DEPA-PO-500MG-27.0

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

DEPALEPT CHRONO 500 MG

Patient safety information card and guide
The marketing of Depalept Chrono is subject to a risk management plan (RMP) including a 'Patient card', 'patient guide', 'Healthcare professionals guide' and 'Physician Checklist' in the frame of Pregnancy Prevention Program. The 'Patient card' and the 'Patient guide' emphasize important safety information on the risk of congenital malformations and neuro-development disorders that the female patients should be aware of before and during treatment.
Please explain to the patient the need to review the card and the guide before starting treatment and discuss the Physician Checklist at intiation of treatment and at least annually.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Depalept Chrono 500 mg
1 divisible prolonged-release tablet contains 333 mg of sodium valproate and 145 mg valproic acid (equivalent to a total of 500 mg sodium valproate).

Excipients with known effect:
Contains 47.21 mg sodium per prolonged-release tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Depalept Chrono 500 mg:
Oblong, practically white, scored film-coated tablets

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy: Treatment of generalized or partial epilepsy secondary epilepsy and mixed forms of epilepsy.

Bipolar disorders: Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproic acid for acute mania.

4.2 Posology and method of administration

Notes
When switching from previous (non-prolonged-release) dosage forms to Depalept chrono, care must be taken to ensure adequate serum levels of valproic acid.

In female children, female adolescents, women of childbearing potential and pregnant women

Depalept chrono should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated (see Section 4.3, 4.4 and Section 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Depalept chrono should 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.

Depalept Chrono is a prolonged-release formulation of Depalept which reduces peak plasma concentrations and ensures more regular plasma levels over a 24-hour period.

In view of the dosage strength this medicinal product is for use in adults and children weighing over than 17 kg only.

This dosage form is not appropriate for children under the age of 6 years (risk of choking).

Dosage

Epilepsy

The Initial daily dosage is usually 10-15 mg/kg, after which doses are increased up to the optimum dose (see Initiation of Depalept therapy)

The mean dosage is 20 -30 mg/kg per day. However, if seizures are not brought under control at this dosage it may be increased and patients must be closely monitored.

- In children, the usual dosage is about 30 mg/kg per day.
- In adults, the usual dosage is 20 to 30 mg/kg per day.
- In elderly patients, the dosage should be determined based on the control of seizures.

The daily dosage should be determined based on age and body weight, however, the significant variations in inter-individual sensitivity to valproate must be taken into account.

No clear correlation between the daily dose, serum levels and the therapeutic effect has been established: the dosage should be determined on the basis of the clinical response.
Determination of valproic acid plasma levels should be considered along with clinical monitoring when control of seizures is not achieved or when adverse effects are suspected. The effective therapeutic range is usually between 40 and 100 mg/L (300 to 700 µmol/L).

Initiation of Depalept therapy (oral administration):

- In patients in whom appropriate control has been obtained with immediate-release forms of Depalept, it is recommended that the daily dose be maintained when replacing treatment with Depalept Chrono.

- If the patient is already being treated and is taking other antiepileptics, begin administering Depalept Chrono gradually, to reach the optimal dose in approximately two weeks, then reduce the concomitant treatments if necessary on the basis of treatment efficacy.
- If the patient is not taking any other antiepileptics, the dosage should preferably be increased step-wise every 2 or 3 days, in order to reach the optimal dose in approximately one week.
- If necessary, combination treatment with other antiepileptics should be instituted gradually (see 4.5 Interaction with other medicinal products and other forms of interaction).

Manic episodes in bipolar disorder

Adults

The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg sodium valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to determine the lowest effective dose for the individual patient. The average daily dose usually ranges between 1000 and 2000 mg sodium valproate. Patients receiving daily doses higher than 45 mg/kg body weight/day should be carefully monitored. Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Children and adolescents

The efficacy of Ergenyl chrono for the treatment of manic episodes in bipolar disorder have not been established in patients aged less than 18 years.
For information on the safety profile in children, see section 4.8.

Method of administration

Oral use.

