APPROVED
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INSTRUCTION
for medical use

VINITEL®

Composition:
active substance: sodium valproate;
5 ml of syrup contain 200 mg of sodium valproate;
excipients: concentrated hydrochloric acid or sodium hydroxide for pH adjustment, sodium methyl parahydroxybenzoate (E 219), sodium propyl parahydroxybenzoate (E 217), sodium saccharin, sucrose, sorbitol solution, non-crystallizing (E 420), Ponceau 4R (E 124), flavor "Cherry", purified water.

Pharmaceutical form. Syrup.
Basic physical and chemical properties: red syrup with a characteristic odor.

Pharmacotherapeutic group. Anti-epileptics. ATC Code N03A G01.

Pharmacological properties.
Pharmacodynamics.
Sodium valproate is an anti-epileptic. The most likely mode of its action is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through effect on the synthesis or metabolism of GABA.
In certain *in vitro* studies it was reported that valproate could stimulate human immunodeficiency virus (HIV) replication. However, this effect is moderate, variable, unrelated to the dose of valproate and has not been documented in man.
Pharmacokinetics.
The therapeutic effectiveness of valproic acid is seen in a wide range of concentrations – from 40 to 100 mg/l (278 – 694 μmol/l). This range may depend on the time of blood sampling and presence of co-medication.
Distribution
The percentage of free (unbound) drug is usually from 6 to 15 % of the total plasma levels. An increased incidence of adverse reactions may be observed with plasma levels of valproic acid above the effective therapeutic range.
The pharmacological (or therapeutic) effects of the drug Vinitel® may not be clearly correlated with the total or free (unbound) plasma levels of valproic acid.
Placental transfer (see section "Use during pregnancy or breastfeeding").
Valproate crosses the placental barrier in animals and humans:
- in animals, valproate crosses the placenta in the same manner as in humans;
- in humans, the concentration of valproate in umbilical cord plasma, 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 %) which mainly occurs with enzymes UGT1A6, UGT1A9 and UGT2B7.
Elimination

The elimination half-life of valproate is usually in the range of 8 – 20 hours. This period is usually shorter in children.
In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free valproic acid plasma concentrations.
Interaction with estrogen-containing products
Interpatient variability has been noted. There are insufficient data to establish a robust pharmacokinetic-pharmacodynamic relationship resulting from this interaction.

Clinical characteristics.
Indications.
Treatment of generalized, focal or other types of epilepsy.

Contraindications.
The drug Vinitel® is contraindicated in the following situations:
- during pregnancy, unless there is no suitable alternative treatment (see sections "Administration details" and "Use during pregnancy or breastfeeding");
- in women of childbearing potential, unless the conditions of the "Pregnancy prevention programme" are fulfilled (see sections "Administration details" and "Use during pregnancy or breastfeeding");
- active liver disease;
- personal or family history of severe hepatic dysfunction, especially drug-associated;
- urea cycle disorders (see section "Administration details");
- hypersensitivity to sodium valproate or to any component of the drug;
- porphyria;
- known mitochondrial disorders caused by mutations in the gene encoding the mitochondrial enzyme γ-polymerase, for example, in patients with Alpers-Huttenlocher Syndrome and in children under 2 years of age with a suspected γ-polymerase-related disorder (see section "Administration details").

Interaction with other medicinal products and other forms of interaction.
Effect of valproate on other medicinal products
Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Valproate may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines. Clinical monitoring of the patient's condition and, if necessary, adjusting the dosage of other antipsychotics is advised.
It is suggested that adding olanzapine to therapy with valproate or lithium may significantly increase the risk of certain adverse reactions associated with olanzapine (for example, neutropenia, tremor, dry mouth, increased appetite, body weight gain, speech disorder and somnolence).
Lithium
Valproate does not affect plasma lithium levels.
Olanzapine
Valproic acid may lower plasma olanzapine concentrations.
Phenobarbital
Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) which may cause sedation, particularly in children. Therefore, clinical monitoring of the patient's condition is recommended during the first 15 days of combined treatment, with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels, if necessary.
Primidone
Valproate increases plasma primidone concentrations which may result in the exacerbation of adverse reactions (such as sedation). These signs cease with long term treatment. Clinical monitoring of the patient's condition is advised, especially at the beginning of therapy, with dose adjustment when appropriate.
Phenytoin
Valproate decreases total phenytoin plasma concentrations. Moreover, valproate increases the concentration of the free form of phenytoin and, as a consequence, the possibility of overdose symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic

