• RM-SODIUM VALPROATE Insert (Sun)

FRONT

RiteMED®

SODIUM VALPROATE

200 mg Enteric-Coated Tablet
ANTICONVULSANT / ANTIEPILEPTIC

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FORMULATION
Each enteric-coated tablet contains:
Sodium Valproate, BP ..... 200 mg

CLINICAL PHARMACOLOGY
Sodium valproate is an anticonvulsant.

MECHANISM OF ACTION
The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino-butyric acid through an action on the further synthesis or further metabolism of GABA.

PHARMACOKINETICS
The half life of sodium valproate is usually within the range of 8-20 hours. It is usually shorter in children. The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 microml/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free drug is usually between 6% and 15% of the total plasma levels.

INDICATIONS
It is used particularly in the treatment of primary generalised seizures, has notable benefit in absence and myoclonic seizures, also in partial seizures. It is also used to treat the acute manic phase of bipolar disorder and for the prophylaxis of migraine.

CONTRAINDICATIONS
- Active liver disease or family history of severe hepatic dysfunction, particularly drug related, porphyria.
- Known hypersensitivity to the drug.

WARNINGS AND PRECAUTIONS
Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies. This may give false positives in the urine testing of possible diabetics.

Liver dysfunction, including hepatic failure resulting in fatalities has reported to occur in patients on valproic acid or sodium valproate. Patients most at risk are children, especially those under the age of three and those with congenital, metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with severe mental retardation. Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk. An abnormally prolonged prothrombin time particularly in association with other relative abnormalities requires cessation of treatment.

If hyperammonaemia occurs with associated clinical symptoms such as vomiting, ataxia and increasing clouding of consciousness, the drug should be discontinued.

There have been reports of pancreatitis including, rarely, fatalities in patients usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their pancreatic enzymes including serum amylase estimated; if these levels are elevated then treatment should be discontinued.

Valproic acid inhibits the second stage of platelet aggregation leading to prolongation of bleeding time and frequently to thrombocytopenia. These effects are usually associated with doses above the recommended limits and are reversible.

Pregnancy & Lactation
An increased incidence of congenital abnormalities including facial dysmorphia, neural tube defects and multiple malformations particularly of the limbs has been demonstrated in offspring born to mothers with epilepsy both untreated and treated including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube effects in the offspring of women at high risk.

Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Pregnancy should be carefully screened and women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy that may be related to hypofibrinaemia which is associated with a decrease of coagulation factors. Afibrinaemia has also been reported and may be fatal. It should be noted however that haemorrhagic syndrome may also be induced by phenobarbital and other enzyme-inducers.

Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

There appears to be no contraindications to breast feeding by patients on valproate as the concentration of valproic acid found in the breast milk is very low, between 1% & 10% of total maternal plasma levels. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

DRUG INTERACTIONS
Valproate has appreciably less enzyme inducing effect than certain other anticonvulsants and the efficacy of oral contraceptive agents does not appear to be affected.

Concurrent treatment with valproate may affect the performance of some drugs and so clinical monitoring is recommended especially at the beginning of combined therapy.

The effects of neuroleptics, monoamine oxidase inhibitors, antidepressants and benzodiazepines may be potentiated.

Phenobarbitone and primidone plasma levels may increase and sedation may occur. The dose should be reduced immediately. Clinical monitoring is recommended throughout the first two weeks of combined treatment.

Phenytoin plasma levels particularly of the free form may increase following an initial decrease in total levels.

The toxic effect of carbamazepine may be potentiated. Dosages should be adjusted when appropriate.

The metabolism of lamotrigine may be inhibited and the half life lengthened. Dose should be adjusted when appropriate. Coadministration may increase the risk of rash.

Zidovudine plasma concentration may be raised leading to increased zidovudine toxicity.

Protein-binding of warfarin and other coumarin anticoagulants may be reduced. The prothrombin time should be closely monitored.

Anti-epileptic drugs with enzyme-inducing effects may decrease valproate serum concentrations.

Cimetidine and erythromycin may prolong the half life and reduce clearance of valproate as a result of reduced hepatic metabolism.

Mefloquine may increase valproic acid metabolism and may have a convulsant effect.

Cholestyramine may decrease the absorption of valproate.

Salicylates such as aspirin may displace valproate from protein-binding sites.

Felbamate may increase valproate serum concentration.

220 mm

140 mm

BACK

SIDE EFFECTS
Hepatic: Liver dysfunction including hepatic failure resulting in fatalities have been reported. Serious or fatal hepatotoxicity may be preceded by symptoms such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice.

Neurological: Ataxia, tremor, sedation, lethargy, confusion, stupor, hallucination or convulsions. Rare cases of encephalopathy, coma and reversible dementia associated with reversible cerebral atrophy have been reported. An increase in alertness, occasionally aggression, hyperactivity and behavioural deterioration have been reported. Hearing loss either reversible or irreversible has been reported rarely.

Gastrointestinal: Increase in appetite, weight gain, gastrointestinal irritation at the start of therapy and less commonly, nausea may occur.

Dermatological: Transient hair loss has often been noted in some patients. In exceptional cases toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme have been reported. Rarely signs of an immune disorder have occurred, therefore, caution should be observed when using the drug in patients with lupus erythematosus. The occurrence of vasculitis has occasionally been reported.

Haematological: Rare cases of red cell hypoplasia, leucopenia and pancytopenia have been reported. Isolated reduction of fibrinogen may occur.
Other side effects include hyperammonaemia, oedema, pancreatitis, irregular periods or amenorrhoea, gynaecomastia and reversible Fanconi's syndrome.

OVERDOSAGE
At plasma concentration of up to 5 to 6 times the maximum therapeutic levels there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose i.e., with plasma concentration 10 to 20 times the maximum therapeutic levels, there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizure have been reported in the presence of very high plasma levels. Deaths have been reported following large overdoses. Hospital management of overdosage including induced vomiting, gastric lavage, assisted ventilation and other supportive measures is recommended.

Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

DOSAGE AND ADMINISTRATION
Adults: Initially 600mg daily in divided doses. Increase by 200mg at three day interval until control is achieved which is usually within the dosage range of 1000 to 2000mg/day. Where adequate control is not achieved within this range the dose may be further increased to 2500mg/day.

Children over 20kg: Initial dosage should be 400mg/day irrespective of weight with spaced increases until control is achieved which is usually within the range 20- 30mg/kg body weight per day. When adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg: The usual dose is 20mg/kg/day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored.

Elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control.

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 children requiring doses higher than 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Combined therapy: When starting therapy in patients already on other anticonvulsants; dose of this drug should be tapered slowly 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 e.g., phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose. When barbiturates are being administered concomitantly and particularly if sedation is observed, the dose of barbiturate should be reduced.

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

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

AVAILABILITY
Ritemed® Sodium Valproate 200 mg Enteric-Coated Tablet, in Aluminum Foil Strip x 10's (Box of 100's).

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND RiteMED at (+632) 8-726-0835 or e-mail productsafety@ritemed.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

Date of First Authorization:
Date of Revision: March 2021
DRP-8660-01

Manufactured by Sun Pharmaceutical Industries Ltd.
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Silvassa-396230, U.T. of Dadra & Nagar Haveli, India
Imported by Sun Pharma Philippines, Inc.
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Salcedo Village, Makati City
Distributed by **RiteMED Phils., Inc.**
56 Epifanio Delos Santos Ave., Mandaluyong, Metro Manila

RTM700911IN01

Reg. IPOPHIL

• PRINT COLOR

Pantone 2756 C

INGRAFIX DESIGN STUDIO

• F.A. Revision Date: 3 March 2021