For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory xxxxxxxx-8883

VALPARIN CHRONO 300 / VALPARIN CHRONO 500

(Controlled Release Tablets of Sodium Valproate and Valproic acid)

DESCRIPTION

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

COMPOSITION

VALPARIN CHRONO 300 :

Each film coated controlled release tablet contains:
Sodium Valproate B.P.....200 mg
Valproic Acid U.S.P. .....87 mg
(Both together correspond to Sodium Valproate 300 mg)

VALPARIN CHRONO 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 500 mg)

CLINICAL PHARMACOLOGY

Valproate exerts its effect primarily on the central nervous system. Its anticonvulsant properties are exerted against a wide variety of epilepsies experimental animal models and humans. Its main mechanism of action seems to be related to reinforcement of the gabanergic pathway.
The various pharmacokinetic studies conducted with valproate demonstrate the following points, some of which may have practical consequences on prescription:

- the blood bioavailability of valproate following oral administration approaches 100%.
- the volume of distribution is primarily limited to the blood and to rapid-exchange extracellular fluids. Valproate diffuses into the C.S.F. and brain.
- half-life is approximately 8 to 20 hours and is usually shorter in children.
- Significant therapeutic results are achieved with serum concentrations between 40 to 100 mg/l, but there is no definite correlation between serum level and therapeutic response.
- the steady state plasma concentration is achieved rapidly (3 to 4 days).
- valproate is extensively bound to proteins. Binding is dose-dependent and saturable.
- valproate is primarily excreted in the urine following glucuronic acid conjugation and beta- oxidation.
- valproate molecule is dialyzable, but hemodialysis only affects the free fraction of valproate in the blood (approximately 10 percent).
- valproate does not induce enzymes involved in cytochrome P450 metabolism: in contrast to most other antiepileptics, it therefore does not accelerate its own degradation nor that of other substances such as oral contraceptives and oral anticoagulants.

In comparison to the enteric form, the slow-release form sodium valproate, is characterized at equal doses by:

- disappearance of the absorption latency time;
- prolonged absorption;
- similar bioavailability,
- lowering of maximum plasma concentrations (C_{max}) of the total and free fractions (C_{max} decreased by approximately 25%, but relatively stable in a plateau, between the 4th and 14th hour), this flattening of the peaks makes it possible to achieve more even valproic acid concentrations which are more evenly distributed over the 24-hour cycle: Following twice daily administration of the same dose, the amplitude in plasma fluctuations is reduced by half.
- more linear correlation between the dose and plasma concentration (total and free fractions).

INDICATIONS

Generalized or partial epilepsy:

- primary generalized : petit mal, grand mal, atonic, mixed, myoclonic epilepsies.
- partial : with simple or complex seizures.
- secondary generalized seizures.
- specific syndromes (Lennox-Gastaut).

CONTRAINDICATIONS

Acute hepatitis; chronic hepatitis; family history of severe hepatitis; notably drug-induced hepatitis; porpyria; hypersensitivity to sodium valproate.

PRECAUTIONS

Liver damage resulting in fatalities have been exceptionally reported. Patients most at-risk, especially in cases of multiple anti-convulsant therapies, are infants and young children under the age of 3 with severe seizure disorders. After the age of 3 the incidence reduces significantly and progressively decreases with age. Monotheraphy is recommended in children under 3 yrs. of age, but the potential benefit of Valparin Chrono should be weighed against the risk of liver damage. Liver function tests are required before beginning treatment (see contraindications) as is periodic monitoring during the first 6 months, especially in at-risk patients.
It should be underlined that like most antiepileptics, there may be an isolated and transient increase in liver enzymes, in the absence of any clinical signs especially at the beginning of treatment. In such cases, a complete laboratory workup should be performed (including prothrombin time), dosage may be reconsidered an workups should be repeated on the basis of the changes in the parameters.
In children, under 3 yrs of age salicylates should not be prescribed concurrently due to the risk of liver toxicity.
In patients with renal insufficiency, increased serum concentrations of free valproic acid should be taken into account, and dosage should be consequently be adjusted.
In case of acute abdominal pain, serum amylase level should be determined before deciding on surgery, as exceptional cases of pancreatitis have been reported.
Blood tests including cell count, platelet count, bleeding time and coagulation tests are recommended prior to initiation of therapy and surgery, and in case of spontaneous bruising or bleeding.
Immune disorders have been noted only exceptionally and hence benefit Valparin chrono should be weighed against potential risk in patients with SLE.
In pregnancy
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. Facial dysmorphia, neural tube defects, like myelomeningocele, spinabifida have been reported. The frequency of these is estimated to be 1 to 2%.
In view of the above data:
If a women plans a pregnancy, it is the opportunity of reviewing the indication for antiepileptic therapy; folate supplementation should considered.
During pregnancy, valproate antiepileptic treatment should not be discontinued if it has been effective. The minimum effective daily dosage in several divided doses over the day should be used.
In lactation
Excretion of valproate in breast milk is low, with a concentration between 1% and 10% of maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects.

