xxxxxxxx-5253

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

VALPARIN XR 500 MG TABLET

(Sodium Valproate B.P. 333 mg + Valproic Acid U.S.P 145 mg)

DESCRIPTION

Valparin XR 500 mg Tablet is a broad spectrum antiepileptic drug containing sodium valproate in a Sustained Release Form.

COMPOSITION

VALPARIN XR 500 MG TABLET

Each film coated controlled release tablet contains:

Sodium Valproate B.P	333 mg
Valproic Acid U.S.P	145 mg

(Both together correspond to Sodium Valproate 500mg)

PHARMACODYNAMIC PROPERTIES

Broad spectrum antiepileptic agent.

Valproate exerts its effects mainly on central nervous system.

Pharmacological studies in animals have demonstrated that Valparin XR 500 mg Tablet has anticonvulsant properties in various model of experimental epilepsy (generalized and partial seizures). In human, Valparin XR 500 mg Tablet has also demonstrated antiepileptic activity in various types of epilepsy.

Its main mechanism of action seems to be related to a reinforcement of the GABAergic pathway.

PHARMACOKINETIC PROPERTIES

Sodium valproate bioavailability is close to 100% following oral administration.

The volume of distribution is mainly limited to blood and rapid exchange of extra cellular liquid. Valproic acid concentration in cerebrospinal fluid is close to free plasma concentration. Valparin XR 500 mg Tablet is transferred through placenta. When given to breast feeding mothers, Valparin XR 500 mg Tablet is excreted in breast milk at very low concentrations (between 1 to 10% of the total serum concentration).

Steady state plasma concentration is rapidly reached (3 to 4 days) following oral administration; Valproate is highly bound to plasma proteins; protein binding is dose dependent and saturable. Valproate molecule can be dialyzed but only the free form (approximately 10%) is excreted.

Unlike the other antiepileptics, sodium valproate does not increase its own degradation neither that of other agents such as estroprogestatives. This is due to the absence of enzyme inducing effect involving cytochrome P450.

Half-life is approximately 8 to 20 hours. It is usually shorter in children.

Sodium valproate is mainly excreted in urine following metabolization via glucuro-conjugation and beta-oxidation.

INDICATIONS

In the treatment of generalized or partial epilepsy, particularly with the following patterns of seizures:

Absence, Myoclonic, Tonic-clonic, Atonic, mixed.

As well as, for partial epilepsy:

Simple or complex seizures

Secondary generalized seizures

Specific syndromes (West, Lennox-Gastaut)

DOSAGE AND METHOD OF ADMINISTRATION

Valparin XR 500 mg Tablets are for oral administration.

Valparin XR 500 mg Tablet is a prolonged release formulation of VALPARIN which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Valparin XR 500 mg Tablet may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.

Daily dosage requirements vary according to age and body weight. In patients where adequate control has been achieved, Valparin XR 500 mg Tablet formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Monotherapy:

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 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.

Elderly: Although the pharmacokinetics of valproate 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 to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

In patients with hepatic insufficiency: Salicylates should not be used concomitantly with valproate 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. In addition, in conjunction with VALPARIN, concomitant use in children under 3 years can increase the risk of liver toxicity.

Combined Therapy:

When starting VALPARIN in patients already on other anticonvulsants, these should be tapered slowly; initiation of VALPARIN 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, eg phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of VALPARIN. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

Female children and women of childbearing potential

Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warnings and precautions and Fertility, pregnancy and lactation sections). The benefit and risk should be carefully reconsidered at regular treatment reviews. Sodium valproate 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.

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.

CONTRAINDICATIONS

Acute hepatitis; chronic hepatitis; Personal or family history of severe hepatitis, especially drug related; hypersensitivity to sodium valproate; Porphyria; Active liver disease; family history of severe hepatic dysfunction.

