduced if necessary.

Method of administration

The tablets - or half tablets if required - should be taken with a glass of plain water (carbonated drinks should not be used) and swallowed without chewing. If at the start or during treatment gastrointestinal irritation occurs, the tablets should be taken with or after food.

Contraindications hypersensitivity to sodium valproate, valproic

acid or any of the excipients

- hepatic and/or pancreatic impairment

- personal or family history of severe hepatic dysfunction, especially drug related.

- hepatic porphyria

- haemorrhagic diathesis

Special warnings and precautions for use

Haematological Monitoring of the blood count, including platelet count, bleeding time and coagulation tests, is advisable prior to initiation of therapy and before a surgical or dental operation, and in cases of spontaneous haematomas or bleeding (see section 4.8). Bone marrow damage Patients with previous bone marrow damage must be strictly monitored.

Hepatic dysfunction

Rare cases of severe liver damage following ingestion of sodium valproate, sometimes with a fatal outcome, have been reported.

Infants and children of less than 3 years of age with severe epilepsy, and especially epilepsy in combination with cerebral abnormalities, mental retardation, genetic degenerative conditions and/or known metabolic disturbances such as carnitine

deficiency, deficiency of urea cycle enzymes, and/or a history of hepatic dysfunction, have the highest risk of hepatotoxicity, especially during the first 6 months of treatment. Above 3 years, the risk decreases with increasing age. The risk of hepatotoxicity is greater in combined treatment with other antiepileptic agents, especially in very young children.

In children of less than 3 years of age, concomitant use of salicylates is not recommended on account of the possibility of hepatotoxicity.
Monotherapy is recommended for children of less than 3 years of age if prescribing of Valproate chrono is considered. However, the possible benefits must be weighed against the risk of liver damage and pancreatitis in such patients before treatment is initiated.

Valproate chrono should not be normally used in small children less than 3 years of age as a first line therapy. Valproate chrono should be used with caution in small children, only if benefits outweight the risks, and if possible monotherapy should be preferred.

Clinical symptoms Clinical symptoms are essential for early diagnosis. In particular, attention must be paid to the following disorders, which may precede jaundice:

- non-specific symptoms such as asthenia, anorexia, apathy, somnolence, sometimes accompanied by repeated vomiting and abdominal pain
- recurrence or exacerbation of convulsions
- prolongation of the bleeding time.

It is also advisable to warn the patient or parents about these symptoms, and to instruct them that, if they occur, the attending physician must be informed immediately.

Monitoring of liver function for hepatotoxicity
Liver function should be monitored prior to initiation of therapy and then periodically during the first 6 months. In particular, abnormally high thromboplastin time, representative of disturbed protein synthesis, is important. In cases of severely disturbed liver function tests (transaminases and/or bilirubin, and/or fibrinogen coagulation factors), treatment should be discontinued. As a precaution, concomitant use of salicylates (if these are used) should also be stopped, as hepatotoxicity caused by valproic acid can strongly resemble Reye's syndrome.

As with most antiepileptic agents, at the beginning of treatment an isolated transient increase in the transaminases may occur without clinical symptoms.

If this occurs, more extensive investigations (including determination of PTT) are recommended; adjustment of the dosage may be considered, and the investigations should be repeated if necessary.

Interaction with other medicinal products and other forms of interaction

Effects of Divalproex Sodium Extended Release Tablets USP 500 mg on other

drugs - ***Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines***

Divalproex Sodium Extended Release Tablets USP 500 mg may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Clozapine and haloperidol***

No significant interaction was observed when clozapine and haloperidol were administered concurrently with Divalproex Sodium Extended Release Tablets USP 500 mg .

- ***Lithium***

Co-administration of Divalproex Sodium Extended Release Tablets USP 500 mg and lithium does not appear to affect the steady state kinetics of lithium. Divalproex Sodium Extended Release Tablets USP 500 mg has no effect on serum lithium levels.

