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INSTRUCTION
for medical use

VINITEL®

Composition:
active substance: sodium valproate;
5 ml of syrup contain 200 mg 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. Antiepileptics. ATC Code N03A G01.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Sodium valproate is an antiepileptic drug (AED). The most likely mode of its action is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through effect on the further synthesis or further metabolism of GABA.
Clinical safety
In certain *in vitro* studies it was reported that valproate could stimulate human immunodeficiency virus (HIV) replication, but studies on peripheral blood mononuclear cells from HIV-infected subjects show that it does not have a mitogen-like effect on inducing HIV replication. Indeed, the effect of 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 humans.
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 the presence of co-medication.
Distribution
The percentage of free (unbound) fraction of valproic acid 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 valproic acid levels.
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 usually lies in the range of 8–20 hours.

Interaction with estrogen-containing products

Interpatient variability has been noted. There is insufficient data to establish a robust pharmacokinetic-pharmacodynamic relationship resulting from this interaction.

Special groups of patients

Renal insufficiency

In patients with pronounced renal insufficiency, it may be necessary to alter the dosage in accordance with free plasma valproic acid levels (see section "Dosage and administration").

Children

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

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 exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.

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

Reproductive 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 2nd and 3rd generation, and those were less pronounced in the 3rd 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 are unknown.

Testicular toxicity

In sub-chronic and chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in the weight of testes were reported in adult rats and dogs after oral administration starting at doses of 465 mg/kg/day and 150 mg/kg/day, respectively.

The safety margin based on plasma valproate concentrations is unknown, however body-surface-area comparisons indicate that there may be no safety margin.

In juvenile (sexually immature) and young adult rats (pubertal), a significant dose-related reduction in the weight of testes was observed at 240 mg/kg/day following intravenous and intraperitoneal administration of valproate with no apparent histopathological changes. However, testicular atrophy was observed in young adult rats at an intravenous dose of 480 mg/kg/day. Despite the absence of apparent histopathology changes, the testicular weight reductions were considered part of a dose-

related spectrum leading to testicular atrophy. There is no safety margin for the effect on testicular weight.
There is a limited number of published papers which report findings in juvenile animals consistent with those reported in the GLP adult and juvenile studies, with respect to testicular weights. Reductions in testicular weight are associated with adverse effects on the adult male reproductive tract in *in vivo* studies and impaired fertility in adult patients (see section "Use during pregnancy or breastfeeding"). The toxicological significance of the testicular findings in juvenile animals has not been evaluated and hence the relevance to human testicular development, particularly in the pediatric population, is unknown. The sensitivity of testes to valproate in young animals has not been evaluated, therefore its effects on the pediatric population are also unknown.

Clinical characteristics.

Indications

Female patients

- All female patients under 55 years of age: for the treatment of generalized, partial or other types of epilepsy only when there is no other effective or tolerated treatment.
- All female patients over 55 years of age: for the treatment of generalized, partial or other types of epilepsy.

Male patients

- All male patients under 55 years of age initiating treatment with valproates: for the treatment of generalized, partial or other types of epilepsy only when there is no other effective or tolerated treatment.
- All male patients established on treatment with valproate or male patients over 55 years of age: For the treatment of generalized, partial or other types of epilepsy.

Contraindications.

The drug Vinitel® is contraindicated in the following situations:

- during pregnancy, unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections "Administration details" and "Use during pregnancy or breastfeeding");
- in women of childbearing potential under the age of 55, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the "Pregnancy prevention programme" are fulfilled (see sections "Administration details" and "Use during pregnancy or breastfeeding");
- hypersensitivity to sodium valproate or to any component of the drug;
- active liver disease, or personal or family history of severe hepatic dysfunction, especially drug-related;
- patients with known urea cycle disorders (see section "Administration details");
- porphyria;
- patients with 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").
- patients with uncorrected systemic primary carnitine deficiency (see section "Administration details").

Interaction with other medicinal products and other types of interaction

Effect of valproate on other medicinal products

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines

Valproate may potentiate the effect of other psychotropic drugs 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 combined therapy, with dose adjustment when appropriate.

