United Pharmaceuticals

UNIVAL ENTERIC COATED TABLET 200MG

Sodium valproate

Name and strength of Active Ingredient
Sodium valproate 200mg

Product Description
White to off white 11mm biconvex enteric coated tablet.

Pharmacodynamic
- Sodium valproate is an anticonvulsant.
- The most likely mode of action for sodium valproate is potentiation of the inhibitory action of gamma amino-butyric 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 reported effective therapeutic range for plasma valproic acid levels is 40 – 100 mg/L (278 – 694 µmol/L). This reported range may depend on time of sampling and presence of co-medication.

Distribution
The percentage of free (unbound) drug is usually between 6 – 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.
Placental transfer
Valproate crosses the placental barrier in animal species and in humans:
• In animal species, valproate crosses the placenta to a similar extent as in humans.
• In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism
The major pathway of valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9 and UGT2B7.

Elimination
The half-life of Sodium valproate is usually reported to be within the range 8 – 20 hours.
Interaction with oestrogen-containing products Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.

Special populations
Renal insufficiency
In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

Paediatric population
Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 – 67 hours. In children aged 2 – 10 years, valproate clearance is 50% higher than in adults.

Indication
In the treatment of generalized or partial epilepsy, particularly with the following patterns of seizures - Absence - Myoclonic - Tonic-clonic - Atonic - Mixed
As well as, for partial epilepsy - Simple or complex seizures – Secondary generalized seizures - Specific syndromes (West, Lennox-Gastaut).

Posology and method of administration
UNIVAL Enteric Coated Tablet is for oral administration.
Daily usage requirements vary according to age and body weight.
UNIVAL Enteric Coated Tablet may be given twice daily.

Female children and women of childbearing potential
Sodium Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warning and precautions and Fertility, pregnancy and lactation sections). The benefit and risk should be carefully reconsidered at regular treatment reviews. Sodium valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

Monotherapy
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 100mg to 200mg per day, i.e 20-30mg/kg 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.

Elderly
Although the pharmacokinetics of sodium 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.

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. In addition, in conjunction with sodium valproate, concomitant use in children under 3 years can increase the risk of liver toxicity.

Combined Therapy
When starting sodium valproate in patients already 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, phenobarbitone 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. In children requiring doses higher than 40mg/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.

Contraindications
Sodium valproate is contraindicated in the following situations:
• In epilepsy
- Sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
- Sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section).
• In bipolar disorder
- Sodium valproate is contraindicated in pregnancy.
- Sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section).
• Known hypersensitivity to sodium valproate
• Personal or family history of severe hepatic dysfunction, especially drug related
• Active liver disease
• Urea cycle disorder
• Porphyria
• Sodium 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 Special Warnings and Precautions for Use).

Warning and Precautions

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, the incidence of occurrence is significantly reduced and progressively decreases with age.
The concomitant use of salicylates should be avoided in children under 3 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'):
- nonspecific 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 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 antiepileptic 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: CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING SODIUM VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HAEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, SODIUM VALPROATE SHOULD BE DISCONTINUED.

Female children, Women of childbearing potential, and pregnant women:
Sodium valproate has high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformation and neurodevelopmental disorders.

Sodium valproate is contraindicated in the following situations:
• In pregnancy unless there is no suitable alternative treatment for epilepsy indication
• In pregnancy for bipolar disorder indication.
• In women of childbearing potential unless below conditions are fulfilled.

Conditions of Pregnancy Prevention Programme:
The prescriber must ensure that:
• Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of risks and the measures needed to minimize the risks.
• The potential for pregnancy is assessed for all female patients.
• The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.
• The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see Fertility, Pregnancy and Lactation).
Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a physician experienced in the management of epilepsy.
• The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with sodium valproate.
• The patient understands the need for regular (at least annual) review of treatment by a prescriber experienced in the management of epilepsy.
• The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
• The patient understands the need to urgently consult her physician in case of pregnancy.
• The patient has received the Patient Guide.
• The patient has acknowledged that she has understood the hazards and necessary precautions associated with sodium valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children
The prescriber must ensure that:
• The parents/caregivers of female children understand the need to contact the doctor once the female child using sodium valproate experiences menarche.
• The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.

In patient who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the prescriber to switch female children to alternative treatment before they reach adulthood.

Pregnancy test
Pregnancy must be excluded before start of treatment with sodium valproate. Treatment with sodium valproate must not be initiated in women of childbearing potential without a negative pregnancy test) plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception
Women of childbearing potential who are prescribed sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium valproate. These patients must be
provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by the prescriber
The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber should discuss the Annual Risk Acknowledgement Form at initiation and during each annual revoew and ensure that the patient has understood its content.

Pregnancy planning
If a woman is planning to become pregnant, a prescriber experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy
If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in perinatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:
• The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.
• Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, The Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide the guidance regarding use of sodium valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber at treatment initiation, the annual visit, and when a woman plans a pregnancy or is pregnant.

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by the doctor experienced in the management of epilepsy.

Use in male patients of reproductive potential:
A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam (see Pregnancy). Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk. The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

The male patient should be advised:
• not to donate sperm during treatment and for 3 months after stopping the treatment,
• of the need to consult his doctor to discuss alternative treatment options,
as soon as he is planning to father a child, and before discontinuing contraception,
• that he and his female partner should contact their doctor for counseling
in case of pregnancy if he used valproate within 3 months prior to conception.
The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use (Annual Risk Acknowledgement Form). Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to all men of reproductive potential using valproate.

