Summary of Product Characteristic

Valproxa

1. Name of the Medicinal Product

Valproxa, Solution for injection/infusion

2. Quality and Quantitative Composition

Each mL contains 100 mg sodium valproate. Each 4 ml contains 400 mg sodium valproate. Each 5 ml contains 500 mg sodium valproate.

3. Pharmaceutical Form

Solution for injection/infusion

4. Clinical Particulars

4.1 Therapeutic indication

The treatment of epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

4.2 Posology and method of administration

Method of administration

Sodium valproate injection may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, dextrose saline, or lactated ringer's injection.

Posology

Dosage requirements vary according to age and body weight.

Each vial of sodium valproate injection is for single dose injection only. For instructions on preparation and dilution of sodium valproate injection before administration.

Sodium valproate injection should not be administration via the same IV line as other IV additives. The intravenous solution is suitable for infusion by PVC, polyethylene or glass containers.

Patients already satisfactorily treated with oral sodium valproate may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Sodium valproate injection should be replaced by oral valproate therapy as soon as practicable.

Use in children:

Daily requirement for children is usually in the range 20-30 mg/kg body weight per day and method of administration is as above. Where adequate control is not achieved within this range, the dose may be increased to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and hematological parameters should be monitored.

Used in 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 (see aspirin/salicylate product information on Reye's syndrome). In addition, in conjunction with sodium valproate, concomitant use in children under 3 years can increase the risk of liver toxicity.

Female children and women of childbearing potential

Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme. The benefits and risks should be carefully reconsidered at regular treatment reviews.

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.

Combined Therapy:

When starting sodium valproate injection in patients already on other anticonvulsants these should be tapered slowly. Initiation of sodium valproate injection therapy should then be gradual, with target dose reached after about two weeks.

In certain cases, it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g., phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of sodium valproate injection.

When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturates should be reduced.

N.B. In children requiring doses higher than 40 mg/kg/day clinical chemistry and hematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

4.3 Contraindications

Contraindicated in the following situation:

- In pregnancy unless there is no suitable alternative treatment.
- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Patients with known urea cycle disorders
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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.

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 switching between different manufacturer's valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

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 injection, but the potential benefit of sodium valproate injection 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 seizure

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 anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, sodium valproate should be discontinued.

Female children, women of childbearing potential and pregnant women:

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders.

Contraindicated in the following situations:

- in pregnancy unless there is no suitable alternative treatment.
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.

Condition 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 the 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 valproate *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- 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 valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist 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 valproate use.

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 prescribers must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using 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 valproate *in utero*.

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

Pregnancy test

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

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with 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 from such as an intrauterine 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.

Estrogen-containing products

Concomitant use with estrogen-containing products, including estrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy. Prescribers should monitor clinical response (seizure control) when initiating, or discontinuing estrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist

The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess 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 valproate risks for the unborn child to support her informed decision making regarding family planning.

In case of pregnancy

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

Pharmacist must ensure that

- The patient card is provided with every valproate dispensing and that the patients understand its content.
- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorization Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist 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.

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 behavior. 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 behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

Carbapenem agents:

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

Patients with known or suspected mitochondrial disease

Valproate may trigger or worsen clinical signs of underlying mitochondrial disease caused by mutation of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute live 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 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, ophthalmoplegia 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.

4.4.2 Precautions

Hematological tests:

Blood test (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).

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 section 4.2 and 5.2).

Patients with systemic lupus erythematosus:

Although immune disorders have only rarely been noted during the use of sodium valproate injection, the potential benefit of sodium valproate injection should be weighed against its potential risk in patients with systemic lupus erythematosus (see section 4.8).

Urea cycle disorders:

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of risk of hyperammonemia with sodium valproate injection (see section 4.3).

Weight gain:

Sodium valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimize it (see section 4.8).

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 valproate.

4.5 Interaction with other medicinal products and other forms of interactions

4.5.1 Effects of sodium valproate injection on other drugs

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines:

Sodium valproate may potentiate the effect of other psychotropics such as antipsychotics, monoamine oxidase inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g., neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

Lithium:

Sodium valproate has no effect on serum lithium levels.

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 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 sodium valproate was administered with carbamazepine as sodium valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine:

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

Felbamate:

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

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:

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.

4.5.2 Effects of other drugs on Sodium valproate injection

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 hyperammonemia.

On the other hand, combination of ***felbamate*** and sodium valproate decreases valproic acid clearance by 22% to 50% and consequently increases valproic acid plasma concentrations. Sodium valproate injection dosage should be monitored.

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 imipenem, panipenem and meropenem)

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilized

on valproic acid should be avoided. 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, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

Protease inhibitors

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

Cholestyramine

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

Estrogen-containing products, including estrogen-containing hormonal contraceptives

Estrogens are inducers of the UDP-glucuronosyltransferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Consider monitoring of valproate serum levels.

On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of estroprogestative agents in women receiving hormonal contraception.

4.5.3 Other Interactions

Caution is advised when using sodium valproate injection 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 hyperammonemia. 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.

4.6 Fertility, pregnancy and lactation

- Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.

Teratogenicity and developmental effects

Pregnancy Exposure Risk related to valproate

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

Valproate was shown to cross the placental barrier both in animal species and in humans.

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits.

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 that 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.

In utero exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness and hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

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 ad 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 by 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 from a population-based study 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 to the unexposed population in the study.