Phenytoin

Valproate decreases total phenytoin plasma concentrations. 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 of the patient's condition is recommended. When determining plasma phenytoin levels, the concentration of the free form of the medicinal product should also be evaluated.

Carbamazepine

Clinical toxicity has been reported when sodium valproate was co-administered with carbamazepine as valproate may potentiate toxic effects 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 mean elimination half-life of lamotrigine by 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 dose adjustment (reduction of the lamotrigine dose) 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 considered to be clinically significant.

Effect of other medicinal products on valproate

Antiepileptic drugs (AEDs)

AEDs that induce enzyme activity (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. The dosages of medicinal products should be adjusted according to the 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.

Antimalarial 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 (e.g. 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 or 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-glucuronosyltransferase (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 contrary, valproate has no enzyme-inducing effect. As a consequence, valproate does not reduce the efficacy of estrogen-progestogen hormonal contraceptives in women.

Metamizole

Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased clinical efficacy of the drug Vinitel®. Prescribers should monitor the clinical response (seizure control) and consider monitoring valproate serum levels if necessary.

Methotrexate

Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor the clinical response (seizure control) and consider monitoring valproate serum levels as appropriate.

Other interactions

<u>Risk of liver damage</u>

The concomitant use of valproates and salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section “Administration details”).

Concomitant use of valproate and several antiepileptic drugs increases the risk of liver damage, especially in young children (see section “Administration details”).

Concomitant use with cannabidiol increases the incidence of transaminases elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19 % of patients. Appropriate liver monitoring should be exercised when valproate is concomitantly used with other anticonvulsants with potential hepatotoxicity, including cannabidiol. Dose reduction or discontinuation of treatment should be considered in case of significant abnormalities of liver parameters (see section "Administration details").

Newer AEDs (including topiramate and acetazolamide)

Caution is advised when using valproate in combination with newer AEDs 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.

Pivalate-conjugated medicines

Concomitant administration of valproate and pivalate-conjugated medicines (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section "Administration details"). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinemia.

Quetiapine

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

Clozapine

Concurrent use of valproate with clozapine may lead to an increased risk of neutropenia and clozapine-induced myocarditis. If concurrent use of valproate with clozapine is necessary, careful monitoring for signs and symptoms of the above adverse reactions is required.

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 doctor. 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 disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see sections "Contraindications" and "Administration details") or degenerative disease associated with mental retardation. This risk is significantly reduced in children over the age of 3 and progressively decreases with age.

Concomitant use of salicylates should be avoided in children under the age of 3 due to the risk of hepatotoxicity (see section "Interaction with other medicinal products and other types of interaction"). Additionally, salicylates should not be used in children under the age of 16 (due to Reye's 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 (see section "Interaction with other medicinal products and other types of interaction").

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 somnolence, 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 medicinal product.
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 of the high-risk group and those with a history of liver disease. Upon changes in concomitant medicinal products (dose increase or additions) that are known to impact the liver, liver monitoring should be restarted as appropriate (see section "Interaction with other medicinal products and other types of interaction").
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 AEDs, 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.
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 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, 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 (see section "Contraindications").
Urea cycle disorders and risk of hyperammonemia
When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to initiation of treatment with valproate because of the risk of hyperammonemia (see section "Contraindications" and "Administration details").
Patients at risk of hypocarnitinemia
Valproate administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonemia and lead to hyperammonemic encephalopathy. Other symptoms such as liver toxicity, hypoketotic hypoglycemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Patients at increased risk for symptomatic hypocarnitinemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see section "Administration details"), impairment in carnitine nutritional intake, patients younger than 10 years old, patients concomitantly using pivalate-conjugated medicines or of other AEDs.