The daily dose should be administered in 1 dose or 2 divided doses, preferably during meals and should be swallowed whole with a glass of water, but not carbonated mineral water.
Administration of a single daily dose is possible in well controlled epilepsy.

In view of the sustained release process and the nature of the excipients in the formula, the inert matrix is not absorbed by the digestive tract; it is eliminated in the stools after the active substances have been released.

Initiation of Depalept therapy (oral administration):

- Liver function tests should be performed before starting treatment (see Section 4.3) and then periodically for the first 6 months, particularly in patients at risk (see Section 4.4).
- Blood tests (complete blood count including platelets, bleeding time and coagulation parameters) are recommended prior to treatment, then after 15 days and at the end of treatment, and also before any surgery, and in the event of hematomas or spontaneous bleeding (see Section 4.8).
- In patients with renal insufficiency, elevated circulating valproic acid concentrations in the blood should be taken into account and the dosage should be reduced accordingly.

4.3 Contraindications

Depalept Chrono is contraindicated in the following situations:

– hypersensitivity to the active substance or to any of the excipients listed in section 6.1,

- a personal or family history of liver disease or manifest severe hepatic or pancreatic dysfunction,
- disorders of hepatic function with a fatal outcome during valproic acid treatment in siblings,
- hepatic porphyria,
- blood coagulation disorders,
- mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4),
- known urea cycle disorders (see section 4.4).
- in uncorrected systemic primary carnitine deficiency (see section 4.4 “Patients at risk of hypocarnitinaemia”).

Treatment of epilepsy
- in pregnancy unless there is no suitable alternative treatment (see sections 4.4 and 4.6),
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilled (see sections 4.4 and 4.6).

Treatment of bipolar disorder
- in pregnancy (see sections 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilled (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Damage to the liver and/or pancreas
Uncommon cases of severe liver damage and rare cases of damage to the pancreas have been observed. Infants and young children under 3 years of age who suffer from severe epileptic seizures are most often affected.
The risk of liver or pancreatic damage is increased, especially in combination treatment with multiple antiepileptic drugs or in the case of brain damage, mental retardation and/or a congenital metabolic disease including mitochondrial diseases such as carnitine deficiency, urea cycle disorders, POLG mutations (see sections 4.3 and 4.4) or degenerative disease. In these patients, valproic acid should be used with particular caution and as monotherapy.

In the majority of cases, liver damage was observed within the first six months of treatment and in particular between the second and twelfth week. The incidence of disorders decreases considerably in children over 3 years of age and particularly over the age of 10.
These disorders can be fatal. If hepatitis and pancreatitis occur together, the risk of a fatal outcome increases.

Signs of damage to the liver and/or pancreas
Serious or fatal damage to the liver and/or pancreas may be preceded by non-specific symptoms, usually of sudden onset, such as a recurrence or increase in the frequency or severity of epileptic seizures, reduced levels of consciousness with confusion, restlessness, movement disorders, physical malaise and asthenia, loss of appetite, aversion to familiar foods, aversion to valproic acid, nausea, vomiting, upper abdominal symptoms, lethargy, drowsiness and, particularly with liver damage, abnormally frequent haematomas, nosebleeds and oedema, either variably localised or generalised. Patients, particularly infants and young children, should be monitored closely by a doctor with respect to these signs.

If the aforementioned symptoms are persistent or serious, appropriate laboratory tests should be performed (see section “Measures for the early detection” below) in addition to a thorough examination. However, as the blood test results of patients with a disorder may not necessarily be abnormal, the treating doctor should not rely exclusively on changes in blood test results. Particularly

at the start of treatment, in isolated cases, liver enzyme values can be temporarily elevated even independent of any impairment of hepatic function. Therefore, medical history and the clinical picture are always of critical importance to the assessment.

In case salicylates are taken concomitantly they should be discontinued as a precautionary measure, since they follow the same metabolic pathway as valproic acid.

