Sodium Valproate 200 mg /500mg Gastro-resistant Tablets

1. Name of the medicinal product

Sodium Valproate 200 mg Gastro-resistant Tablets Taj Pharma
Sodium Valproate 500mg Gastro-resistant Tablets Taj Pharma

2. Qualitative and quantitative composition

Each Enteric coated tablet contains	
Sodium Valproate	200 mg
Excipients	q.s
Colour: Ponceau 4R & Sunset Yellow FCF	

Each Enteric coated tablet contains	
Sodium Valproate	500 mg
Excipients	q.s
Colour: Ponceau 4R & Sunset Yellow FCF	

3. Pharmaceutical form

Gastro-resistant Tablet.

4. Clinical particulars

4.1 Therapeutic indications

In the treatment of generalised, partial or other epilepsy.

4.2 Posology and method of administration

Sodium Valproate 200 mg Gastro-resistant Tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Sodium valproate tablets may be given twice daily. The tablets should be swallowed whole and not crushed or chewed.

Dosage

Usual requirements are as follows:

Adults

Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg – 2000 mg per day, i.e. 20 – 30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg

Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20 – 30 mg/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.

Children under 20 kg

20 mg/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 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly

Although the pharmacokinetics of valproate are 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 (see section 5.2 Pharmacokinetic properties).

In patients with hepatic insufficiency

Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

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 (see section 4.4.1 Special warnings).

Combined Therapy

When starting sodium valproate in patients already on other anti-convulsants, 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 10 mg/kg/day when used in combination with anti-convulsants 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 40 mg/kg/day clinical chemistry and haematological 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 (see section 5.2 Pharmacokinetic properties).

Female children, female adolescents and 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 (see section 4.4 and 4.6) 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.

4.3 Contraindications

• Active liver disease

• Personal or family history of severe hepatic dysfunction, especially drug related

• Patients with known urea cycle disorders (see section 4.4)

• Hypersensitivity to sodium valproate

• Porphyria

• Valproate is contraindicated in 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 (see section 4.4).

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision 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 the clinical implications of possible variations in plasma concentrations.

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.

4.4.1 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 anti-convulsant therapy, are infants and in particular young children under the age of 3 years 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 precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.

- in patients with epilepsy, recurrence of seizures.

These are 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 case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most anti-epileptic drugs, increased liver enzymes are common, particularly at the beginning of 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; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anti-convulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

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 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 limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus 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 (see section 4.3).

Female children/Female adolescents/Women of childbearing potential/Pregnancy:

Sodium valproate should not be used in female children, in women of child-bearing 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 puberty and urgently when a woman of child bearing potential treated with sodium valproate plans a pregnancy or if she becomes pregnant.

Women of child-bearing potential must use effective contraception during treatment and be informed of the risks associated with the use of sodium valproate during pregnancy (see section 4.6).

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 an appropriate alternative treatment prior to conception, if possible (see section 4.6).

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.

Aggravated convulsions:

As with other anti-epileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

4.4.2 Precautions

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 (see section 4.8 Undesirable Effects).

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 (see sections 4.2 Posology and Method of Administration and 5.2 Pharmacokinetic Properties).

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 (see also section 4.8 Undesirable Effects).

Hyperammonaemia:

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with 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 (see section 4.8 Undesirable Effects).

Pregnancy:

Women of childbearing potential should not be started on sodium valproate without specialist neurological advice. Adequate counselling 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 to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients:

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.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking sodium valproate.

Alcohol:

Alcohol intake is not recommended during treatment with valproate.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Valproate on other drugs

- Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines

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.

- Olanzapine

Valproic acid may decrease the olanzapine plasma concentration.

- Phenobarbital

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***

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***

Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdose 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 valproate was administered with carbamazepine as 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 falbamate mean clearance by up to 16%.