Sodium valproate is contraindicated in the following situations:

- In epilepsy
  - sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
  - sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Warnings and precautions and Fertility, pregnancy and lactation sections)
- In bipolar disorder
  - sodium valproate is contraindicated in pregnancy
  - sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section)

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Special warnings

- Liver dysfunction.
- Conditions of occurrence:
  Severe liver damage resulting sometimes in fatalities has been exceptionally reported.
  Experience in epilepsy has indicated that patients most at risk especially in cases of multiple anticonvulsant therapy are infants and young children under the age of 3 with severe seizure disorders, particularly those with brain damage, mental retardation and (or) congenital metabolic or degenerative disease. After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.
  In most cases, such liver damage occurred during the first 6 months of therapy.
- Suggestive signs:
  Clinical symptoms are essentially 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”):
- Nonspecific 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 or children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.
- Detection:
  Liver function should be performed before and then periodically monitored during the first 6 months of therapy. Amongst usual investigations, test 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 transaminase) requires cessation of Valparin XR 500 mg Tablet therapy.
  As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

PANCREATITIS:
CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE.

PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED; VALPROATE SHOULD BE DISCONTINUED

WARNING AND PRECAUTIONS:

Potential for an increase of suicidal thoughts or behaviours.

- 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, mild increased liver enzymes may be noted, particularly at the beginning of the therapy; they are transient and isolated, without clinical sign.
  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.
- Monotherapy is recommended in children under the age of 3 years when prescribing Valparin XR 500 mg Tablet, but the potential benefit of Valparin XR 500 mg Tablet should be weighed against the risk of liver damage in such patients prior to initiation of therapy (see “warnings”).
  The concomitant use of salicylates should be avoided in those children under 3 due to the risk of liver toxicity.
- 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 the case of spontaneous bruising or bleeding.
- In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentration may be misleading, dosage should be adjusted according to clinical monitoring (see “Pharmacokinetic properties”).
- Although immune disorders have been only exceptionally noted during the use of Valparin XR 500 mg Tablet, the potential benefit of Valparin XR 500 mg Tablet should be weighed against its potential risk in patients with systemic lupus erythematosus.
- Exceptional cases of pancreatitis have been reported; therefore patients experiencing acute abdominal pain should have pancreatic enzymes estimated prior to surgery.
- When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate.

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

Valparin XR 500 mg Tablet should not be used in female children, in female adolescents, in women of childbearing 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.

Sodium valproate has a high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders.

Sodium valproate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment for epilepsy indication.
- In pregnancy for bipolar disorder indication.
- In women of childbearing potential unless below conditions are fulfilled.

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

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

The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Valparin XR 500 mg Tablet plans a pregnancy or if she becomes pregnant.

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

- 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 sodium valproate.
- The patient understands the need for regular (at least annual) review of treatment by a prescriber 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 need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with sodium valproate use (Annual Risk Acknowledgement Form).

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

Female children

The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the doctor once the female child using sodium valproate experiences menarche.
- The 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 sodium valproate in utero.

In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the prescriber to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with sodium valproate. Treatment with sodium valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium valproate.

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 by the prescriber

The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review and ensure that the patient has understood its content

Pregnancy planning

If a woman is planning to become pregnant, a prescriber experienced in the management of epilepsy must reassess sodium valproate 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. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.
- Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of sodium valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber. at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a doctor experienced in the management of epilepsy.

Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Valparin XR 500 mg Tablet during pregnancy (see Fertility, Pregnancy and Lactation).

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:

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.

Use in male patients of reproductive potential

A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam (see Pregnancy). Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk. 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 risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

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 male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use (Annual Risk Acknowledgement Form). Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to all men of reproductive potential using valproate

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of Valproate on other drugs

Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines Valproate 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.

Phenobarbital

- Valproate 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

- Valproate 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

- Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage 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 administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine

- Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Valparin XR 500 mg Tablet might increase the risk of rash.

Zidovudine

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

Vitamin K-dependent 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.

Effects of other drugs on Valproate

Antiepileptics with enzyme inducing effect (including **phenytoin, phenobarbital, carbamazepine**) decrease valproic acid plasma concentrations, dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of **felbamate** and valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore, epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Valparin XR 500 mg Tablet may need adjustment.

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

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 **imipenem** and **meropenem:**

Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended.

Cholestyramine may decrease the absorption of valproate.

Other Interactions

Caution is advised when using Valparin XR 500 mg Tablet in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate usually has no enzyme-inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

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

FERTILITY, PREGNANCY AND LACTATION

Valparin XR 500 mg Tablet should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments areineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

- Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Sodium valproate is contraindicated for use in women of childbearing potential unless the above-mentioned conditions of Pregnancy Prevention Programme are fulfilled (see Contraindications and Warnings and precautions sections)

Pregnancy Exposure Risk related to sodium valproate

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

Teratogenicity and developmental effects

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 sodium 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.