Patients should be warned to report immediately any signs of hyperammonemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinemia are observed.
Patients with systemic primary carnitine deficiency and corrected for hypocarnitinemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative. In these patients, carnitine monitoring should be implemented.
Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. Carnitine supplementation should be considered in these patients (see also sections "Interaction with other medicinal products and other types of interaction", "Adverse reactions", "Overdose").
Pancreatitis
Severe 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). This risk is the highest in young children and decreases with increasing age. Risk factors include severe epilepsy, severe neurological impairment, and use of combined antiepileptic 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 under 55 years of age 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 (11 %) and neurodevelopmental disorders (up to 30–40 %) which may lead to permanent disability (see section "Use during pregnancy or breastfeeding").
Valproate must only be prescribed by two specialists who independently consider and document that there is no other effective or tolerated treatment.
The drug Vinitel® is contraindicated in the following situations:
- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections "Contraindications" and "Use during pregnancy or breastfeeding");
- in women of childbearing potential under the age of 55, unless two specialists independently consider and document that there is no other effective or tolerated treatment, and the conditions of the pregnancy prevention programme are fulfilled (see sections "Contraindications" and "Use during pregnancy or breastfeeding").
Conditions of the "Pregnancy prevention programme"
The prescriber must:
- evaluate individual circumstances in each case, involve the patient in the discussion, 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 which may lead to permanent disability, in particular the significance 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 "Guide for female patients";
- ensure that the patient understands the hazards and necessary precautions associated with the use of valproate ("Annual risk acknowledgement form for female patients").

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.

Female children

The prescriber should:

- ensure that the parents/caregivers of female children understand the need to contact a 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 which may lead to permanent disability 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 experience menarche.

Pregnancy test

Pregnancy must be excluded prior to initiation of treatment with valproate. 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 drugs

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

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

Annual treatment review by a specialist

The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss and complete the "Annual Risk Acknowledgement Form for Female Patients" with the patient and/or carer at initiation and during each annual review and ensure that the patient has understood its content.

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 appropriate 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").

The pharmacist 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”. A “Guide for female patients” and “Patient card” should be provided to all women of childbearing potential using valproate.

An “Annual risk acknowledgement form for female patients” should be discussed and duly completed by the patient and/or carer 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.

Use in male patients

All male patients and/or carers should be informed of the potential risk to children born to men treated with valproate in the 3 months before conception (see also section “Use during pregnancy or breastfeeding”), of the risk of infertility in men (see sections “Dosage and administration”, “Use during pregnancy or breastfeeding” and “Adverse reactions”) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section “Preclinical safety data”).

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section “Use during pregnancy or breastfeeding”).

Doctors should inform male patients about this potential risk (see section “Use during pregnancy or breastfeeding”) and discuss the need for male patients and their female partner to consider using effective contraception, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescribing physician to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case. If necessary, it is recommended to consult a specialist with experience in treating epilepsy.

Educational materials are available for healthcare professionals and male patients. A “Guide for male patients” should be provided to male patients using valproate.

Male patients under 55 years of age

Upon initiation of treatment with valproate the specialist should discuss and complete the “Risk acknowledgement form for male patients starting valproate” with the patient and/or carer to ensure that all male children and men under 55 years of age are informed of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

Aggravation of convulsions

As with other AEDs, 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 ideation and behavior in patients treated with AED in several indications. A meta-analysis of data obtained from randomized placebo-controlled trials of antiepileptic 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.

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, as well as in case of spontaneous bruising or bleeding (see section "Adverse reactions").

Renal insufficiency

In patients with renal insufficiency, it may be necessary to lower the dose. As monitoring of plasma concentrations may be misleading, the dose should be adjusted according to the 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").

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 minimize it (see section "Adverse reactions").

Patients with diabetes mellitus

As valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies, urine testing for ketone bodies may give false positive results in 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.

Alcohol

Alcohol intake is not recommended during treatment with valproate.

Severe cutaneous adverse reactions (SCARs) and angioedema

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens–Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and the need to monitor them closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued immediately the diagnosis is confirmed.

Excipients

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

The medicinal product contains Ponceau 4R (E 124) dye, sodium methyl parahydroxybenzoate (E 219) and sodium propyl parahydroxybenzoate (E 217) which may cause allergic reactions (possibly delayed).

This medicinal product contains less than 29.3 mg of sodium/dose. Caution should be exercised when using the drug in patients following a low-sodium diet.

Use during pregnancy or breastfeeding.

Pregnancy and women of childbearing potential.

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

- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections "Contraindications" and "Administration details");
- in women of childbearing potential under 55 years of age, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled (see sections "Contraindications" and "Administration details").