catabolism). Clinical monitoring of the patient's condition is recommended. When determining plasma phenytoin levels, the concentration of the free form of the drug should also be evaluated.

Carbamazepine

In case of co-administration, valproate may potentiate the toxicity of carbamazepine. Clinical monitoring of the patient's condition is recommended, especially at the beginning of combined therapy, with dosage adjustment when appropriate.

Lamotrigine

Valproate reduces the metabolism of lamotrigine and increases the elimination half-life of lamotrigine nearly twofold. This interaction may lead to increased lamotrigine toxicity, in particular to serious cutaneous reactions. Clinical monitoring of the patient's condition is therefore recommended, with lamotrigine dosage adjustment when appropriate.

Felbamate

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

Rufinamide

Valproic acid may cause an increase in plasma concentrations of rufinamide. This effect depends on the concentration of valproic acid. Caution should be exercised with such therapy, in particular in children, as this effect is more significant in this population.

Propofol

Valproic acid may cause an increase in plasma concentrations of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

Zidovudine

Valproate may increase zidovudine plasma concentrations and, as a result, lead to an increase in zidovudine toxicity.

Nimodipine

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

Temozolomide

Co-administration of temozolomide and valproate may lead to an insignificant decrease of temozolomide clearance which is not thought to be clinically relevant.

<u>Effects of other drugs on valproate</u>

Anti-epileptics

Anti-epileptics that induce enzyme activity (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. The dosages of medicinal products should be adjusted according to clinical response and their plasma levels in case of combined therapy.

Valproic acid metabolite levels may increase in case of co-administration with phenytoin or phenobarbital. Therefore, patients treated with these two drugs should be carefully monitored for signs and symptoms of hyperammonemia.

On the other hand, the combination of felbamate and valproate decreases valproic acid clearance by 22 – 50 % and consequently increases its plasma concentrations. The dosage of valproate should be monitored.

Anti-malarial agents

Mefloquine and chloroquine increase the metabolism of valproic acid and may lower the seizure threshold. Therefore, epileptic seizures may occur in case of combined therapy. Accordingly, the dosage of valproate may need to be adjusted.

Highly protein-bound drugs

In case of concomitant use of valproate and highly protein-bound drugs (for example, acetylsalicylic acid), the plasma levels of free valproic acid may be increased.

Vitamin K-dependent anticoagulants

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following their displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

Cimetidine or erythromycin

Valproic acid plasma concentrations may be increased in case of its concomitant use with cimetidine and erythromycin (as a result of reduced hepatic metabolism).

Carbapenem antibiotics (such as panipenem, imipenem and meropenem)

There have been reports of decreased plasma levels of valproic acid upon co-administration with carbapenem antibiotics. Sometimes the concentration of valproic acid decreased by 60 – 100 % of the baseline level within two days and was at times associated with convulsions. Due to the rapid onset and the extent of the decrease of valproic acid plasma concentrations, co-administration of carbapenem antibiotics in patients stabilized on valproic acid should be avoided (see section "Administration details"). If treatment with this group of antibiotics cannot be avoided, close monitoring of valproic acid plasma levels should be performed.

Rifampicin

Rifampicin may decrease valproic acid plasma concentrations resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary upon co-administration with rifampicin.

Protease inhibitors

Protease inhibitors such as lopinavir and ritonavir decrease plasma valproate levels upon co-administration.

Cholestyramine

Cholestyramine may lead to a decrease of plasma valproate levels upon co-administration.

