# SODIUM VALPROATE + VALPROIC ACID

# VALPARIN XR 500

## 500 mg Controlled Release Tablet

## Anticonvulsant

**FORMULATION**

Each controlled release tablet contains:

Sodium Valproate ..... 333 mg

Valproic Acid .....145 mg

(equivalent to Sodium Valproate.....500 mg)

**PRODUCT DESCRIPTION**

Sodium Valproate + Valproic Acid (Valparin XR 500) 500 mg controlled release tablet is a white oblong shaped film coated tablets with break line on both side.

**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 gabaergic 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 distribution is primarily limited to the blood and to rapid-exchange extracellular fluids. Valproate diffuses into the cerebrospinal fluid 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 anti-epileptics, it therefore does not accelerate its own degradation not that of other substances such as oral contra-ceptives 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 bioavalability,
- lowering of maximum plasma concentrations (Cmax) of the total and free fractions (Cmax decreased by approximately 25%, but relatively stable in 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**

Treatment of generalized epilepsy particularly with absence, myoclonic, tonic-clonic, atonic and mixed patterns of seizures, and partial epilepsy particularly with simple or complex, secondary generalized, specific syndromes (Lennox Gastaut).

Treatment and prevention of mania associated with bipolar disorders.

**DOSAGE AND ADMINISTRATION**

**Epilepsy**

The dose should be adjusted to the needs of individual patient to achieve adequate control of seizures.

**Adults** – 600 mg daily in 2 divided doses. May be increased by 200 mg every 3 days to a usual range of 1 g to 2 g daily (20 to 30 mg /kg daily) up to maximum of 2.5 g daily may be necessary if adequate control has not been achieved.

**Children** – Usual range 20 to 30 mg /kg daily, which may be increased to 40 mg /kg daily in severe cases, but only with monitored plasma levels.

**Elderly** – dosage should be determined be seizure control.

**In combination with anticonvulsants** – When starting Sodium Valproate + valproic acid in patients on other anticonvulsants (phenytoin, phenobarbital, and carbamazepine) these should be tapered slowly. Initiation therapy should be gradual, with target dose being reached after about 2 weeks. To raise the dose by 5 to 10 mg /kg/day.

**In patients with renal insufficiency** – It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring of plasma concentrations may be misleading.

**Bipolar**

**Recommended Initial Dose:** 20 mg/kg/day. The dose may be adjusted according to individual clinical response. The maximum dose should not exceed 3,000 mg daily.

**Recommended Maintenance Dose:** 1,000 mg - 2,000 mg/day. Doses should be adjusted according to individual clinical response. Prophylactic treatment should be established individually with the lowest effective dose.

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

**CONTRAINDICATIONS**

Acute and chronic hepatitis, family history of severe hepatitis, notably drug-induced hepatitis, propyria, hypersensitivity to sodium valproate.

Contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme ploymerase γ(POLG).

**WARNINGS AND PRECAUTIONS**

Liver damage resulting in fatalities have been exceptionally reported. Patients most-at-risk, especially in cases of multiple anti-convulsant therapy, are infants and young children under the age of 3 with severe seizure disorders. After the age of 3 the incidences reduces significantly and progressively decreases with age. Mono-therapy is recommended in children under 3 years of age, but the potential benefit of Sodium Valproate + Valproic acid should be weighed against the risk of liver damage. Liver function tests are required before beginning treatment 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 work up should be performed (including prothrombin time), dosage may be reconsidered and work ups should be repeated on the basis of the changes in the parameters. In children, under 3 years of age salicylates should not be prescribed concurrently due to 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 and bleeding. Immune disorders have been noted only exceptionally and hence benefit Sodium Valproate + Valproic Acid should be weighed against potential risk in patients with SLE.

Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hyperammonemia should be also be considered in patients who present with hypothermia. If ammonia is increased, sodium valproate + valproic acid therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders. Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered. Hypothermia has been reported in association with sodium valproate + valproic acid therapy both in conjunction with and in the absence of hyperammmonemia.

Sodium Valproate + Valproic Acid is partially eliminated partially eliminated in the urine as keto-metabolite which may lead to a false interpretation of the urine ketone test.

Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. Patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients and caregivers of patients should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

Sodium Valproate + Valproic Acid should not be used in 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 development disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at a regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Sodium Valproate + Valproic Acid plans a pregnancy or if she becomes pregnant. Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Sodium Valproate + Valproic Acid (Valparin XR 500) during pregnancy.

**PREGNANCY AND LACTATION**
Sodium Valproate + Valproic Acid (Valparin XR 500) should not be used in female children, in women of childbearing potential and in pregnant women unless other treatments are ineffective 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.
Valproate is excreted in human milk with a concentration between 1% and 10% of maternal serum level, up to now children breastfed. A decision must be made whether to discontinue breast-feeding or to discontinue /abstain from valproate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

**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 phenobarbital dose reduction when signs of sedation develop; if necessary, monitor plasma phenobarbital levels.
Phenytoin - Generally, decreases total phenytoin plasma concentrations. In particular, increase in the concentrations of free phenytoin, which may lead to signs of overdosage (valproic 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.
Carbamazepine - Clinical toxicity has been reported when administered with carbamazepine, as sodium valproate + valproic acid may potentiate toxic effects of carbamazepine.
Lamotrigine - Valproate may reduce lamotrigine metabolism necessitating dosage reduction of latter.
Felbamate - Valproic acid may decrease felbamate mean clearance by up to 16%.
Zidovudine - Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.
Mefloquine and Chloroquine - Increases valproic acid metabolism and has a convulsant effect; therefore epileptic seizures may occur in combined therapy.
Carbapenem antibiotics such as imipenem, panipenem and meropenem: A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control.
Colestyramine may decrease the absorption of sodium valproate + valproic acid.
Rifampicin - May decrease the valproic acid blood levels resulting in lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.
Topiramate - Concomitant administration of sodium valparoate + valproic acid and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients, taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.
Miscellaneous - In case of concomitant use of valproate and highly bound protein drugs (like aspirin), freeserum levels of valproate may be increased.
The serum levels of valproate may be increased (as a result of reduced hepatic metabolism) 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.

**ADVERSE REACTIONS**
- Rare cases of liver dysfunction (please see Precaution)
- Confusion or convulsions: a few cases of stupor either isolated or associated with an upsurge in convulsions with sodium valproate have been observed, and they regress on discontinuation of treatment or dosage reduction. These states usually occur in the 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 anemia, leucopenia or pancytopenia
- Isolated hyperammonaemia without change in liver function tests may occur. This should not cause treatment discontinuation
- Rarely pancreatitis, vasculitis, hearing loss.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".

Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

**OVERDOSAGE AND TREATMENT**
The clinical picture of massive acute intoxication usually includes coma, with hypotonia, decreased reflexes, myosis, 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, cardiorespiratory monitoring. In very severe cases, dialysis or exchange transfusion may be necessary. Naloxone has been successfully used in a few isolated cases. Such intoxications usually have a good prognosis, though deaths have occurred following massive overdosage.

**STORAGE AND CONDITION**
Store at temperatures not exceeding 30ºC.

**CAUTION**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**AVAILABILITY**
Sodium Valproate + Valproic Acid (Valparin XR 500) 500 mg Controlled Release Tablet - Aluminum Foil Strip x 10's (Box of 100's) - DRP-2768

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