Teratogenicity and developmental effects from in utero exposure

Pregnancy exposure risk related to valproate

In women, the use of valproate monotherapy or as part of polytherapy is associated with adverse clinical consequences of pregnancy. Available data suggest that polytherapy with AEDs including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy.

Valproate crosses the placental barrier both in animals and in humans (see section "Pharmacokinetics").

In animals, teratogenic effects have been demonstrated in mice, rats, and rabbits (see section "Preclinical safety data").

Congenital malformations from in utero exposure

Data derived from a meta-analysis, which included registries and cohort studies, has shown that approximately 11 % of children born to epileptic women receiving valproate monotherapy during pregnancy had congenital malformations. This risk of the most common malformations is higher than that in the general population, for whom the risk is about 2–3 %.

The risk of major congenital malformations in children after *in utero* exposure to AED polytherapy including valproate is higher than that of AED polytherapy not including valproate.

This risk is dose-dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate polytherapy. However, 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 malformations observed are: neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral radial aplasia), 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.

In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Neuro-developmental disorders from in utero exposure

The available data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neuro-developmental disorders which may lead to permanent disability (including autism) seems to be dose-dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists cannot be established based on available data.

When valproate is administered in polytherapy with other AEDs during pregnancy, the risks of neuro-developmental disorders in the offspring which may lead to permanent disability were also significantly increased as compared with those in children from the general population or those born to untreated women with epilepsy.

The exact gestational period of risk for these effects is uncertain, therefore, the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool-age children exposed *in utero* to valproate monotherapy show that up to 30–40 % of them experienced various delays in the development such as delays in talking, walking, lower intellectual abilities, poor language skills (speaking and understanding), and memory problems.

The intelligence quotient (IQ) measured in school-age children (age 6) with a history of valproate exposure *in utero* was on average 7–10 points lower than in children exposed to other AEDs, although the role of confounding factors related to intellectual disability cannot be excluded. There is evidence that the risk of intellectual impairment in children exposed to valproate may be independent from maternal IQ.

There are limited data regarding 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 3-fold) and childhood autism (approximately 5-fold) compared to the general study population.

Available data from a 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 women of childbearing potential under 55 years of age (see above and section "Administration details").
Estrogen-containing products
Estrogen-containing medicinal products including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which is thought to result in decreased plasma concentration of valproate and potentially decrease its efficacy (see sections "Interaction with other medicinal products and other types 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
The use of valproate for treatment of 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 valproate into several doses to be taken throughout the day;
- use a prolonged release formulation which may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section "Dosage and administration").
All pregnant patients receiving valproate during pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the detected pregnancy. Specialized 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 that it prevents the birth defects or malformations due to valproate exposure.
Risk for the neonate
- Cases of hemorrhagic syndrome have been very rarely reported 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, which may be fatal, has also been reported. However, this syndrome must be distinguished from the decrease of vitamin K levels induced by phenobarbital and enzyme inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates immediately after birth.
- Cases of hypoglycemia have been reported in neonates whose mothers have taken valproate during the third trimester of the 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 third trimester of the pregnancy.
Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception.
A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95 % CI:

1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0 % to 5.6 % in the valproate group versus between 2.3 % to 3.2 % in the composite lamotrigine / levetiracetam group. The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing new spermatogenesis without valproate exposure).
Physicians should inform male patients about this potential risk and discuss the need for male patients and their female partner to consider using effective contraception, while using valproate and for at least 3 months after treatment discontinuation (see section "Administration details"). Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.
Male patients treated with valproate should be regularly reviewed by their prescribing physician to evaluate whether valproates are the most suitable treatment for the patient. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options. Individual circumstances should be evaluated in each case. If necessary, it is recommended to consult a specialist with experience in treating epilepsy.
Breastfeeding
Valproate is excreted in human breast milk with a concentration ranging from 1 to 10 % of maternal plasma levels. Hematological disorders have been observed in breastfed newborns / infants of women receiving treatment with this drug (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
Amenorrhea, 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 sections "Dosage and administration", "Administration details" and "Adverse reactions"). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. A limited number of case reports suggest that dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

Effect on reaction rate when driving motor transport or using other mechanisms.
The use of valproate may provide sufficient seizure control such that the patient may be eligible to hold a driving license.
Patients should be warned of the risk of transient drowsiness, especially in cases of combined antiepileptic therapy or concomitant administration of the medicinal product with benzodiazepines (see section "Interaction with other medicinal products and other types of interaction").