Estrogen-containing drugs, including estrogen-containing hormonal contraceptives

Estrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which may result in decreased plasma concentrations of valproate and, accordingly, decreased efficacy of the drug (see section "Administration details").

The possibility of monitoring plasma valproate levels should be considered. On the opposite, valproate has no enzyme inducing effect. As a consequence, valproate does not reduce the efficacy of estrogen-progestogen hormonal contraceptives in women.

Other interactions

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

Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonemia. Careful monitoring of signs and symptoms of the above-mentioned adverse reactions is advised in patients taking these two drugs. This is particularly relevant in patients with encephalopathy.

Quetiapine

Concomitant administration of valproate and quetiapine may increase the risk of neutropenia/leukopenia.

Administration details.

Although there is no evidence of sudden recurrence of the main symptoms of the disease following withdrawal of valproate, discontinuation of the drug should be performed gradually and only under the supervision of a specialist. This is due to the possibility of sudden alterations in plasma concentrations of the drug giving rise to a recurrence of symptoms. Experts from NICE do not recommend using valproate preparations from different manufacturers due to possible fluctuations in plasma concentrations of the active substance and emergence of corresponding clinical consequences.

<u>Liver dysfunction</u>

Conditions of occurrence

Severe liver damage, including hepatic failure, sometimes lethal, has been very rarely reported. Practical experience in treating epilepsy indicates that patients most at risk, especially in cases of multiple anti-convulsant therapy, are infants and children under the age of 3 with severe epilepsy, organic brain disease, mental retardation and/or congenital metabolic or degenerative disease. This risk is significantly reduced and progressively decreases with age in children over the age of 3.

Concomitant use of salicylates should be avoided in children under the age of 3 due to the risk of hepatotoxicity. Additionally, salicylates should not be used in children under the age of 16 (due to Reye syndrome).

Valproate monotherapy is recommended in children under the age of 3, but the expected benefit of using the drug and risk of liver damage or pancreatitis should be evaluated prior to initiation of therapy. In most cases, such liver damage occurred during the first 6 months of therapy, most commonly within the period of 2−12 weeks.

Suggestive signs
Clinical symptoms are essential for early diagnosis. In particular, the following symptoms, 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: asthenia, malaise, anorexia, lethargy, edema and drowsiness, sometimes associated with repeated vomiting and abdominal pain;
- in patients with epilepsy – recurrence of epileptic seizures.
These symptoms are an indication for immediate withdrawal of the drug.
Patients (or their family, if patients are children) should be instructed to immediately seek medical attention if these symptoms occur. Investigations including clinical examination and laboratory assessment of liver function should be performed immediately.
Detection.
Liver function assessment should be performed before the initiation of therapy, and then regularly during the first 6 months of treatment, especially in patients most at risk and those with a history of liver disease.
Amongst usual investigations, tests that reflect protein synthesis, especially prothrombin synthesis, are most informative.
Valproate therapy should be discontinued immediately in case of confirmation of an abnormally low prothrombin level, particularly in combination with other abnormal laboratory findings (significant decrease in fibrinogen and coagulation factors, elevated bilirubin and liver transaminase levels).
As a precautionary measure, combined therapy with valproate and salicylates should also be discontinued since the latter employ the same metabolic pathway.
As with most anti-epileptic drugs, valproate use is associated with a possibility of isolated and transient elevation of transaminases, especially at the beginning of therapy. More extensive laboratory investigations (including the assessment of prothrombin levels) are recommended in such cases. If necessary, the dose of valproate should be reduced and laboratory investigations repeated based on the dynamics of findings.
Pancreatitis
Pancreatitis, sometimes lethal, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should undergo prompt additional medical examination (including measurement of plasma amylase). Young children are at particular risk, the risk decreases with increasing age. Risk factors include severe epilepsy, severe neurological impairment and use of combined anti-convulsant therapy. Hepatic failure with pancreatitis increases the risk of fatal outcome. Valproate should be discontinued immediately in case of pancreatitis.

