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

This package insert is continually updated. Please read carefully before using a new pack.

Sodium Valproate Tablets I.P.

VALPARIN®200 ALKALETS
Each enteric coated tablet contains Sodium Valproate IP 200mg

VALPARIN® 500 ALKALETS
Each enteric coated tablet contains Sodium Valproate I.P. 500mg

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Controlled Release Tablets of Sodium Valproate and Valproic Acid

VALPARIN® CHRONO 200
Sodium Valproate I.P. 133mg + Valproic Acid I.P. 58mg

VALPARIN® CHRONO 300
Sodium Valproate I.P. 200mg + Valproic Acid I.P. 87mg

VALPARIN® CHRONO 500
Sodium Valproate I.P. 333mg + Valproic Acid I.P. 145mg

Sodium Valproate Oral Solution I.P.

VALPARIN® 200
Sodium Valproate I.P. 200mg/5ml

INDICATIONS

- In the treatment of generalized or partial epilepsy, particularly with the following patterns of seizures:
  - absence
  - tonic-clonic
  - myoclonic
  - atonic
  - mixed

as well as, for partial epilepsy:

  - simple or complex seizures
  - secondary generalised seizures
  - specific syndromes (West, Lennox-Gastaut)
- Valparin is indicated for the treatment of the manic episodes associated with bipolar disorders.

DOSAGE AND METHOD OF ADMINISTRATION

For Seizure Control

Daily dosage should be established according to age and body weight; nevertheless the wide individual sensitivity to valproate should also be considered.

A good correlation has not been established between daily dose, serum concentration and therapeutic effect and optimum dosage should be determined essentially according to the clinical response; the

determination of valproic acid plasma levels may be considered in addition to clinical monitoring when adequate seizure control is not achieved or when adverse effects are suspected. The reported effective range is usually between 40-100mg/litre (300-700mmol/litre).

Initiation of Valparin therapy

- In patients without other anti-epileptic drugs, the dosage should be preferably increased by successive dose levels at 2-3 day intervals in order to reach the optimum dosage in about 1 week.

- In patients previously receiving anti-epileptic agents, substitution with Valparin should be progressive, the optimum dosage being reached in about 2 weeks and other treatments being tapered and then stopped.

- Addition of another anti-epileptic agent should be done progressively where it is necessary (see *"Interactions"*).

Practical Considerations
Dosage
Initial daily dosage is usually 10-15mg/kg, then doses are titrated up to the optimum dosage *(*see *"Initiation of Valparin therapy")*

This is generally within the range 20-30mg/kg. Nevertheless, where seizure control is not achieved within this range, the dose may be further increased adequately; patients should be carefully monitored when receiving daily doses higher than 50mg/kg (see *"Precautions"*).

In children, usual dosage is about 30mg/kg per day.

In adults, usual dosage is within the range 20-30mg/kg per day.

Administration
The use of a controlled release form (Valparin® Chrono) allows to give the drug once daily.

Valparin® Chrono may be used in children provided that they are able to take such a form. The breakable forms of Valparin® Chrono allow a fine dose adjustment.

For Treatment of Mania
Initially dosage should start with 600mg daily increasing by 200mg / day at three-day intervals until control is achieved.

This is generally within the range 1000 to 2000mg/day (i.e., 20 to 30 mg/kg/day). Where adequate control is not achieved within this range the dose may be further increased to 2500mg /day

The Bowden et al study provides a strong support for a greater efficacy of serum levels above 45micrograms (these levels achieved 20% or greater improvement on both subscales of the Mania Rating Scale). Bowden noted that > 125 micrograms / ml had greater drug related adverse events. Between these extremes there does not appear to be a clear dose-response relationship.

General
Hepatic Impairment: Hepatic dysfunction including hepatic failure resulting in fatal outcomes has occurred in patients whose treatment included valproic acid or sodium valproate (see *" " "Precautions"*).

Renal impairment: Lower doses may be required since free drug levels may be high owing to lowered serum albumin and poor urinary excretion of free drug metabolites (see *" "Precautions"*).

Use in Elderly: Although the pharmacokinetics of Valparin 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.