Dosage and administration.
Vinitel® syrup is for oral administration.
The daily dose depends on the age and body weight. The medicinal product may be given twice daily.
Dosage
Adults
The initial dose is 600 mg daily, with gradual increases by 200 mg at three-day intervals until seizure control is achieved. Control is usually achieved within the dosage range of 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.
Special populations
Pediatric population
Children with body weight over 20 kg

The initial dose should be 400 mg/day (irrespective of body weight) with gradual increases until seizure control is achieved. Control is usually achieved within the range of 20–30 mg/kg/day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg/day. If doses higher than 40 mg/kg/day are used, complete blood count and biochemical blood test parameters should be monitored.

Children with body weight under 20 kg

The daily dose is 20 mg/kg. In severe cases it 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 the complete blood count and biochemical blood test should be monitored.

Elderly patients

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

Patients with renal insufficiency

It may be necessary to reduce or increase the dosage in patients with renal insufficiency undergoing hemodialysis. Valproate is dialyzable (see section "Overdose"). Dosing should be modified according to clinical monitoring of the patient (see section "Administration details").

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").

Cases of liver dysfunction, including hepatic failure resulting in fatalities, were observed in patients whose treatment included valproic acid (see sections "Contraindications" and "Administration details").

The use of salicylates is not recommended in children under 16 years of age. In addition, concomitant use of salicylates with valproate, in children under 3 years of age increases the risk of hepatotoxicity (see section "Administration details").

Female children and women of childbearing potential under 55 years of age

Valproate treatment should not be initiated in female patients under 55 years of age unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections "Contraindications", "Administration details" and "Use during pregnancy or breastfeeding").

Valproate treatment should be supervised by a specialist experienced in the management of epilepsy.

Valproate should not be prescribed in female children and women of childbearing potential under 55 years of age two specialists independently consider and document that there is no other effective or tolerated treatment (see sections "Contraindications", "Administration details" and "Use during pregnancy or breastfeeding").

Where possible female children and women of childbearing potential under 55 years of age should be switched to another treatment unless two specialists independently consider and document there is no other effective or tolerated treatment. For those continuing to receive valproate, the benefits and risks of valproate should be carefully reconsidered at regular treatment reviews, at least annually (see section "Administration details").

Valproate should be prescribed and dispensed according to the "Pregnancy prevention programme" (see sections "Contraindications" and "Administration details").

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").

Males

It is recommended that treatment with the drug Vinitel® is initiated and supervised by a specialist experienced in the management of epilepsy (see sections "Administration details" and "Use during pregnancy or breastfeeding").

Male patients under 55 years of age

Valproate treatment should not be initiated in male children or men under the age of 55 unless two specialists independently consider and document that there is no other effective or tolerated treatment or that the risk of infertility or potential risk of testicular toxicity are not applicable (see sections "Administration details" and "Use during pregnancy or breastfeeding").

The specialist should discuss and complete the "Risk acknowledgement form for male patients starting valproate" with the patient and/or carer to ensure that all male children and men under 55 years of age are informed of the risk of infertility in males (see sections "Administration details", "Use during pregnancy or breastfeeding" and "Adverse reactions") and of the data available indicating testicular toxicity in animals exposed to valproate and the uncertain clinical relevance of these data (see section "Preclinical safety data").
Combined therapy (see section "Interaction with other medicinal products and other types of interaction")
When starting valproate in patients already treated with other AEDs, the dose of the latter should be slowly reduced. Initiation of valproate therapy should be gradual, with the 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 using valproate in combination with antiepileptic drugs which induce liver enzyme activity (e.g. phenytoin, phenobarbital and carbamazepine). Once known liver enzyme inducers have been completely withdrawn, appropriate seizure control should be maintained on a reduced dose of valproate. When barbiturates are administered concomitantly, in particular if sedation is observed (particularly in children), the dosage of barbiturates should be reduced.
The 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 where adverse reactions are suspected (see section "Pharmacokinetics").