Available data from another population-based study show that children exposed to valproate in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

Female children and woman of childbearing potential.

Estrogen-containing products

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

If a woman plans a pregnancy

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess 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 valproate risks for the unborn child to support her informed decision making regarding family planning.

Pregnant women

Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment.

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

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

If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of 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 a valproate exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medication for evaluation and counselling regarding the exposed pregnancy. Specialized 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 which may occur in all

pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate

Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should therefore be investigated in neonates.

Cases of hypoglycemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, 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% to 10% of maternal serum levels.

Hematological disorders have been shown in breastfed newborns/infants of treated women.

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

Fertility

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

4.7 Effects on ability to drive and use machine

Not applicable – use of intravenous formulation restricted to patients unable to take oral therapy. However, note use of sodium valproate injection may provide seizure control such that the patient may again be eligible to hold a driving license.

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

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (< 1/10,000); not known (cannot be estimated from the available data)

Congenital malformations and developmental disorders

Hepatobiliary disorder:

Common: liver injury

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported. Increased liver enzymes are common, particularly early in treatment, and may be transient.

Gastrointestinal disorders:

Very common: nausea occurs a few minutes after intravenous injection with spontaneous resolution within a few minutes.

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

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.

Nervous system disorders:

Very common: tremor

Common: extrapyramidal disorder, stupor*[1], somnolence, convulsion*[1], memory impairment, headache, nystagmus, dizziness may occur a few minutes after intravenous injection and it usually resolves spontaneously within a few minutes.

Uncommon: coma*[1], encephalopathy, lethargy*[1], reversible Parkinsonism, ataxia, paresthesia, aggravated convulsions.

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

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.

*[1]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 behavioral deterioration have been reported.

Psychiatric disorders:

Common: confusional state, hallucinations, aggression*[2], agitation*[2], disturbance in attention*[2]
Rare: abnormal behavior*[2], psychomotor hyperactivity*[2], learning disorder*[2]
*[2]These ADRs are principally observed in the pediatric population.

Metabolism and nutrition disorders:

Common: hyponatremia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome.

Rare: obesity, hyperammonemia*[3]

*[3]Cases of isolated and moderate hyperammonemia 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 injection should be discontinued.

Hyperammonemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered.

Endocrine disorders:

Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased).

Rare: hypothyroidism

Blood and lymphatic system disorders:

Common: anemia, thrombocytopenia

Uncommon: pancytopenia, leucopenia

Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anemia macrocytic, macrocytosis

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

Isolated findings of a reduction in blood fibrinogen and/or increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.

Skin and subcutaneous tissue disorders:

Common: nail and nail bed disorders, hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within six months, although the hair may become curlier than previously.

Uncommon: angioedema, rash, hair disorder (such as hair texture abnormal, hair color changes, abnormal hair growth).

Rare: toxin 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 gynecomastia has occurred

Vascular disorders:

Common: hemorrhage

Uncommon: vasculitis

Ear and labyrinth disorders:

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

Renal and urinary disorders:

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 condition:

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

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

Pediatric population

The safely profile of valproate in the pediatric population is comparable to adults, but some ADRs are more severe or principally observed in the pediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age. Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in pediatric patients than in adult patients.

4.9 Overdose

Cases of accidental and deliberate over dosage 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 acute 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, hypotension and circulatory collapse/shock. A favorable outcome is usual, however some deaths have occurred following massive overdose.

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

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

The presence of sodium content in the sodium valproate formulations may lead to hypernatremia 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.

Hemodialysis and hemoperfusion 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 hemodialysis and hemoperfusion have been used successfully.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antiepileptics; Fatty acid derivatives, ATC code: N03AG01

Sodium valproate is an anticonvulsant

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 Pharmacokinetics Properties

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

The reported effective therapeutic range for plasma valproic acid levels is 40-100 mg/liter (278-694 micromole/liter). 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% 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.

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. It is usually shorter in children.

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

Interaction with estrogen-containing products

Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.

Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In pediatric patients below the age of 10 years, the systemic clearance of valproate varied 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 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults.

5.3 Preclinical Safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanged in epileptic patients exposed to valproate as comparing to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in epileptic patients treated with valproate with those in untreated epileptic patients. The clinical relevance of these DNA/chromosome finding is unknown.

Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproductive and developmental toxicity

Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.

Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

Behavioral abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure. Some behavioral changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings and unknown.

6. Pharmaceutical Particulars

6.1 List of excipients

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for Injections

6.2 Incompatibilities

Sodium valproate Intravenous should not be administered via the same line as other IV additives.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After dilution according to the directions in section 6.6: Chemical and physical in-use stability has been demonstrated for 24 hours at store below 30^{o}C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Store below 30 ºC. Do not freeze.

6.5 Nature and contents of container

4 mL and 5 mL in clear glass vial (Type I) closed with rubber stopper and flip-off cap, packed or unpacked in a box of 1, 2, 5, 6, 10, 12, 20, 25 and 30 vials

6.6 Special precautions for disposal and other handling

For infusion the product may be diluted in 0.9% saline, 5% dextrose or lactate ringer injection. Tests with the recommended infusion solutions over 24 hours at store below 30^{o}C show compatibility.

Prior to use sodium valproate solution for injection and the diluted solution should be visually inspected. Only clear solutions without particles should be used.

7. Marketing Authorization Holder

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8. Marketing Authorization Numbers

1A 15003/67

9. Date of authorization

25 January 2024

10. Date of revision of the text

25 January 2024