Size : 250x160 mm
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Front Side

100% Pantone 485 C

160 mm

BRAIPORIN SYRUP

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

Sodium Valproate Oral Solution BP

COMPOSITION

Each 5 ml contains:

Sodium Valproate BP	200 mg
Flavoured Syrupy base	q.s.
Colour : Ponceau 4R	

PHARMACOLOGY

PHARMACODYNAMIC

Sodium valproate increases levels of gamma-aminobutyric acid and prolongs the recovery of inactivated sodium channels. These properties may be responsible for its action as a CNS depressant. Sodium valproate interacts with voltage-sensitive sodium channels. Its presence inhibits repetitive firing of neurons and is frequency dependent. In this way, its action is similar to those of phenytoin and carbamazepine.

Sodium valproate affects the action of gamma-aminobutyric acid (GABA). Unlike sedative-hypnotics that enhance the postsynaptic action of GABA (eg, phenobarbital, benzodiazepines), Sodium valproate appears to indirectly increase the amount of GABA available to the CNS. In vitro studies have shown that Sodium valproate increases GABA levels by increasing the activity of glutamic acid decarboxylase and by inhibiting GABA transaminase.

PHARMACOKINETIC

Sodium valproate is usually absorbed rapidly from the GI tract. The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2.

INDICATION

In the treatment of generalised, partial or other epilepsy.

DOSAGE AND ADMINISTRATION

Sodium valproate Syrup is for oral administration.
Daily dosage requirements vary according to age and body weight.
Sodium valproate Syrup may be given twice daily. If it is necessary to dilute Sodium valproate Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14-day shelf life.

Dosage
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/day 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.

Children under 20kg
20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

CONTRAINDICATION

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

WARNING AND PRECAUTIONS

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Sodium valproate should be discontinued.

Women of childbearing potential: This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Sodium valproate is prescribed for the first time, or when a women of child bearing potential treated with Sodium valproate plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Suicidal ideation and behaviour: Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Haematological: 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 case of spontaneous bruising or bleeding.

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Sodium valproate, the potential benefit of Sodium valproate should be weighed against its potential risk in patients with systemic lupus erythematosus.

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Sodium valproate.

Weight gain: Sodium valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it.

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Diabetic patients: Sodium 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.

In addition, care should be taken when treating diabetic patients with Sodium valproate Syrup since it contains 3.6g sucrose per 5ml.

Alcohol: Alcohol intake is not recommended during treatment with valproate

DRUG INTERACTION

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Sodium valproate may potentiate the effect of other psychotropics such as antpsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

Lithium
Sodium valproate has no effect on serum lithium levels

Phenobarbital
Sodium 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
Sodium 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
Sodium valproate decreases phenytoin total plasma concentration. Moreover Sodium 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 Sodium valproate was administered with carbamazepine as Sodium valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine
Sodium valproate reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

Felbamate
Valproic acid may decrease the felbamate mean clearance by up to 16%.

Zidovudine
Sodium 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.

Temozolomide
Co-administration of temozolomide and Sodium valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

PREGNANCY AND LACTATION

Pregnancy
In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73% (95% CI: 8.16 – 13.29). Available data indicate dose dependency of this effect.

Lactation
Excretion of Sodium valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Sodium valproate, specifically haematological disorders.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Use of Sodium valproate may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines.

SIDE EFFECTS

Liver injury, Nausea, Gastralgia, Diarrhoea, Extrapyramidal disorder, Stupor, Somnolence, Convulsion, Memory impairment, Headache, Nystagmus, Tremor, Confusional state, Aggression, Agitation, Disturbance in attention, Hyponatraemia, Anaemia, Thrombocytopenia, Dysmenorrhea, Haemorrhage, Deafness, Weight increased.

OVERDOSE

Cases of accidental and deliberate Sodium 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.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels.

Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

STORAGE

Store below 30°C, protected from light & moisture.
Keep medicine out of reach of children.

Product from
Unosource Pharma Ltd.

Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
22, Sector-6A, I.I.E., SIDCUL,
Haridwar-249 403, INDIA.

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