Developmental disorders

Data have shown that exposure to sodium 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 sodium 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 sodium 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 sodium valproate 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 sodium 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.

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

Female children and woman of childbearing potential (see Contraindications and Warnings and precautions sections)

If a Woman wants to plan a Pregnancy

- During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.
- In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed
- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy.

Pregnant women

Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy.

It is recommended to:

- Use the lowest effective dose and divide the daily dose valproate 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 valproate exposure.
- Use the lowest effective dose and divide the daily dose sodium valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations.

All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor 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 which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to sodium valproate exposure.

- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Teratogenicity and developmental effects from female and male exposure

Risk to children of fathers treated with valproate

A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neurodevelopmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07).

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. 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, at least annually (see Warnings/Precautions).

Fertility

Valproate administration may also impair fertility in men (see Section Adverse Reactions). In the few cases in which valproate 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.

UNDESIRABLE EFFECTS

- Rare cases of liver dysfunction (see “Warnings”)
- Teratogenic risk (see “pregnancy”)
- Neurological disorders: confusion; a few cases of stupor or lethargy sometimes leading to transient coma (encephalopathy) have been described during sodium valproate therapy; they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreases on withdrawal of treatment or reduction of dosage. These cases have most often been reported during combined therapy (in particular with phenobarbital) or after a sudden increase in valproate doses.
- Very rare cases of reversible dementia associated with reversible cerebral atrophy have been reported
- Digestive disorders (nausea, gastralgia) frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing the treatment.
- Transient and (or) dose related undesirable effects have often been reported: hair loss, fine postural tremor and somnolence.
- Isolated reduction of fibrinogen or increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation (see “pregnancy”).
- Haematologic side effects: frequent occurrence of thrombocytopenia, rare cases of anemia, leucopenia or pancytopenia.
- Cases of pancreatitis, sometimes lethal, have been occasionally reported.
- The occurrence of vasculitis has been reported.
- Cases of isolated and moderate hyperammonemia without change in liver function tests may frequently occur and should not cause treatment discontinuation.
  Hyperammonemia associated with neurological symptoms has also been reported. In such cases further investigation should be considered (see “precautions”)
- Increase in weight may occur, amenorrhea and irregular periods have also been reported.
- Hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has been established.
- Cutaneous reactions may occur with valproates such as exanthematous rash. In exceptional cases, toxic epidermal necrolysis, Steven-Johnson syndrome, erythema multiforme have been reported.
- There have been isolated reports of a reversible Fanconi’s syndrome associated with valproate therapy but the mode of action is yet unclear

Reproductive system and breast disorders:

Rare: male infertility

OVERDOSAGE

Cases of accidental and deliberate valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Clinical signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with mascular hypotonia, hyporeflexia, miosis, impaired respiratory function.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also Pharmacokinetic Properties).

Cases of Intracranial hypertension related to cerebral odema have been reported.

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

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in few isolated cases, sometimes in association with activated charcoal given orally. Deaths have occurred following massive overdose; nevertheless, a Favourable outcome is usual.

STORAGE

Keep in a dry place at a temperature not exceeding 30^{0}C

EXPIRY DATE

36 months from the date of manufacturing.

PRESENTATION

It is available as white, oblong shaped film coated tablets with breakline on both sides. Valparin XR 500 mg Tablets are packed in Alu-Alu blister of 10 tablets. Such blisters containing 10 Tablets are packed into boxes of 10’s, 30’s and100’s.

Not all presentations may be available locally.

DATE OF REVISION OF PACKAGE INSERT:

February 09, 2026

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

PRODUCT NAME	:	Valparin XR 500 mg Tablet	COUNTRY : Malaysia		LOCATION : Chhatral	Supersedes A/W No. :	
ITEM / PACK	:	Insert	NO. OF COLORS: 1		REMARK : Folding Size 30 mm		
DESIGN STYLE	:	Front/Back	PANTONE SHADE NOS. :		SUBSTRATE :		
CODE	:	xxxxxxxx-5253		Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	:	180 x 440		Prepared By	Pkg_Dev			
ART WORK SIZE	:	S/S		Reviewed By	Pkg_Dev			
DATE	:	09-02-2026		Approved By	Quality			

Black

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.