Female children, women of childbearing potential and pregnant women
"Pregnancy prevention programme"
Valproate has a high teratogenic potential, therefore, children exposed *in utero* to valproate have a high risk of congenital malformations and neurodevelopmental disorders (see section "Use during pregnancy and breastfeeding").
The drug Vinitel® is contraindicated in the following situations:
- in pregnancy unless there is no suitable alternative treatment (see sections "Contraindications" and "Use during pregnancy or breastfeeding");
- in women of childbearing potential unless the conditions of the "Pregnancy prevention programme" are fulfilled (see sections "Contraindications" and "Use during pregnancy and breastfeeding").
Conditions of the «Pregnancy prevention programme»
The prescriber must:
- evaluate individual circumstances in each case, involve the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure the patient's understanding of the risks and measures needed to minimize the risks;
- assess the possibility of pregnancy in all female patients;
- ensure that the patient understands and acknowledges the risks of congenital malformations and neurodevelopmental disorders including the singnificance of these risks for children exposed to valproate *in utero*;
- ensure that the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, if necessary.

- advise the patient to use contraception and ensure that she is capable of complying with the need to use effective contraception (additional information is provided in the subsection "Contraception" of this boxed warning) without interruption during the entire duration of treatment with valproate;
- ensure that the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy;
- ensure that the patient understands the need to consult her physician if she is planning pregnancy in order to ensure timely discussion of this subject and switching to alternative treatment options prior to conception and before contraception is discontinued;
- ensure that the patient understands the need to urgently consult her physician in case of pregnancy;
- provide the patient with the Information booklet;
- ensure that the patient understands the hazards and necessary precautions associated with the use of valproate (Annual risk acknowledgement form).

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

<u>Female children</u>

The prescriber should:
- ensure that the parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche;
- ensure that the parents/caregivers of female children have been provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the significance of these risks for children exposed to valproate *in utero*.

In female patients who have experienced menarche, the prescribing specialist should annually reassess the need for valproate therapy and consider alternative treatment options. If 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 specialist to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded prior to initiation of treatment with valproic acid. To rule out unintended use in pregnancy, treatment with valproate must not be initiated in women of childbearing potential without a negative plasma pregnancy test result confirmed by a healthcare provider.

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 should 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 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 precautions. Even if the patient has amenorrhea, she must follow all the advice on effective contraception.

Estrogen-containing products

Concomitant use of valproate with estrogen-containing products, including estrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section "Interaction with other medicinal products and other forms of interaction"). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing estrogen-containing products.

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

Annual treatment reviews by a specialist

The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the "Annual risk acknowledgement form" upon initiation and during each annual review of treatment in order to ensure the patient's understanding of the information presented in it.

Pregnancy planning

If a woman is planning a pregnancy, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch the

patient to appropriate alternative treatment prior to conception and before contraception is discontinued (see section "Use during pregnancy or breastfeeding"). If such switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to provide her with information for her informed decision-making regarding family planning.

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 treatment options. Pregnant patients receiving valproate during pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counselling regarding the use of the drug during pregnancy (see section "Use during pregnancy or breastfeeding").

Pharmacists must ensure that:

- a patient card is provided with every valproate dispensation and the patient understands the information presented in it;
- patients are advised not to stop valproate administration 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 the use of valproate during pregnancy, the owner of the registration certificate provides educational materials to draw additional attention to the warnings about the teratogenicity (ability to cause congenital malformations) and fetotoxicity (ability to cause neurodevelopmental disorders) of valproate and to familiarize the patients with the instructions on the use of valproate in women of childbearing potential with details on the requirements of the "Pregnancy prevention programme". The information booklet should be provided to all women of childbearing potential using valproate.

An "Annual risk acknowledgement" form should be used and duly filled in and signed at the 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 treatment with valproate for the patient by a specialist experienced in the management of epilepsy.

Aggravation of convulsions

As with other anti-epileptic drugs, the use of valproate may cause a reversible worsening of the frequency and severity of convulsions (including status epilepticus) or the onset of new types of convulsions instead of improvement. Patients should be advised to consult their physician immediately in case of aggravation of convulsions (see section "Adverse reactions").