- ***Olanzapine***

Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***

Divalproex Sodium Extended Release Tablets USP 500 mg increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Divalproex Sodium Extended Release Tablets USP 500 mg increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Divalproex Sodium Extended Release Tablets USP 500 mg decreases phenytoin total plasma concentration. Moreover, Divalproex Sodium Extended Release Tablets USP 500 mg increases phenytoin free form with possible overdose symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore, clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***

Clinical toxicity has been reported when Divalproex Sodium Extended Release Tablets USP

500 mg was administered with carbamazepine as Divalproex Sodium Extended Release Tablets USP 500 mg may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Divalproex Sodium Extended Release Tablets USP 500 mg reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended, and dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***

Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Rufinamide***

Valproic acid may lead to an increase in plasma levels 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.

- ***Propofol***

Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- ***Zidovudine***

Divalproex Sodium Extended Release Tablets USP 500 mg may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Nimodipine***

In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***Temozolomide***

Co-administration of temozolomide and Divalproex Sodium Extended Release Tablets USP 500 mg may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.2 Posology and method of administration

Posology Adults

Unless otherwise prescribed, the following doses are recommended:

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Method of administration

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4.3 Contraindications

-hypersensitivity to sodium valproate, valproic acid or any of

the excipients

- hepatic and/or pancreatic impairment

- personal or family history of severe hepatic dysfunction, especially drug related.

- hepatic porphyria

- haemorrhagic diathesis

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Infants and children of less than 3 years of age with severe epilepsy, and especially epilepsy in combination with cerebral abnormalities, mental retardation, genetic degenerative conditions and/or known metabolic disturbances such as carnitine deficiency, deficiency of urea cycle enzymes, and/or a history of hepatic dysfunction, have the highest risk of hepatotoxicity,
especially during the first 6 months of treatment. Above 3 years, the risk decreases with increasing age. The risk of hepatotoxicity is greater in combined treatment with other antiepileptic agents, especially in very young children.

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- ***Felbamate***

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- ***Rufinamide***

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- ***Propofol***

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- ***Zidovudine***

Divalproex Sodium Extended Release Tablets USP 500 mg may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Nimodipine***

In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***Temozolomide***

Co-administration of temozolomide and Divalproex Sodium Extended Release Tablets USP 500 mg may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

- ***Anti-epileptics***

Anti-epileptics with enzyme inducing effects (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

Valproic acid metabolite levels may be increased in the case of concomitant use with phenytoin or phenobarbital. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of felbamate and Divalproex Sodium Extended Release Tablets USP 500 mg decreases valproic acid clearance by 22 – 50%

and consequently increase the valproic acid plasma concentrations. Divalproex Sodium Extended Release Tablets USP 500 mg dosage should be monitored.

- ***Anti-malarial agents***

Mefloquine and chloroquine increase valproic acid metabolism. Accordingly, the dosage of Divalproex Sodium Extended Release Tablets USP 500 mg may need adjustment.

- ***Highly protein bound agents***

In case of concomitant use of Divalproex Sodium Extended Release Tablets USP 500 mg and highly protein bound agents (e.g. aspirin), free valproic acid plasma levels may be increased.

- ***Vitamin K-dependent factor anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Cimetidine or erythromycin***

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin**.**

- ***Carbapenem antibiotics (such as panipenem, imipenem and meropenem)***

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60 – 100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

- ***Rifampicin***

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

- ***Protease inhibitors***

Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when coadministered.

- ***Cholestyramine***

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

- ***Oestrogen-containing products, including oestrogen-containing hormonal contraceptives***

Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.

On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

Other interactions

Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Quetiapine

Co-administration of Divalproex Sodium Extended Release Tablets USP 500 mg and quetiapine may increase the risk of neutropenia/leucopenia.

4.6 Pregnancy and Lactation

- Valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Valproate is contraindicated for use in women of childbearing potential unless the conditions of the

Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and developmental effects

Pregnancy exposure risk related to valproate

Both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy.

Valproate was shown to cross the placental barrier in both animal species and humans (see section 5.2).

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

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 valproate 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.

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 or deafness 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. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

Developmental disorders

Data have shown that exposure to valproate *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.
Available data from a population-based study show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.

Available data from another population-based study show 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 unexposed population in the study.

Female children and woman of childbearing potential (see above and section 4.4)
Oestrogen-containing products

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4 and 4.5).