Measures for the early detection of damage to the liver and/or pancreas
Before treatment starts, a detailed medical history should be taken, covering, in particular, metabolism disorders, hepatopathies, pancreatic disorders and coagulation disorders in the patient and his/her family. Clinical examinations and chemical laboratory tests (e.g. PTT, fibrinogen, coagulation factors, INR, total protein, blood count with platelets, bilirubin, AST, ALT, gamma-GT, lipase, alpha-amylase in the blood, blood sugar) should also be performed.
Four weeks after the start of treatment, follow-up chemical laboratory tests should be performed with measurement of coagulation parameters such as INR and PTT, AST, ALT, bilirubin and amylase.

In children who are clinically normal, a blood count with platelets, AST and ALT, and at every second medical examination, also the clotting parameters should be determined.

In clinically normal patients with pathologically elevated results after 4 weeks, follow-up tests should be performed three times at intervals of no more than 2 weeks, then once a month until the sixth month of treatment.

In adolescents (from the age of about 15) and adults, it is advisable to check the clinical findings and laboratory parameters every month for the first six months and in any case before starting treatment.

After 12 months of treatment with no abnormalities, only 2–3 medical check-ups a year are necessary.

Liver function should be monitored again where necessary if there are changes in concomitant medication (dose increase or new addition) known to have an effect on the liver (see also section 4.5 on the risk of liver damage from salicylates, other anticonvulsants including cannabidiol).

Parents should be instructed to look for possible signs of damage to the liver and/or pancreas (see “Signs of damage to the liver and/or pancreas”) and urged to inform the treating doctor of clinical abnormalities immediately, regardless of this time schedule.

Bleeding and other hematopoietic disorders

Valproate is associated with dose-related thrombocytopenia. In a clinical trial of divalproex sodium as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 × 109/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects. Valproate use has also been associated with decreases in other cell lines and myelodysplasia.

Because of reports of cytopenias, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen, coagulation factor deficiencies, acquired von Willebrand's disease), measurements of complete blood counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving valproic acid capsules be monitored for blood counts and coagulation parameters prior to planned surgery and during pregnancy. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reaction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking valproate. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Valproate should be discontinued and not be resumed if an alternative etiology for the signs or symptoms cannot be established.

Immediate withdrawal of the treatment should be considered in the event of:
an inexplicable disturbance in the patient's general condition, clinical signs of a hepatic or pancreatic disorder or a bleeding tendency, a more than two- to three-fold increase in liver transaminases, even in the absence of clinical signs (consider enzyme induction by any concomitant medication), a slight (one and a half- to two-fold) increase in liver transaminases with a concomitant acute febrile infection, or a severe coagulation disorder.

Pregnancy Prevention Program

Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Depalept Chrono is contraindicated in the following situations:

Treatment of epilepsy
- in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6),
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder
- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Program:

The prescriber must ensure that
- individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and explain her the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- The prescriber explained the patient the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- The prescriber explained the patient the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection "Contraception" of this boxed warning), without interruption during the entire duration of treatment with valproate.
- The prescriber explained the patient the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders.

- The prescriber explained the patient the need to consult her physician as soon as she is planning a pregnancy to ensure timely discussion and switching to alternative treatment prior to conception, and before contraception is discontinued.
- The prescriber explained the patient the need to urgently consult her physician in case of pregnancy.

- The prescriber explained the patient the risks to the unborn child and the patient herself of untreated epilepsy or bipolar disorder.

- the patient has received the Patient Guide.
- The prescriber explained the patient the risks and necessary precautions associated with valproate use (according to Physician Checklist).

- Keep a copy of the checklist in the patient's file and give a copy to the patient or her legal guardian

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

Female children

- Valproate should not be prescribed to female children or women of childbearing potential, unless there is no suitable alternative treatment.

- The prescriber must ensure that parents/caregivers of female children had received an explanation about the need to contact the specialist once the female child using valproate experiences menarche.
- The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention program should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test

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

Contraception

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

Estrogen-containing products

Concomitant use with estrogen-containing products, including estrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products.
On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist
The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the Physician Checklist, at initiation and during each annual review and ensure that its content was explained to the patient.