Use in Children:
Epilepsy indication: Among the oral pharmaceutical forms, the oral solution is more appropriate for administration to children less than 11 years.

Bipolar indication
In children and adolescents: The safety and efficacy of Valparin for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Female children, female adolescents, women of childbearing potential and pregnant women
Valparin should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated (see *"Warnings"* and *"Pregnancy")* and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Valparin should 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 during pregnancy.

Estrogen-containing products
Valproate does not reduce efficacy of hormonal contraceptives.
However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels. (See Section Interactions)

Administration
In view of the sustained release process and the nature of the excipients in the formula, the inert matrix of the granules is not absorbed by the digestive tract; it is eliminated in the stools after the active substances have been released

CONTRAINDICATIONS

- Hypersensitivity to sodium valproate or valproic acid.
- Acute or chronic hepatitis
- Patient or family history of severe hepatitis, especially drug related
- Hepatic porphyria
- 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 in children under two years of age who are suspected of having a POLG-related disorder (see "Warnings").
- Patients with known urea cycle disorders (see "Precautions")

WARNINGS

- ***Severe liver damage***

-Conditions of occurrence:
Severe liver damage resulting sometimes in fatalities has exceptionally been reported.
Experience indicates that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disease.

After the age of 3 years, the risk is significantly reduced and it progressively decreases with age. In most cases, such liver damage occurred during the first 6 months of therapy.

-Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk *(*see above *"Conditions of occurrence")*:

- non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.

-Detection :
Liver function tests should be performed before therapy and then periodically during the first 6 months of therapy. Among the usual investigations, tests which reflect protein synthesis particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Valparin therapy. As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued since they follow the same metabolic pathway.

- ***Pancreatitis***

Severe pancreatitis, which may result in fatalities, has been very rarely reported. Young children are at particular risk but this risk decreases with increasing age. Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, valproate should be discontinued.

- ***Female children, female adolescents, women of childbearing potential and pregnant women***

Valparin should not be used in female children, in female adolescents, in women of child-bearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate.
The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of child bearing potential treated with Valparin plans a pregnancy or if she becomes pregnant.
Women of child-bearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Valparin during pregnancy (see*"Section Pregnancy"*).

Estrogen-containing products
Valproate does not reduce efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels. (See Section Interactions)

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:
• The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
• The need to use effective contraception.
• The need for regular review of treatment.

• The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see *"Pregnancy").*

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy or bipolar disorder.

- ***Suicidal ideation and behaviour***

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this effect is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

- ***Carbapenem agents***

The concomitant use of valproate and carbapenem agents is not recommended. (See *"Interactions")*

- ***Patients with known or suspected mitochondrial disease***

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear- encoded POLG gene. In particular, acute liver failure and liver-related deaths have been associated with valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial enzyme polymerase γ (POLG; e.g. Alpers-Huttenlocher Syndrome). 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 un-explained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see *"Contraindications"*).

- ***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 valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately.(see *Adverse Reaction*)

PRECAUTIONS

- Liver function tests

Liver function tests should be carried out before therapy (see *"Contraindications*") and periodically during the first 6 months especially in patients at risk *(*see *"Warnings").* As with most antiepileptic drugs, a slight increase in liver enzymes may be noted, particularly at the beginning of the therapy; they are transient and isolated. More extensive biological investigations (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

- Haematological tests

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding *(*see *"Adverse Reactions")*

- ***Patients with systemic lupus erythematosus***

Although immune disorders have been noted only exceptionally during the use of Valparin, the potential benefit of Valparin should be weighed against its potential risk in patients with systemic lupus erythematosus.

- ***Urea cycle disorders***

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate. (see *"Contraindications"*)

- ***Weight gain***

Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimize the risk. (see *"Adverse Reactions"*)

- ***Carnitine palmitoyltransferase (CPT) type II deficiency***

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

- ***Alcohol***

Alcohol intake is not recommended during treatment with valproate.

- ***Children*:**

Monotherapy is recommended in children under the age of 3 years when prescribing Valparin, but the potential benefit of Valparin should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see *"Warnings"*).
The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity.