If a woman plans a pregnancy

If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.

Pregnant women

Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. 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 valproate exposure.

<u>Risk in the neonate</u>

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers

have taken valproate during pregnancy. This haemorrhagic 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 valproate

during the third trimester of their pregnancy.

- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate

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.

Studies in preschool children exposed *in utero* to valproate 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.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate 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 valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long-term outcomes.

Breast-feeding

Valproate is excreted in human milk with a concentration ranging from 1 – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Divalproex Sodium Extended Release Tablets USP 500 mg 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 valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

Undesirable effects

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

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Divalproex Sodium Extended Release Tablets USP 500 mg in the treatment of manic episodes have been identified.

Congenital malformations and developmental disorders: (see sections 4.4 and 4.6).

Hepatobiliary disorders:

Common: liver injury (see section 4.4.1)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment and may be transient (see section 4.4.1).

Gastrointestinal disorders:

Very common: nausea

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea

The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Divalproex Sodium Extended Release Tablets USP 500 mg with or after food.

Uncommon: pancreatitis, sometimes lethal (see section

4.4) Nervous system disorders:

Very common: tremor

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

Uncommon: coma*, encephalopathy*, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:

Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*

Rare: abnormal behaviour*, psychomotor hyperactivity*, learning

disorder* *These ADRs are principally observed in the paediatric

population.

Metabolism and nutrition disorders:

Common: hyponatraemia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

Rare: hyperammonaemia* (see section 4.4.2), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Divalproex Sodium Extended Release Tablets USP 500 mg should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2). In such cases further investigations should be considered.

Endocrine disorders:

Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism
(hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)

Rare: hypothyroidism (see section 4.6)

4.8 Undesirable effects

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable, and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Divalproex Sodium Extended Release Tablets USP 500 mg formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Antipsychotics; Other Antipsychotics, ATC code:
N05AX.

Divalproex Sodium Extended Release Tablets USP 500 mg exerts its effects mainly on the central nervous system.

The most likely mode of action for Divalproex Sodium Extended Release Tablets USP 500 mg is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

5.2 Pharmacokinetic properties

Following oral administration of Divalproex Sodium Extended Release Tablets USP 500 mg , the absolute bioavailability of valproic acid approaches 100%. Mean terminal half-life is about 14 hours, steady state conditions usually being achieved within 3 - 4 days. Peak plasma concentrations are achieved within 3 – 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Distribution

Plasma protein binding of Divalproex Sodium Extended Release Tablets USP 500 mg ranges from 85 - 94% over plasma drug concentrations of 40 - 100 µg/ml. It is concentrationdependent, and the free fraction increases non-linearly with plasma drug concentration.

Placental transfer (see section 4.6)

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

Divalproex Sodium Extended Release Tablets USP 500 mg is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the

dose). Plasma clearance ranges from 0.4 – 0.6 L/h and is independent of hepatic blood flow.

The major pathway of valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9, and UGT2B7.

Elimination

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

Interaction with oestrogen-containing products

Inter-individual variability has been noted. There are insufficient data to establish a robust PKPD relationship resulting from this PK interaction.

5.3 Preclinical safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in epileptic patients exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in epileptic patients treated with valproate with those in untreated epileptic patients. The clinical relevance of these DNA/chromosome findings is unknown.

Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproductive and developmental toxicity

Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.

Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

Behavioural abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose monohydrate
Hypromellose (RLQ-350)
Colloidal silicon Dioxide
Isopropyl alcohol
PVPK-30
Talc
Magnesium Stearate
Magnesium Aluminium Silicate
Titanium Dioxide
Hypromellose E15
Colour: Yellow oxide of iron
Methylene dichloride

6.2 Incompatibilities

None

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store in a dry & dark place at temperature below 30°C. Keep medicine out of reach of children.

6.5 Nature and Content of container
03 Alu-Alu packs in one carton along with insert.

6.6 Special precautions for disposal and other handling
No Special Requirements.

7. Marketing Authorization Holder

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8. Marketing Authorization Number
CTD8774

9. Date of first authorization/renewal of the authorization
29/06/2023

10. Date of revision of the text
12/05/2025