Pregnancy planning
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and, if needed, switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. All patients with a valproate exposed pregnancy and their partners should be referred to a Teratology center for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:
- Reinforce the safety messages including the need for effective contraception. Dispense valproate in the original package with an outer warning. Do not unpack.
- the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, a Patient Card, a Patient Guide, a Physician Checklist, and a Guide for prescribers involved in the care of women of childbearing potential using valproate and the details of the Pregnancy Prevention Program will be available to inform healthcare professionals and patients/caregivers on the risks of valproate and the conditions for use. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

Physician Checklist needs to be used by the specialists at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Suicidal ideation and suicidal behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a slightly increased risk of suicidal ideation and suicidal behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproic acid.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents
The concomitant use of valproic acid/valproates and carbapenem agents is not recommended (see section 4.5).

Alcohol should be avoided during treatment with valproate.

Urea cycle disorders and risk of hyperammonaemia
An increase in the ammonia serum level (hyperammonaemia) may occur during treatment with products containing valproic acid. Therefore, serum levels of ammonia and valproic acid should be determined in the event of symptoms such as apathy, somnolence, vomiting, hypotension, and an increase in seizure frequency; the dose of the product should be reduced if necessary.

When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed before starting valproic acid therapy to avoid the occurrence of hyperammonaemia (see sections 4.3 and 4.4 “Patients at risk of hypocarnitinaemia” and “Liver and/or pancreatic damage”).

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

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including 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 4.3).

Patients at risk of hypocarnitinaemia
Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 “Known or suspected mitochondrial disease” and “Urea cycle disorders and risk of hyperammonaemia”), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicinesor other antiepileptics.

Patients should be warned to report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed.

Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia 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 treated with valproic acid. Carnitine supplementation should be considered in these patients.

See also sections 4.5, 4.8 and 4.9.

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

Bone marrow damage
Patients with previous bone marrow damage must be strictly monitored.

Immune system reactions
Although immune system disorders have only rarely been observed during treatment with medicinal products containing valproic acid, the latter should not be used in patients with systemic lupus erythematosus until a strict risk-benefit analysis has been carried out.

Renal insufficiency and hypoproteinaemia
In patients with renal insufficiency and hypoproteinaemia, the rise in free valproic acid in serum must be considered and the dose reduced accordingly (see also section 4.2). As monitoring of plasma concentrations alone may be misleading, dosage should be adjusted according to the clinical picture.

Investigations
It should be noted that, as with other anti-epileptics, transaminases can rise temporarily without any clinical symptoms at the start of treatment with valproic acid. In these cases, more extensive laboratory tests (including INR) are recommended. In rare cases, harmless, usually temporary nausea, sometimes with vomiting and loss of appetite, can also occur and regresses spontaneously or after a reduction in the dose.

Coagulation status should be checked before a surgical procedure and in case of injuries or spontaneous bleeding (including blood cell count with platelets, bleeding time and coagulation factors).
If the patient is taking a vitamin K antagonist concomitantly, close monitoring of the INR is recommended.

Patients should be informed about possible weight gain at the start of treatment. Suitable weight control measures should be taken.

Further note:
If undesirable effects that are not dose-dependent are observed, withdrawal of the medicinal product is indicated.

Paediatric population
Monotherapy is recommended in children under the age of 3 years when perscribing Depalept Chrono, but the potential benefit should be weighed against risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see above “Damage to the liver and/or pancreas”, see also section 4.5).

Concomitant treatment with salicylates in children under 12 years of age should be avoided due to the risk of liver damage (see also section 4.5).

One prolonged-release tablet of Depalept Chrono 500 mg contains 47.21 mg sodium per prolonged-release tablet, equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on valproic acid:

Enzyme-inducing anti-epileptics such as **phenobarbital**, **primidone**, **phenytoin** and **carbamazepine** reduce serum levels of valproic acid, thereby reducing the effect. In the case of combined therapy, the dosage should be adjusted in accordance with the clinical efficacy and serum level.

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

Mefloquine increases the degradation of valproic acid and also has potential convulsant effects. Concomitant use can therefore lead to epileptic seizures.

Decreases in serum concentrations of valproic acid have been reported when it is co-administered with **carbapenems**, resulting ina 60–100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, the consequences of an interaction between valproic acid and carbapenems in patients stabilised on valproic acid are considered to be unmanageable and therefore co-administration should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, the blood level of valproic acid should be closely monitored.

