xxxxxxx-5343

SODIUM VALPROATE

VALPARIN-200

200 mg / 5 mL Syrup
ANTICONVULSANT

FORMULATION
Each 5 mL contains:
Sodium Valproate, BP ..... 200 mg
PRODUCT DESCRIPTION
Sodium Valproate (Valparin-200) 200 mg / 5 mL Syrup is a yellow colour, clear, syrup liquid with pineapple flavour.
PHARMACOLOGY
Pharmacodynamics
Sodium Valproate is an anticonvulsant. The most likely mode of action for Sodium Valproate is potentiation of the inhibitory action of gamma-amino acid (GABA) through an action on the further synthesis or further metabolism of GABA.
In certain in-vitro studies it was reported that Sodium Valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Sodium Valproate does not have a mitogen-like effect on inducing HIV replication. Indeed, the effect of Sodium Valproate on HIV replication ex-vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.
Pharmacokinetics
The half-life of Soduim Valproate is usually reported to be within the range of 8-20 hours. It is usually shorter in children.
In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic levels.
The reported effective therapeutic range for plasma valproic acid levels is 70-100 mg/L (278694 micromole/L). This reported range may depend on time of sampling and presence of comedication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels.
An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. The pharmacological (or therapeutic) effects of Sodium Valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.
INDICATION
For the 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 syndrome (Lennox Gastaut).
DOSAGE AND ADMINISTRATION
Usual requirements are as follows:
Adults - Dosage should start at 600mg daily by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 2030mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg/day.
For Children:
Over 20 kg - Initial dose 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 35 mg/kg body weight per day.
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.
Use in the elderly - Although the pharmacokinetics of Sodium Valproate is 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 the 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 Sodium 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 (see aspirin/salicylate product information on Reye's Syndrome). In addition in conjunction with Sodium valproate , concomitant use in children under 3 years can increase the risk of liver toxicity.
Female children, female adolescents, women of childbearing potential and pregnant women - Sodium valproate should be initiated and supervised by a specialist experienced in the management of epilepsy.
Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Sodium valproate should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.
Combined Therapy - When starting Sodium Valproate in patients already on the on other anticonvulsants, these should be tapered slowly: initiation of Sodium valproate 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, e.g. Phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Sodium valproate. 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 hematological 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
- Active liver disease
- Hypersensitivity to sodium valproate
- Personal or family history of severe hepatic dysfunction, especially drug related• Porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG related disorder.

WARNINGS AND PRECAUTIONS
Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawals of valproate, discontinuation should normally only be done under the provision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to clinical implications of possible variations in plasma concentrations.
Special Warnings
Liver dysfunction:
Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.
The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).
Monotherapy is recommended in children under the age of 3 years when prescribing Sodium valproate, but the potential benefit of Sodium valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.
In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.
Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may proceed to jaundice, should be taken into consideration, especially in patients at risk.
- Non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, edema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- In patients with epilepsy, recurrence of seizures.

There is an indication for immediate withdrawal of the drug.
Patients (or their family for 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 measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.
Amongst usual investigations, tests which reflect protein synthesis, 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 transaminases) requires cessation of Sodium valproate therapy.
As a matter of precaution and in the case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.
As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of the therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.
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; the 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.
Female children/Female adolescents/Women of childbearing potential/Pregnancy: Sodium valproate should not be used in female 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 developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at the puberty and urgently when a women of childbearing potential treated with Sodium valproate 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 during pregnancy.
The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.
In particular the prescriber must ensure the patient understands:
- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to contraception, if possible.
Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.
Suicidal ideation and behavior: Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications.
A meta-analysis of randomized placebo controlled trials of anti-epileptic drugs has also shown a small increased risk for of suicidal ideation and behavior. The mechanism of the risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate.
Therefore, patients should be advised to seek medical device should signs of suicidal ideation and behavior 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.
Carbapenem agents: The concomitant use of valproate and carbapenem agents is not recommended.
Patients with known or suspected mitochondrial disease: Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate induced acute liver failure and liver related deaths have been reported at a higher rate in Patients with hereditary neurometabolic syndromes caused by the mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers- Huttenlocher Syndrome.
POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not only limited to unexplained encephalopathy, refractory epilepsy (focal myoclinic), status epilipticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor , neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.
Precautions
This product contains FD&C Yellow No. 5 (Tartrazine) which may cause allergic type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (Tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.
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 minimize it.
Pregnancy: Women of childbearing potential should not be started on Sodium valproate without specialist neurological advice. Adequate counseling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk of the fetus.
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.
PREGNANCY AND LACTATION
Sodium valproate should not be used in female children, in female adolescents, 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. Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.
Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16-13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which is no risk exists cannot be established.
Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.
Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long-term outcomes. Available data show that children exposed to valproate in utero are at risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).
If a woman wants to plan a pregnancy
- During pregnancy, maternal tonic-clonic seizures and status epilipticus with hypoxia may carry a particular risk of death for the mother and the unborn child.
- In women planning to become pregnant or who are pregnant, valproate therapies should be reassessed.
- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Valproate therapy should not be discontinued without reassessment of the benefits and risks of the treatment with valproate treatment is continued during the pregnancy, it is recommended to:

- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma Concentrations.
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.
- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Risk in neonate
- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors.

Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin K factors induced by Phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia's, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Sodium valproate therapy taking into account the benefit of therapy for the woman. Fertility
Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using valproate. Valproate administration may also impair fertility in men. Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.
DRUG INTERACTIONS
Effects of Sodium Valproate on other drugs:
Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Sodium valproate may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of 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 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 from 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.
Lamotrigine
Sodium valproate reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by near 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 closely monitored.
Effects of other drugs on Sodium Valproate
Antiepileptics with enzyme including effect (including phenytoin, Phenobarbital and carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.
On the other hand, combination of felbamate and Sodium valproate decreases valproic acid clearance by 22% to 50% and consequently increases the valproic plasma concentrations. Sodium 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 Sodium valproate may need adjustment. In case of concomitant use of Sodium 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, panipenem** and **meropenem:** Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%- 100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients established on valproic acid should be avoided. If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.
Colestyramine may decrease the absorption of Sodium valproate.
Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.
Other Interactions
Caution is advised when using Sodium valproate in combination with newer antiepilieptics whose pharmacodynamics may not be established.
Concomitant administration of valproate 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 those with pre-existing encephalopathy.
Sodium valproate usually has no enzyme-inducing effect; as a consequence, Sodium valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.
ADVERSE EFFECTS
The following CIOMS frequency rating is used, when applicable:
Very Common (> 1/10); Common (>1/100 to <1/10); Uncommon (>1/1000 to < 1/100); Rare (>1/10,000 to <1/1,000); Very Rare (<1/10,000), not known (cannot be estimated from available data).
Congenital malformations and developmental disorders (see warnings and precautions & Fertility, pregnancy & lactation).
Hepatobiliary disorders
Common: liver injury
Severe liver damage, including hepatic failure sometimes resulting to death, has been reported. Increased liver enzymes are common, particularly early in treatment, and may transient.
Gastrointestinal disorders
Very common: nausea
Common: gastralgia, diarrhoea
The above three adverse events frequently occur at the start of the treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Sodium valproate with or after food or by using Enteric Coated Sodium valproate (Sodium Valproate Gastro-resistant tablets) Uncommon: pancreatitis, sometimes lethal.
Nervous System disorders
Very Common: tremor
Common: extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus
Uncommon: coma, encephalopathy, lethargy, reversible parkinsonism, ataxia, paresthesia.
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.
Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy, it occurred early in treatment on rare occasions and is usually transient.
Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.
Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other reversible on withdrawal of treatment or reduction of dosage.
An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioral deterioration have been reported.
Psychiatric disorder
Common: confusional state, aggression, agitation, disturbance in attention
Rare: abnormal behavior, psychomotor hyperactivity, learning disorder These ADRs are principally observed in the pediatric population.
Metabolic Disorders
Common: hyponatraemia
Rare: hyperammonaemia
Cases of isolated and moderate hyperammonaemia without change in liver function test may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur, Sodium valproate should be discontinued.
Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered.
Endocrine Disorders
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH)
Rare: hypothyroidism
Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia
Uncommon: Pancytopenia,leucopenia
The blood picture returned to normal when the drug was discontinued.
Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anemia, macrocytic, macrocytosis Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin 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). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.
Skin and subcutaneous tissue disorders
Common: hypersensitivity, transient and or dose related alopecia (hair loss). Regrowth normally begins within six months, although the hair may become more curly than previously. **Uncommon:** angioedema, rash
Hirsutism and acne have been very rarely reported.
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.
Reproductive system and breast disorders
Common: dysmenorrheal
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries Very rarely gynecomastia has occurred.
Vascular disorders
Common: hemorrhage
Uncommon: vasculitis
Ear and labyrinth disorders
Common: Deafness, a cause and effect relationship has not been established Renal and urinary disorders
Rare: enuresis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Sodium valproate therapy, but the mode of action is as yet unclear.
General disorders and administration site conditions
Uncommon: non-severe edema peripheral
Musculoskeletal and connective tissue disorders
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long term therapy with Sodium valproate. The mechanism by which Sodium valproate affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus
Respiratory, thoracis and mediastinal disorders Uncommon: pleural effusion
Investigations:
Common: Weight increased
Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, INR prolonged).
Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome.
Neoplasms benign, malignant and unspecified (including cysts and polyps)
Rare: myelodysplasctic syndrome
"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
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 and metabolic acidosis. A favorable 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 edema 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 CONDITION
Store at temperatures not exceeding 30^{O}C. Protect from light.
CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. AVAILABILITY
Sodium Valproate (Valparin-200) 200 mg / 5 mL Syrup - 100 mL Amber Glass Bottle with measuring cup in a box - DR-XY44035
DATE OF FIRST AUTHORIZATION
January 7, 2015
DATE OF REVISION
June 2016

torrent PHARMA

Manufactured by :
ELYSIUM PHARMACEUTICALS LTD.
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Dist: Vadodara, Gujarat 391 440, INDIA.

For :
TORRENT PHARMACEUTICALS LTD.
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PRODUCT NAME	:	Valparin 200 Syrup	**COUNTRY :** Philippines	**LOCATION :** Elysium		**Supersedes A/W No.:**
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1	**REMARK :**		
DESIGN STYLE	:	Front	**PANTONE SHADE NOS.:**	**SUBSTRATE :**		
CODE	:	xxxxxxxxx-5343	■ Black	**Activities**	**Department**	**Name**
DIMENSIONS (MM)	:	150 x 530		Prepared By	**Pkg.Dev**	
ART WORK SIZE	:	S/S		Reviewed By	**Pkg.Dev**	
DATE	:	16-06-2017		Approved By	**Quality**	

Signature | **Date**