- ***Renal insufficiency*:**

It may be necessary to decrease the dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Appearance of ghost tablet/s in the stools: Appearance of ghost tablet/s in stools is a common finding in patients using Valparin Chrono as it is a characteristic of the product. The formulation of Valparin Chrono is designed for controlled release of drug and contains matrix which is made up of high viscosity hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose coating which are pharmacopoeial grade materials. In the process of dissolution, matrix swells due to innate nature while drug gets released in the body from this matrix gradually as per the required acceptance criteria. The matrix forms highly viscous translucent mass due to swelling which depending upon the physiological condition of patient, gets excreted and may look similar to tablet, while the required drug has already been absorbed in the system.

INTERACTIONS
Effects of valproate on other drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

Valparin may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore clinical monitoring is advised and dosage should be adjusted when appropriate.

- ***Lithium***

Valparin has no effect on serum lithium levels.

- ***Phenobarbital***

Valparin increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. 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***

Valparin 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 a combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Valparin decreases phenytoin total plasma concentration. Moreover Valparin increases the 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 valproate was co-administered with carbamazepine as valproate may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Valparin 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 dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Zidovudine***

Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Felbamate***

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

- ***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.

- ***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.

- ***Nimodipine***

Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50 %.

Effects of other drugs on valproate

- ***Antiepileptics***

Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid serum concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of felbamate and valproate decreases valproic acid clearance by 22% to 50%, and consequently increase the valproic acid plasma concentrations. Valproate dosage should be monitored.

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.

- ***Mefloquine***

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy.

- ***Highly protein bound agents***

In case of concomitant use of valproate and highly protein bound agents (aspirin), valproic acid free serum levels may be increased.

- ***Vitamin K dependent factor anticoagulant***

Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent factor anticoagulant.

- ***Cimetidine or Erythromycin***

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

- ***Carbapenem agents***

Carbapenem (panipenem, meropenem, imipenem…): 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, coadministration of carbapenem agents in patients stabilized on valproic acid should be avoided (see Warnings). If treatment with these antibiotics cannot be avoided, close monitoring of Valparin 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, ritonavir decrease valproate plasma level when co-administered.

- **Cholestyramine**

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

- ***Estrogen-containing products***

Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially

decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control), when adding, or discontinuing estrogen-containing products. Consider monitoring of valproate plasma levels
Valproate usually 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 hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.

- ***Quetiapine***

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

PREGNANCY

- ***Risk associated with seizures***

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.

- ***Risk associated with Valparin***

In animals: Teratogenic effects have been demonstrated in the mice, rats and rabbits.

Congenital malformations
In humans: Available data suggest an increased incidence of minor or major malformations including, in particular, neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate, when compared to the incidence for certain other antiepileptic drugs. Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73%. (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

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.

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.

There are data to show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (estimated 3- to 5-fold increased risk), including childhood autism.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

In view of the above data the following recommendations should be taken into consideration:
This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Valparin is prescribed for the first time, or when a woman of child bearing potential treated with Valparin plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Estrogen-containing products

Valproate does not reduce efficacy of hormonal contraceptives.
However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels. (See Section Interactions)

Women of childbearing potential should be informed in detail of the risks and benefits of the use of valproate during pregnancy.

If a woman plans a pregnancy or becomes pregnant, Valparin therapy should be reassessed whatever the indication. :

- In bipolar disorders indication, cessation of Valparin therapy should be considered.
- In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Valparin treatment is to be continued during the pregnancy, it is recommended to use Valparin in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.
- In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5 mg daily) as it may minimize the risk of neural tube defects. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.
- Specialized prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

- ***Risk in the neonate***

Exceptional cases of hemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to 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 the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitterness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of pregnancy.