Suicidal ideations and behavior

There have been reports of suicidal ideations and behavior in patients treated with anti-epileptic drugs in several indications. A meta-analysis of data obtained from randomized placebo-controlled trials of anti-epileptic drugs has also shown a small increase in the risk of suicidal ideations and behavior. The mechanism of this action is unknown, and the available data do not exclude an increase of this risk in association with the use of sodium valproate.

Therefore, patients should be monitored for signs of suicidal ideations and behavior and appropriate treatment should be considered. Patients (and their caregivers) should be advised to immediately seek medical attention should signs of suicidal ideations or behavior emerge.

Carbapenem agents

Concomitant use of valproate and carbapenem is not recommended.

Patients with known or suspected mitochondrial disease

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear gene encoding the mitochondrial enzyme polymerase gamma (POLG). In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the POLG gene (e.g. Alpers-Huttenlocher Syndrome).

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including (but not limited to) unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, opthalmoplegia or complicated migraine

with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section "Contraindications").

Precautions

Blood tests

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 "Adverse reactions").

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 response (see sections "Pharmacokinetics" and "Dosage and administration").

Patients with systemic lupus erythematosus

Although immune disorders have only rarely been noted during the use of valproate, the potential benefit and risk from its use should be weighed in patients with systemic lupus erythematosus (see section "Adverse reactions").

Urea cycle disorders

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia (see section "Contraindications").

Weight gain

Valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section "Adverse reactions").

Diabetic patients

Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; the urine testing for ketone bodies may give false positive result in the diabetic patients.

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

Carnitine palmitoyltransferase (CPT) type II deficiency

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

Alcohol

Alcohol intake is not recommended during treatment with valproate.

Excipients

Medicinal product contains sucrose and sorbitol. In case of intolerance to some sugars, it is necessary to contact your doctor before taking this medicinal product.

Medicinal product contains Ponceau 4R (E124) dye, Sodium methyl hydroxybenzoate (E 219) and Sodium propyl parahydroxybenzoate (E 217) which may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1 mmol (23 mg)/dose of sodium, i.e. is essentially sodium-free.

Use during pregnancy or breastfeeding.

Valproate is contraindicated in the treatment of epilepsy in the following situations:

- in pregnancy unless there is no suitable alternative treatment (see sections "Administration details" and "Use during pregnancy or breastfeeding");
- in women of childbearing potential, unless the conditions of the "Pregnancy prevention programme are fulfilled (see sections "Administration details" and "Use during pregnancy or breastfeeding").

Pregnancy

Teratogenicity and developmental effects

The use of valproate monotherapy or as part of polytherapy is associated with adverse clinical consequences of pregnancy. 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 (see section "Pharmacokinetics").

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 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 abnormal development (minor malformations) and major malformations. The most common malformations are: 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 or hearing impairment. Outcomes were not reported for all described cases. When outcomes were reported, the majority of the patients 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. This risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
Studies in preschool children exposed *in utero* to valproate show that up to 30 – 40% experience delays in their early development such as delays in talking, walking, 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 in children exposed to other anti-epileptics. Although the role of other factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long-term outcomes.
Available data show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the general study population.
Available data from another population-based study show that children exposed to valproate *in utero* are at increased risk of developing attention deficit with hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.
Female children and women of childbearing potential (see above and section “Administration details”).
Estrogen-containing products
Estrogen-containing products including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased plasma concentration of valproate and potentially decrease its efficacy (see sections “Interaction with other medicinal products and other forms of interaction” and “Administration details”).
If a woman plans a pregnancy
If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy should 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 (see section “Administration details”). If such switching is not possible, further counselling regarding the risks of valproate for the unborn child should be received to provide the woman with appropriate information for informed decision-making regarding family planning.
Pregnant women
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections “Contraindications” and “Administration details”). 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 the mother and the fetus. 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 the drug 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 (see section "Dosage and administration").
All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised Prenatal screening 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 haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.
Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1 – 10% of maternal plasma levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section "Adverse reactions").
A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from valproate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section "Adverse reactions"). Valproate administration may also impair fertility in men (see section "Adverse reactions"). Case reports indicate that fertility dysfunctions are reversible and disappear after medicinal product discontinuation.

