805812-5253

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

VALPARIN XR 500

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

DESCRIPTION

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

COMPOSITION

VALPARIN XR 500:

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 has anticonvulsant properties in various model of experimental epilepsy (generalized and partial seizures). In human, Valparin XR 500 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 is transferred through placenta. When given to breast feeding mothers, Valparin XR 500 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 tablets are for oral administration.

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

VALPARIN XR 500 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 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.

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.

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"):
- 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 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 synthesi 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 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, but the potential benefit of Valparin XR 500 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, the potential benefit of Valparin XR 500 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.

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 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 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 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.

PREGNANCY AND LACTATION

Pregnancy

- Risk associated with epilepsy and antiepileptics

  In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the global rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations has been reported in case of multiple drug therapy, the respective part of treatments and disease has not been formally established. Malformations most frequently encountered are labial clefts and cardiovascular malformations.

  Sudden discontinuation in the antiepileptic therapy may be associated with a worsening of the disease in the mother and subsequent untoward effects in the fetus.
- Risk associated with sodium valproate

  In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

  In humans: the global risk of malformations in women receiving valproate during the first trimester of pregnancy is not higher than the risk described with other antiepileptics. Cases of facial dysmorphia have been reported. A few cases of multiple malformations, particularly of the limbs have been observed. The frequency of those effects has not been yet clearly established. Nevertheless sodium valproate preferably induces neural tube defects; myelomeningocele, spina bifida. The frequency of this effects is estimated to be 1 to 2 %.
- In view of the above data

  If a woman plans a pregnancy, it is the opportunity of reviewing the indication for antiepileptic therapy; folate supplementation should be considered.

  During pregnancy, valproate antiepileptic treatment should not be discontinued if it has been effective. Monotherapy is to be recommended; the minimum effective daily dosage should be used, in several divided doses over the day.

  Nevertheless, specialized prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defect or another malformation.
- Risk in the neonate

  Exceptional cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy.

  This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These hypofibrinogenemia are possibly associated with decrease of the vitamin-K dependent factors induced by phenobarbital and enzymatic inducers.

  Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation

- Excretion of valproate in breast milk is low, with concentration between 1 % to 10 % of maternal serum levels; up to now children breast fed that have been monitored during the neonate period have not experienced clinical effects.

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

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^{o}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 and 100's.

Not all presentations may be available locally.

DATE OF REVISION OF PACKAGE INSERT:

14th October, 2014

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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