- ***Rufinamide***

Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

- ***Propofol***

Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- ***Zidovudine***

Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Nimodipine***

In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***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 valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Valproate

Anti-epileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

Valproic acid metabolite levels may be increased in the case of concomitant use with ***phenytoin*** or ***phenobarbital***. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of ***felbamate*** and valproate decreases valproic acid clearance by 22% – 50% and consequently increase the valproic acid plasma concentrations. 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 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 ***panipenem, imipenem*** and ***meropenem***: Decreases in blood levels of valproic acid have been reported when it is co-administered with carabapenem 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 stabilised on valproic acid should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

Protease inhibitors such as ***lopinavir*** and ***ritonavir*** decrease valproate plasma level when co-administered.

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

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.

4.5.3 Other interactions

Caution is advised when using sodium valproate in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

- ***Quetiapine***

Co-administration of sodium valproate and quetiapine may increase the risk of neutropenia/leucopenia.

Valproate usually has no enzyme-inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Sodium Valproate 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.

Pregnancy Exposure Risk related to valproate

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic 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 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 anti-epileptics. 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 increased 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).

Female children and women of childbearing potential (see above and section 4.4)

If a Woman wants to plan a Pregnancy

• During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

• In women planning to become pregnant or who are pregnant, valproate therapy 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 (see section 4.6).

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits 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 specialised prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

<u>Risk in the neonate</u>

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic 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 hypoglycaemia 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, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sodium valproate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 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 anti-convulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common ≥ 1 %; Common ≥ 1 % and ≤ 10 %; Uncommon ≥ 0.1 % and ≤ 1 %; Rare ≥ 0.01 % and ≤ 0.1 %; Very rare ≥ 0.01 %, Unknown (cannot be estimated from available data).

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepatobiliary disorders:

Common: liver injury (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders:

Very common: nausea

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea

The above adverse events frequently occur at the start of 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.

Uncommon: pancreatitis, sometimes lethal (see section 4.4 Special Warnings and Special Precautions for Use)

Nervous system disorders:

Very common: tremor

Common: extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus

Uncommon: coma, encephalopathy, lethargy (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally, usually when in combination with other anti-convulsants. 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 anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder:

Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*

Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:

Common: hyponatraemia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

Rare: hyperammonaemia (see section 4.4.2 Precautions), obesity

Cases of isolated and moderate hyperammonaemia without change in liver function tests 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 (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Endocrine Disorders

Uncommon: Syndrome of inappropriate secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)

Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia (see section 4.4.2 Precautions)

Uncommon: pantoctyopenia, leucopenia

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including red cell aplasia, agranulocytosis, macrocytic anaemia, 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 (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders:

Common: Hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.*Uncommon:* angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

Rare: toxic epidermal necrolysis, Stevens-Johnson, syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:

Common: dysmenorrhea

Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:

Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation)

Uncommon: vasculitis

Ear and labyrinth disorders:

Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:

Uncommon: renal failure

Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi's 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: hypothermia, non-severe peripheral oedema

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, rhabdomyolysis (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:

Uncommon: pleural effusion

Investigations:

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6).

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Cases of accidental and deliberate valproate overdose have been reported. At plasma concentrations of up to 5 – 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. 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 (see also section 5.2 Pharmacokinetic Properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium in the sodium valproate formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 – 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Sodium valproate and valproic acid are anti-convulsants.

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.

5.2 Pharmacokinetic properties

The half-life of sodium valproate is usually reported to be within the range 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 serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40 – 100 mg/litre (278 – 694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. 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.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Povidone, talc, calcium silicate, magnesium stearate, hypromellose, citric acid monohydrate, macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid, titanium dioxide, amaranth lake, indigo carmine lake and hydroxypropyl cellulose.

6.2 Incompatibilities

There are no major incompatibilities.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Sodium valproate is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Sodium Valproate 200mg/500mg Gastro-resistant Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 and 112 tablets.

6.6 Special precautions for disposal and other handling

None.

7. Manufactured By:
Taj Pharmaceuticals Ltd.
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Industrial Estate, At & Post-Moraiya,
Tal-Sanand, Dist- Ahmedabad Gujarat (India)