Effect on reaction rate when driving motor transport or using other mechanisms.
Use of 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 combined anti-epileptic therapy or concomitant administration of the drug with benzodiazepines (see section "Interaction with other medicinal products and other forms of interaction").

Dosage and administration.
Vinitel® Syrup is for oral administration.
Daily dosage varies according to age and body weight. The medicinal product may be given twice daily.
Dosage
Adults
Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until seizure control is achieved. This is generally within the dosage range 1000 – 2000 mg per day, i.e. 20 – 30 mg/kg/day.

Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children with body weight over 20 kg

Initial dosage should be 400 mg/day (irrespective of body weight) with spaced increases until seizure control is achieved. This is usually within the dosing range 20 – 30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children with body weight under 20 kg

Daily dose is 20 mg/kg. In severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. In case of a dose above 40 mg/kg/day, the parameters of general and biochemical blood analysis should be monitored.

Elderly

Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to plasma albumin, the proportion of free valproate is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Patients with renal insufficiency

It may be necessary to decrease the valproate dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section "Pharmacokinetics").

Patients with hepatic insufficiency

The concomitant use of salicylates and valproate is not recommended, since they employ the same metabolic pathway (see sections "Administration details" and "Adverse reactions").

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections "Contraindications" and "Administration details").

Salicylates should not be used in children under 16 years. In addition, concomitant use of salicylates with valproate, in children under 3 years of age may increase the risk of hepatotoxicity (see section "Administration details").

Female children, women of childbearing potential

Valproate treatment should 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 (see sections "Contraindications", "Administration details" and "Use during pregnancy or breastfeeding").

Valproate is prescribed and dispensed according to the "Pregnancy Prevention Programme" (see sections "Contraindications" and "Administration details"). Benefits and risks should be carefully reconsidered at regular valproate 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 (see section "Use during pregnancy or breastfeeding").

Combined Therapy

When starting valproate in patients already treated with other anti-epileptic drugs, the dose of the latter should be slowly reduced. Initiation of 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 – 10 mg/kg/day when used in combination with anti-epileptic drugs 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 valproate. When barbiturates are being administered concomitantly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

Note: In children requiring doses 40 mg/kg/day, the parameters of general and biochemical blood analysis should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma valproate levels is unnecessary. However, a method for measurement of plasma valproate levels is available and may be helpful where there is poor seizure control or adverse reactions are suspected (see section "Pharmacokinetics").

Children.
The drug is approved for use in pediatric practice.

Overdose.
Symptoms
Symptoms other than nausea, vomiting, and dizziness are unlikely to occur in cases of overdose where plasma concentrations of valproate are 5 to 6 times higher than the maximum therapeutic level.
Clinical signs of acute massive overdose, i.e. plasma concentration of valproate 10 – 20 times the maximum therapeutic level, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However, several cases are known to be fatal. It should be noted that symptoms of overdose may be variable. Seizures have been reported in the presence of very high plasma levels (see also section "Pharmacokinetics"). Cases of intracranial hypertension related to cerebral oedema have been reported.
The presence of sodium content in the drug may lead to hypernatraemia in case of overdose.
Treatment
Symptomatic treatment with continuous cardio-respiratory monitoring of patient condition. Gastric lavage is effective up to 10 - 12 hours after valproate overdose. Haemodialysis and haemoperfusion may be helpful. Naloxone has been successfully used, sometimes in combination with activated charcoal given orally.
In case of massive overdose, haemodialysis and haemoperfusion have been used.