Serum valproic acid concentrations may be increased by concomitant administration of **cimetidine** or **erythromycin**, as a result of a reduced metabolism in the liver.

Serum valproic acid concentrations may also be increased by concomitant administration of **fluoxetine**. However, a decrease has also been reported.

Medicinal products with high plasma protein binding, such as **acetylsalicylic acid**, can competitively displace valproic acid from its protein binding sites and increase the concentration of free valproic acid in serum.
Medicinal products containing valproic acid and acetylsalicylic acid should not be administered concomitantly in infants and children with febrile disorders and only on the express instructions of a doctor in adolescents with febrile disorders.

If **vitamin K antagonists** are administered concomitantly, close monitoring of the INR is recommended.

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

Valproate plasma level is decreased in case of concomitant use with protease inhibitors such as **lopinavir** or **ritonavir**.

Estrogen-containing products, 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 would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.
On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

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

Effects of valproic acid on other medicinal products:
The valproic acid-induced increase in the **phenobarbital** concentration, which can manifest itself in the form of severe sedation (particularly in children), is of particular clinical significance. If this occurs, the phenobarbital or primidone dose must be reduced (primidone is partially metabolised to phenobarbital). Careful monitoring is therefore recommended, particularly in the first 15 days of combination treatment.

In patients who are already taking **phenytoin**, additional administration or an increase in the dose of medicinal products containing valproic acid can cause the amount of free phenytoin to rise (the concentration of the non-protein-bound active part) without an increase in total serum levels of phenytoin. This can increase the risk of undesirable effects, particularly brain damage (see section 4.8). Clinical monitoring is therefore recommended; if plasma phenytoin concentrations are determined, the free form should be measured.

During combination treatment with **carbamazepine** and valproic acid, symptoms have been described that may be attributable to potentiation of carbamazepine toxicity by valproic acid. Clinical monitoring is indicated, particularly at the start of combination treatment, and the dose should be adjusted if necessary.

Valproic acid inhibits the metabolism of **lamotrigine** and almost doubles its mean half-life. Combination of lamotrigine and medicinal products containing valproic acid may increase the risk of skin reactions; individual cases of severe skin reactions have been reported occurring within 6 weeks of starting combination treatment and, in some cases, not regressing until the medication was withdrawn or appropriate treatment administered. Clinical monitoring is therefore recommended and, if necessary, the lamotrigine dosage should be adjusted (reduction of the lamotrigine dosage).

In combination with **benzodiazepines**, **barbiturates** and **neuroleptics**, **MAO inhibitors** and **antidepressants**, valproic acid can increase the central depressant effect of these medicinal products. Patients taking corresponding combinations should be monitored carefully and doses adjusted if necessary.

Depalept Chrono has no effect on the **lithium** serum level.

The metabolism and protein binding of other active substances, such as **codeine**, are also affected.

Valproic acid may increase the serum concentration of **zidovudine**, which can lead to an increase in zidovudine toxicity.

Concomitant administration of medicinal products containing valproic acid and **anticoagulants or anti-aggregants** can result in an increased tendency to bleed. Regular monitoring of blood coagulation is therefore recommended in the event of concomitant use (see also section 4.4).

In healthy subjects, valproate displaces **diazepam** from its plasma albumin binding sites and inhibits its metabolism. In patients receiving combination treatment, the concentration of unbound diazepam can be elevated, and the plasma clearance and volume of distribution of the free diazepam fraction reduced (by 25 % and 20 % respectively). However, the half-life remains unchanged.

In healthy subjects, concomitant treatment with valproate and **lorazepam** reduced the plasma clearance of lorazepam by up to 40 %.

In children, serum levels of **phenytoin** may increase after concomitant administration of clonazepam and valproic acid.

Valproic acid may decrease the **olanzapine** plasma concentration.