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 sodium valproate. in case of aggravated convulsions, the patients should be advised to consult their physician immediately.

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 of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data does 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 sign of suicidal ideation and behaviour emerge.

Carbapenem agents: The concomitant use of sodium valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease:
Sodium 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 sodium 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 Contraindications).

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 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 Posology and Method of Administration and 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 Undesirable Effects).

Hyperammonaemia: when a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatments 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 the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimize it (see section Undesitrable Effects).

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.

Carnitine Palmitoyltransferase (CPT) type II deficiency:
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 sodium valproate.

Interaction with other medicinal Products and other forms of interactions
Effect of sodium valproate on other drug
• 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 the other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to sodium 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.

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140 x 380mm

• Olanzapine
Valproic acid may decrease the olanzapine plasma concentration.

• 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 withcarbamazepine 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%.

• 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
Sodium valproate may lead to an increased blood level of propofol. When co-administered with sodium valproate, a dose reduction of propofol may be considered

• Zidovudine
Sodium 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.

• 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.

Effects of other drugs on sodium valproate

• Anti-epileptics
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.

• Anti-malarial agents
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.

• Highly protein bound agents
In case of concomitant use of sodium valproate and highly protein bound agents (e.g. aspirin), free valproic acid plasma levels may be increased.

• Vitamin K-dependent factor 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.

• Cimetidine or erythromycin
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 carbapenem, 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 Special Warnings and Precautions for Use). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

• Rifampicin
Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, sodium valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

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

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

• Oestrogen-containing products, including oestrogen-containing hormonal contraceptives
Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in sodium valproate glucuronidation and may increase the clearance of sodium valproate, which would result in decreased serum concentration of sodium valproate and potentially decreased sodium valproate efficacy. Consider monitoring of sodium valproate serum levels. On the opposite, sodium valproate has no enzyme inducing effect; as a consequence, sodium valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

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

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

Fertility, Pregnancy and lactation

• Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
• Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy.
• Sodium valproate is contraindicated for use in women of childbearing potential unless the above-mentioned conditions of Pregnancy Prevention Programme are fulfilled (See Contraindications and Warnings and Precautions sections).

Pregnancy Exposure Risk related to sodium valproate
Both sodium valproate monotherapy and sodium valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including sodium valproate may be associated with a greater risk of congenital malformations than sodium valproate monotherapy.

Teratogenicity and developmental effects

Risk to children of fathers treated with valproate
A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neurodevelopmental disorders (NDDs) in children (from 0 to11 year sold) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine orlevetiracetam.The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versusbetween 2.3% to 3.2% in the composite lamotrigine/levetiracetammonotherapy group. The pooled adjusted hazard ratio (HR) for NDDsoverall obtained from the meta-analysis ofthe datasets was 1.50 (95% CI:1.09-2.07).
Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability,
communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually(see Warnings/Precautions).

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 sodium 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 sodium 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 sodium 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 sodium 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 sodium 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 sodium 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 sodium valproate in utero may be more likely to develop symptoms of attention deficit/ hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see above and Special Warnings and Precautions for Use)

Oestrogen-containing products
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of sodium valproate, which would result in decreased serum concentration of sodium valproate and potentially decreased sodium valproate efficacy.

If a Woman plans a Pregnancy
If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued.
If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women
Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to consider alternative treatment options.
During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy.

It is recommended to:
- Use the lowest effective dose and divide the daily dose sodium 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.

All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. 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 sodium valproate exposure.

Risk in the neonate
- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken sodium 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 sodium valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken sodium 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 sodium valproate during the last trimester of their pregnancy.

Breast-feeding
Sodium valproate is excreted in human milk. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section Undesirable effects).
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 sodium valproate (see Undesirable effects). Sodium valproate administration may also impair fertility in men (see Undesirable effects). In the few cases in which valproate was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed. Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

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 (see section Interactions with Other Medicaments and Other Forms of Interaction).

Undesirable effects
Congenital malformations and developmental disorders (see Special Warnings and Precautions for Use and Fertility, pregnancy and Lactation).

Hepato-biliary disorders:
Common: liver injury (see Special Warnings)
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see Posology and method of administration, Contraindications and Special warnings). Increased liver enzymes are common, particularly early in treatment, and may be transient (see Special Warnings).

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea

The above three 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 Special Warnings and 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.
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 disorders:
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 warning and precaution).
Rare: hyperammonaemia* (see section Precaution), 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 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 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see Precautions).
Uncommon: pancytopenia, leucopenia
Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis,
anaemia macrocytic, macrocytosis

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

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 Fertility, 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)
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: dysmenorrhea
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries
Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see Precautions; Fertility, pregnancy and lactation).
Uncommon: vasculitis

Eye disorders:
Rare: diplopia

Ear and labyrinth disorders:
Common: Deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Common: urinary incontinence.
Uncommon: renal failure.
Rare: enuresis, tubulointerstitial nephritis, 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: 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 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).

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

Overdose
Symptoms 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, 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 (see also section Pharmacokinetic Properties).
Cases of intracranial hypertension related to cerebral oedema have been reported.
The presence of sodium content 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 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 below 30˚C, Protect from moisture.

Shelf life
36 months

Pack size
50 Enteric Coated Tablets; (10 E/C Tablets/blister, 5 blisters/pack)

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