- ***Fertility***

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see *"Adverse Reactions"*). Valproate administration may also impair fertility in men (see *"Adverse Reactions"*).
Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

LACTATION
Excretion of valproate in breast milk is low, with a concentration between 1% to 10% of maternal serum levels. Based on literature and clinical experience, breastfeeding can be envisaged, taking into account the Valparin safety profile, especially hematological disorders. (see *"Adverse Reactions"*)

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
The patient should be warned of the risk of somnolence especially in cases of anticonvulsant polytherapy or association with benzodiazepines *(*see *"Interactions")*

ADVERSE REACTIONS
The following CIOMS frequency rating is used, when applicable:
Very common ≥10 %; Common ≥1 and < 10 %; Uncommon ≥ 0.1 and <1 %;
Rare ≥0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

*Congenital, familial and genetic disorders (*see *"Pregnancy")*

Blood and lymphatic system disorders
Common: anaemia thrombocytopenia. (see *"Precautions"***)**
Uncommon: pancytopenia, leucopenia
Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.

Investigations
Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see also "*Precautions"* and *"Pregnancy"),*biotin deficiency/biotinidase deficiency.

Nervous system disorders
Very common: tremor
Common:extrapyramidal disorder, stupor*,somnolence,convulsion*,memory impairment, headache, nystagmus, dizziness
Uncommon coma*, encephalopathy*, lethargy*(see below), reversible parkinsonism, ataxia, paresthesia
Uncommon: Aggravated convulsions (see *"Warnings").*
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

*Stupor and lethargy sometimes leading to transient coma /encephalopathy; they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage. These cases mostly occurred during combined therapy (in particular with phenobarbital or topiramate) or after a sudden increase in valproate doses.

Eye disorders
Not known: diplopia

Ear and labyrinth disorders
Common: deafness

Respiratory, thoracic and mediastinal disorders
Uncommon: pleural effusion

Gastrointestinal disorders
Very common: nausea

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, abdominal pain upper, diarrhea frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing the treatment.
Uncommon: pancreatitis, sometimes lethal. (see *"Warnings"*)
Renal and urinary disorders
Common: urinary incontinence
Uncommon: renal failure
Rare : enuresis, tubulointerstitial nephritis,reversible Fanconi syndrome but the mode of action is as yet unclear.

Skin and subcutaneous tissue disorders
Common: hypersensitivity, transient and /or dose related alopecia, nail and nail bed disorders.
Uncommon: angioedema, rash, hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal)
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Musculoskeletal and connective tissue disorders
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with sodium valproate. The mechanism by which sodium valproate affect bone metabolism has not been identified.
Rare: systemic lupus erythematosus (see "Precautions"), rhabdomyolysis (See "Precautions")

Endocrine disorders
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH)**,** hyperandrogenism (hirsutism, virilism, acnea, male pattern alopecia, and/or androgen increased)
Rare: hypothyroidism (See "Precautions").

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 "Precautions").
Rare: hyperammonaemia(see section Precautions), obesity

*****Cases of isolated and moderate hyperammonemia without change in liver function tests may occur and should not cause treatment discontinuation. Hyperammonemia associated with neurological symptoms has also been reported. In such cases, further investigations should be considered (see "Precautions")

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Rare: myelodysplastic syndrome

Vascular disorders
Common: haemorrhage (see Precautions & Pregnancy)
Uncommon: vasculitis

General disorders and administration site conditions
Uncommon: hypothermia**,** non severe oedema peripheral

Hepatobiliary disorders
Common: liver injury (see *"Warnings"*).

Reproductive system and breast disorders
Common: dysmenorrhea
Uncommon : amenorrhea
Rare: male infertility, polycystic ovaries

Psychiatric disorders

Common: confusional state, hallucinations**,** aggression*, agitation*,disturbance in attention*
Rare: abnormal behavior*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

OVERDOSE

Signs and Symptoms
Signs of acute massive overdose usually include a coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis, hypotension and circulatory collapse/shock

Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral edema have been reported.
The presence of sodium content in the valproate formulations may lead to hypernatraemia when taken in overdose.

Management:
Hospital management of overdose should be symptomatic: gastric lavage may be useful up to 10 to 12 hours following ingestion, cardio-respiratory monitoring.

Naloxone has been successfully used in a few isolated cases.
In case of massive overdose, hemodialysis and hemoperfusion have been used successfully.

Interference with Laboratory and Diagnostic Test
Since valproate is excreted mainly through the kidney partly in the forms of ketone bodies, ketone body excretion test may give false positive results in diabetic patients.

Manufactured and Marketed by:
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