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

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

Other interactions

Risk of liver damage
The concomitant use of salicylates should be avoided in children under 12 years due to the risk of liver toxicity (see section 4.4).
Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4).
Concomitant use with cannabidiol increases the incidence of transaminases enzyme 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, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

It is pointed out that potentially hepatotoxic medicinal products as well as alcohol can increase the hepatotoxicity of valproic acid.

With concomitant administration of valproic acid and **topiramate,** encephalopathy and/or an increase in ammonia blood levels (hyperammonaemia) has been reported. Also, concomitant use of valproic acid and **acetazolamide** may lead to hyperammonaemia and therefore there might be an increased risk of encephalopathy. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemic encephalopathy.

Pivalate-conjugated medicinal products
Concomitant administration of valproate and **pivalate-conjugated medicines** (such as cefditorenpivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to an increased risk of carnitine depletion (see section 4.4 “Patients at risk of hypocarnitinaemia”). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

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

The effect of hormonal contraceptives (“the Pill”) is not reduced by valproic acid, as valproic acid has no enzyme-inducing effect.

As valproic acid is partially metabolised to ketone bodies, consideration should be given to the possibility of a false positive reaction to a test for ketone bodies in diabetics with suspected ketoacidosis.

Absences occurred in patients with a history of this type of seizure after concomitant treatment with medicinal products containing valproic acid and **clonazepam**.

Catatonia occurred in a female patient with a schizoaffective disorder after concomitant treatment with valproic acid, sertraline (antidepressant) and risperidone (neuroleptic).

The bioavailability of sodium valproate/valproic acid in the prolonged-release formulation is not significantly affected by the concomitant intake of food.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment of epilepsy

- Valproate is contraindicated during pregnancy, unless there is no suitable alternative treatment.
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see sections 4.3 and 4.4).

Treatment of Bipolar disorder

- Valproate is contraindicated during pregnancy.
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and developmental effects

Pregnancy Exposure Risk related to valproate
Both valproate monotherapy and valproate polytherapy including other antiepileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.

Valproate was shown to cross the placental barrier both in animal species and in humans (see section 5.2).
Teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

Congenital malformations
A meta-analysis (including registries and cohort studies) showed that about 11% of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (about 3 %).

The risk of major congenital malformations in children after in utero exposure to antiepileptic drug polytherapy including valproate is higher than that of anti-epileptic drugs polytherapy not including valproate.

This risk is dose-dependent in valproate monotherapy, and available data suggest it is dose-dependent in 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 types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius) and multiple anomalies involving various body systems.

In utero exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe

both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

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

Neurodevelopmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk of neurodevelopmental disorders (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 anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated epileptic mothers.

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

When valproate is administered in monotherapy, studies in preschool children exposed in utero to valproate show that up to 30–40 % experience delays in their early development, such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7–10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long-term outcomes.

Available data 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 unexposed population in the study.

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

If a woman plans a pregnancy
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder if a woman is planning to become pregnant a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

Pregnant women

Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred to a Teratology center for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest that it prevents the birth defects or malformations due to valproate exposure.

Serum concentrations of valproic acid should be checked regularly, as they apparently fluctuate considerably in the course of a pregnancy, even if the dose remains constant. After remaining roughly the same for the first and second trimester, a three-fold increase in the concentration of free valproic acid in the third trimester up to the delivery date has been observed.

Women of childbearing potential
Estrogen-containing products
Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (sections 4.4 and 4.5).

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, hypofibrinogenaemia and/or to a decrease in other coagulation factors. Afibrinogenaemia 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, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

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

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

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Fertility dysfunctions are in some cases reversible at the least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some other cases, the reversibility of male infertility was unknown.

4.7 Effects on ability to drive and use machines

At the start of treatment with Depalept Chrono, at higher doses and/or in combination with medicinal products that act on the central nervous system, central nervous effects, e.g. somnolence and/or confusion, can affect reactions to such an extent that the ability to drive a vehicle or use machines is impaired, irrespective of the effect of the underlying disorder being treated. This effect is intensified in combination with alcohol.

4.8 Undesirable effects

Assessment of frequency of undesirable effects is based on the following categories:

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

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

Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia (see section 4.4) or leucopenia, which often regresses if treatment continues, but always regresses when valproic acid is withdrawn.
Uncommon: pancytopenia.
Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis, lymphopenia, neutropenia.