ADVERSE REACTIONS

- Rare cases of liver dysfunction: (see Precautions)
- Confusion or convulsions: a few cases of stupor either isolated or associated with an upsurge in convulsion with sodium valproate have been observed, and they regress on discontinuation of treatment or dosage reduction. These states usually occur in a multiple-drug treatment context (especially Phenobarbital) or on abrupt increase of sodium valproate doses.
- Certain subjects may present, at the beginning of treatment, gastrointestinal disturbances (nausea, gastric pain), which generally stop after a few days, without discontinuation of treatment.
- Transient dose-dependent adverse effects have been reported : hair-loss, fine postural tremor.
- Weight-gain has been observed, as have amenorrhea and menstrual disturbances.
- Dose related rise in bleeding time, decrease in fibrinogen have been reported.
- Hematologic side effects : thrombocytopenia, rarely anaemia, luecopenia or pancytopaenia.
- Isolated hyperammonaemia without change in lever function tests may occur. This should not cause treatment discontinuation.
- Rarely pancreatitis, vasculitis, hearing loss.

DRUG INTERACTIONS

Combinations requiring precautions:

Imipramine antidepressant

Imipramine antidepressants may promote generalized convulsions. Clinical monitoring and possibly dosage increase of antiepileptics may be necessary.

Phenobarbital

Increase in plasma phenobarbital concentrations (due to inhibition of liver catabolism), may occur with sedation, most often in children. Clinical monitoring during the first 2 weeks of the combination and immediate pehnobarbital dose reduction when signs of sedation develop; if necessary, monitor plasma phenobarbital levels.

Phenytoin

Generally, increases total phenytoin concentrations. In particular, increase in the concentrations of free phenytoin, which may lead to signs of overdosage (valproic acid displaces phenytoin from its plasma protein binding site and slows its liver catabolism). Clinical monitoring is recommended. If plasma phenytoin are determined, the free form is the most important to consider.

Primidone

Increase in plasma primidone levels with enhancement of its adverse effects (sedation). After prolonged use, this interaction ceases. Clinical monitoring recommended and if necessary, primidone dosage adjustments should be considered, especially at the beginning of the co-administration.

Lamotrigine

Valproate may reduce lamotrigine metabolism necessitating dosage reduction of latter.

Mefloquine

Increases valproic acid metabolism and has a convulsant effect; therefore epileptic seizures may occur in combined therapy.

Miscellaneous

In case of concomitant use of valproate and highly bound protein drugs (like aspirin), free serum levels of valproate may be increased.
The serum levels of valproate may be increased in case of concomitant use with cimetidine or erythromycin.
Close monitoring of prothrombin time should be performed in case of concomitant use of vitamin K dependent anti-coagulant.

DOSAGE AND ADMINISTRATION

Dosage

Initial daily dosage is usually 10-15 mg/kg, then doses are titrated up to the optimum dosage.
This is generally within the range 20-30 mg/kg. Nevertheless, where seizure control is not achieved within this range, the dose may be further increase adequate; patients should be carefully monitored when receiving daily doses higher than 50 mg/kg.
- In children, usual dosage is about 30 mg/kg per day.
- In adults, usual dosage is within the range 20-30 mg/kg per day.
- In elderly, although the pharmacokinetics of Valproate are modified, they have limited clinical significance and dosage should be determined by seizure control.

Administration

The use of a sustained release form allows to give the drug once daily. It may be use in children provided that they are able to take such a form.

DIRECTION FOR USE

To be swallowed whole. Do not chew.

OVERDOSAGE

The clinical picture of massive acute intoxication usually includes coma, with hypotonia, decreased reflexes, myosis, and decreased respiratory function. Seizures have also been reported in presence of very high plasma levels.
The following measures should be implemented in hospitals: gastric lavage useful up to 10 to 12 hours following ingestion, institution of forced diuresis, cardio respiratory monitoring. In very severe cases, dialysis or exchange transfusion may be necessary. Naloxone has been successfully used in 1 case. Such intoxications usually have a good prognosis, though deaths have occurred following massive overdosage.

EXPIRY DATE

Do not use later than the expiry date.

STORAGE

KEEP IN A DRY PLACE AT A TEMPERATURE NOT EXCEEDING 30^{o}C.

KEEP OUT OF REACH OF CHILDREN.

PRESENTATION

VALPARIN CHRONO 300: It is available as white, round, biconvex film coated tablets, in strip of 10 tablets.
VALPARIN CHRONO 500: It is available as white, oblong shaped film coated tablets with breakline on both sides, in strip of 10 tablets

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Manufactured by :
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