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

Overdose.
Symptoms
Cases of accidental and deliberate valproate overdose have been reported.
Symptoms other than nausea, vomiting, and dizziness are unlikely to occur in cases of overdose where plasma concentrations of valproate are 5–6 times higher than the maximum therapeutic level.
Clinical signs of acute massive overdose, with plasma concentrations 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 favorable outcome is usual. However, several fatal cases following massive overdose are known. It should be noted that symptoms of overdose may be variable. Seizures have been reported in the presence of very high plasma valproate levels (see also section "Pharmacokinetics"). Several cases of intracranial hypertension related to cerebral edema have been reported.
The presence of sodium content in the drug may lead to hypernatremia in case of overdose.
Treatment
Hospital management of overdose should be symptomatic: gastric lavage, cardiorespiratory monitoring. Gastric lavage may be useful up to 10–12 hours following ingestion. In case of valproate overdose resulting in hyperammonemia, carnitine can be given through IV route to attempt to normalize ammonia levels.
Naloxone has been successfully used, sometimes in combination with activated charcoal given orally.
In case of massive overdose, hemodialysis and hemoperfusion are 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 unknown (cannot be estimated from the available data).
Congenital malformations and developmental disorders (see sections "Administration details" and "Use during pregnancy or breastfeeding").
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"). Transient increases in liver enzymes are common, particularly at the start of treatment (see section "Administration details").

Gastrointestinal disorders

Very common: nausea.

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 with no need for drug withdrawal. These problems can usually be overcome by taking the 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, paresthesia, aggravated convulsions (see section "Administration details").

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorders.

Sedation has been reported occasionally, usually when valproate was co-administered with other AEDs. In case of valproate monotherapy, sedation occurred very rarely, in the early stages of treatment, and was 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 resulted from combined use of other AEDs (notably phenobarbital or topiramate). Usually, these manifestations disappear after valproate withdrawal or dose reduction.

An increase in alertness may occur. This is generally beneficial but occasionally aggression, hyperactivity and behavioral disorders have been reported.

Psychiatric disorders

Common: confusional state, hallucinations, aggression, agitation, disturbances in attention.

Rare: abnormal behavior, psychomotor hyperactivity, learning disorder.

Metabolic and nutritional disorders

Common: hyponatremia, body weight increased*.

*Body weight increase should be carefully monitored since it is a risk factor for polycystic ovary syndrome (see section "Administration details").

Rare: hyperammonemia* (see section "Administration details"), obesity.

* Rare cases of isolated and moderate hyperammonemia without any significant changes in the results of liver function tests. These changes are usually transient and do not require the discontinuation of treatment. 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. In such cases further investigations should be considered (see section "Contraindications" and "Administration details").

Unknown: hypocarnitinemia (see sections "Contraindications" and "Administration details").

Endocrine disorders

Uncommon: syndrome of inappropriate antidiuretic hormone (ADH) secretion, 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: anemia, thrombocytopenia (see section "Administration details").

Uncommon: pancytopenia, leucopenia.

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

The blood picture returned to normal following the discontinuation of the drug.

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 curlier than before.

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

Rare: toxic epidermal necrolysis, Stevens–Johnson syndrome, erythema multiforme, DRESS-syndrome (drug rash with eosinophilia and systemic symptoms syndrome).

Unknown: hyperpigmentation.

Reproductive system and breast disorders

Common: dysmenorrhea.

Uncommon: amenorrhea.

Rare: polycystic ovary syndrome, male infertility (see section "Use during pregnancy or breastfeeding").

Very rare: gynecomastia.

Vascular disorders

Common: hemorrhage (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 tract 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, aminoaciduria, phosphaturia, and uricosuria), associated with valproate therapy, but the mode of action is as of yet unclear.

General disorders

Uncommon: hypothermia, non-severe peripheral edema.

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 (eosinophilic).

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.

Unknown: acquired Pelger–Huet anomaly.

Children

The safety profile of valproate in the pediatric population is comparable to that in adults, but some adverse reactions are more severe or mainly 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. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section

“Administration details”). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are mainly 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.
Reporting of suspected adverse reactions.
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua.

Shelf life.
2 years.

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

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

or

Manufacturer.
LLC “GLADPHARM LLC”.

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

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