Endocrine disorders
Uncommon: syndrome of inappropriate secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia and/or androgen increased).
Rare: hypothyroidism.

Metabolism and nutrition disorders
Very common: hyperammonaemia (see section 4.4).
Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, but do not require treatment discontinuation. However, cases have also been reported in which neurological symptoms occur. In such cases, further investigations should be considered (see sections 4.3 and 4.4 "Urea cycle disorders and risk of hyperammonaemia" and "Patients at risk of hypocarnitinaemia").

Common: weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4). or - weight decrease, increased appetite or also loss of appetite, hyponatraemia.
Rare: obesity.
Not known: hypocarnitinaemia (see sections 4.3 and 4.4).

Psychiatric disorders
Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*.
Uncommon: irritability, hyperactivity.
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*.

*These adverse events are principally observed in the paediatric population.

Nervous system disorders
Very common: tremor.
Common: extrapyramidal disorder (may be irreversible), stupor*, somnolence, paraesthesia, convulsion*, memory impairment, headache, nystagmus and dizziness.
Uncommon: coma*, encephalopathy*, lethargy* (see below), reversible parkinsonism, spasticity, ataxia, aggravated convulsions (see section 4.4).
There have been uncommon reports of encephalopathy shortly after the use of medicinal products containing valproic acid. Its pathogenesis has not been clarified and it is reversible after withdrawal of the medicinal product. In some of these cases, there were reports of elevated ammonia levels and, in patients receiving combination treatment with phenobarbital, of a rise in the phenobarbital level.
Rare: Diplopia. Reversible dementia associated with reversible cerebral atrophy, cognitive disorder.
Rarely and especially with high doses or in combination with other anti-epileptics, chronic encephalopathy with neurological symptoms and disorders of higher cortical functions have also been reported. The pathogenesis has also not been clarified adequately.
Frequency not known: sedation.

*Cases of stupor and lethargy sometimes leading to transient coma/encephalopathy have been reported; they were in part associated with an increase in the occurrence of convulsions and their symptoms decreased on withdrawal of treatment or reduction of dosage.
These cases mostly occurred during combined therapy (in particular with phenobarbital or topiramate) or after a sudden increase in doses.

During **long-term treatment** with a combination of Depalept Chrono and other anti-epileptics, particularly phenytoin, signs of brain damage (encephalopathy) may be seen: an increase in seizures, listlessness, stupor, muscle weakness (poor muscle tone) and severe general changes in EEG.

Ear and labyrinth disorders
Common: reversible or irreversible hearing loss.
Frequency not known: tinnitus.

Vascular disorders
Common: haemorrhage (see sections 4.4 and 4.6).
Uncommon: vasculitis.

Respiratory, thoracic and mediastinal disorders
Uncommon: pleural effusion.

Gastrointestinal disorders
Very common: nausea.
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, diarrhoea, particularly at the start of treatment, upper abdominal pain, which usually regress after a few days despite continuation of the treatment.

Uncommon: pancreatic damage, in some cases with a fatal outcome (see section 4.4), hypersalivation (particularly at the start of treatment).

Hepatobiliary disorders
Common: Serious (sometimes fatal) non-dose-dependent liver injuries. The risk of liver damage is significantly higher in children, particularly those taking other anti-epileptics concomitantly (see section 4.4).

Skin and subcutaneous tissue disorders
Common: hypersensitivity, transient and/or dose related alopecia, nail and nail bed disorders.
Uncommon: angioedema, rash, hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal).
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.

Musculoskeletal and connective tissue disorders
There have been reports of decreased bone mineral density like osteoporosis as well as pathological fractures in patients on long-term therapy with valproic acid. The mechanism by which valproic acid affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4).

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

Reproductive system and breast disorders
Common: dysmenorrhoea.
Uncommon: amenorrhoea.
Rare: male infertility (see section 4.6), elevated testosterone levels and polycystic ovaries.

Congenital, familial and genetic disorders
Congenital malformations and developmental disorders (see sections 4.4 and 4.6).