Adverse reactions.
Adverse reactions are classified according to the frequency rate: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (≥1/10000); frequency is not known (cannot be estimated from the available data).
Congenital malformations and developmental disorders (see sections "Administration details" and "Use during pregnancy or breasfeeding").
Hepatobiliary disorders
Common: liver injury (see section "Administration details").
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see sections "Contraindications", "Administration details" and "Dosage and administration"). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section "Administration details").
Gastrointestinal disorders
Very common: nausea.
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea.
The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days with no need for drug withdrawal. These problems can usually be overcome by taking medicinal product with or after food.
Uncommon: pancreatitis, sometimes lethal (see section "Administration details").
Nervous system disorders
Very common: tremor.
Common: extrapyramidal disorder, stupor*, somnolence, convulsions*, memory impairment, headache, nystagmus.
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonian syndrome, ataxia, paraesthesia, aggravated convulsions (see section "Administration details").
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorders.
Sedation has been reported occasionally, usually when valproate is co-administered with other anti-epileptic drugs. In case of valproate monotherapy sedation 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, too rapid a dose escalation or combined use of other anti-epileptic drugs (notably phenobarbital or topiramate). Usually these manifestations disappear after valproate withdrawal or reduction of its 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 adverse reactions occur mainly in children.
Metabolic and nutritional disorders
Common: hyponatraemia, weight increased*.
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section "Administration details").
Rare: hyperammonemia* (see section "Administration details"), obesity.
* Cases of isolated and moderate hyperammonemia without any significant changes in the results of standard liver function tests. These changes are usually transient and should not require treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. If the above symptoms occur, valproate should be discontinued.
Hyperammonemia associated with neurological symptoms has also been reported (see section "Administration details"). In such cases further investigations should be considered.
Endocrine disorders
Uncommon: syndrome of inappropriate secretion of antidiuretic hormone (ADH), hyperandrogenism (hirsutism, virilism, acne, androgenetic alopecia and/or androgen levels increase).
Rare: hypothyroidism (see section "Use during pregnancy or breastfeeding").
Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia (see section "Administration details").
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 valproate doses which has an inhibitory effect on the second phase of platelet aggregation. Spontaneous bruising or bleeding is an indication for withdrawal of medication and additional investigations (see section "Use during pregnancy or breastfeeding").
Skin and subcutaneous tissue disorders
Common: hypersensitivity, transient and or dose-related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth).
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, DRESS-syndrome (Drug Rash with Eosinophilia and Systemic Symptoms syndrome).
Reproductive system and breast disorders
Common: dysmenorrhea.
Uncommon: amenorrhea.
Rare: male infertility, polycystic ovaries.
Very rare: gynaecomastia.
Vascular disorders
Common: haemorrhage (see sections "Administration details" and "Use during pregnancy or breastfeeding").
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, proteinuria, phosphaturia, and uricosuria), associated with valproate therapy, but the mode of action is as yet unclear.
General disorders
Uncommon: hypothermia, non-severe peripheral oedema.
Musculoskeletal and connective tissue disorders
Uncommon: decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with valproate. The mechanism by which valproate affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus, rhabdomyolysis (see section "Administration details").
Respiratory, thoracic and mediastinal disorders
Uncommon: pleural effusion.
Investigation findings
Common: decreased coagulation factors (at least one), abnormal coagulation tests (such as prolonged prothrombin time, prolonged activated partial thromboplastin time, prolonged thrombin time, increased international normalized ratio) (see sections "Administration details" and "Use during pregnancy or breastfeeding").
Neoplasms benign, malignant and unspecified (including cysts and polyps)
Rare: myelodysplastic syndrome.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the State Enterprise "State Expert Center of MOH of Ukraine" and to the applicant via the feedback form at the website: https://kusum.ua/pharmacovigilance/.

Shelf-life.
2 years.

Storage conditions.
Store at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
100 ml or 200 ml are in a glass bottle with tamper evident cap. Each bottle is in a carton box with a 5 ml syringe dispenser and syringe adapter.
100 ml or 200 ml are in a glass bottle with child proof cap. Each bottle is in a carton box with a 5 ml syringe dispenser and syringe adapter.

Conditions of supply.
Prescription only.

Manufacturer.
"KUSUM PHARM" LLC.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str., 54.

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