General disorders and administration site conditions
Uncommon: hypothermia, non-severe peripheral oedema.

Investigations
Rare: Valproic acid can reduce the concentration of at least one coagulation factor and inhibit the secondary phase of platelet aggregation, resulting in a prolonged bleeding time.
This may result in abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged, see sections 4.4 and 4.6).
Biotin/biotinidase deficiency may occur.

Paediatric population
The safety profile of valproate in the paediatric population is comparable to adults, but some adverse drug reactions are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children, especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4).
Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Every assessment of intoxication should consider the possibility of multiple intoxication, e.g. taking several medicinal products, perhaps with suicidal intent.

At therapeutic serum levels (40–100 mg/l), valproic acid has relatively low toxicity. Acute valproic acid intoxication with serum levels of over 100 mg/l has been very rare in both adults and children. There are isolated cases of acute and chronic overdose with a fatal outcome in the literature.

Symptoms of intoxication
The symptoms of intoxication are characterised by states of confusion, sedation to the point of coma, muscle weakness, hyporeflexia and areflexia. Miosis, respiratory disorders, metabolic acidosis, cardiovascular disorders, hypotension and circulatory collapse/shock have been observed. Deaths have occurred sporadically following a massive overdose.

High serum levels have caused abnormal neurological disorders, e.g. increased tendency to seizures and behavioural changes, in adults and in children. Cases of increased intracranial pressure associated with cerebral oedema have been reported.

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

Treatment of overdose
There is no known specific antidote. Clinical measures depend on the symptoms. The Administration of activated charcoal or gastric lavage may be useful up to 12 hours after the overdose. Vital signs should be monitored and, if necessary, supported.
Haemodialysis and forced diuresis can be effective at removing the valproic acid that is not bound to protein from the blood. Peritoneal dialysis is of little use. Experience of the efficacy of complete plasma replacement and transfusion is inadequate. For this reason, intensive general measures that do not include specific detoxification procedures, particularly in children, but which include monitoring of serum concentration are recommended.

Intravenous administration of naloxone to improve a reduced level of consciousness has been described as effective in some cases. In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-epileptics/fatty acid derivatives/antipsychotics,
ATC code: N03AG01/N05 AX.

Valproic acid is an anti-epileptic with no structural similarity to other anticonvulsant drugs. Potentiation of GABA-mediated inhibition caused by a presynaptic effect on GABA metabolism and/or a direct postsynaptic effect on the ion channels of the neuronal membrane are assumed to be the mechanism of action of valproic acid.

5.2 Pharmacokinetic properties

Absorption
After oral administration, valproic acid and its sodium salt are rapidly and almost completely absorbed in the gastrointestinal tract.

The time taken to reach the peak serum concentration depends on the pharmaceutical form:
Peak serum concentrations after one Depalept Chrono 500 mg prolonged-release tablet are reached within 6.3 ± 0.95 hours.

Distribution
The mean therapeutic range of serum concentrations is reported as 50–100 mg/l. Above 100 mg/l, an increase in undesirable effects to the point of intoxication should be expected. Steady-state serum levels are usually reached within three to four days.

Cerebrospinal fluid concentrations of valproic acid are 10 % of the respective serum concentration.

The volume of distribution depends on age and is usually 0.13–0.23 l/kg of body weight or, in younger people, 0.13–0.19 l/kg of body weight.

90–95% of valproic acid is bound to plasma proteins, primarily albumin. At higher doses, protein binding decreases. Plasma protein binding is lower in elderly patients and in patients with impaired renal or hepatic function. In one study, higher levels of free active substance (8.5 % to over 20 %) were seen in patients with significantly impaired renal function. The total valproic acid concentration, consisting of a free and a protein-bound form, may be largely unchanged in patients with hypoproteinaemia, but can also be reduced as a result of increased metabolism of the free form.

Biotransformation
Biotransformation takes place through glucuronidation as well as beta-, omega- and omega-1-oxidation. The major pathway of valproate biotransformation is glucuronidation (~40%), mainly via UGT1A6, UGT1A9, and UGT2B7. About 20 % of the administered dose is found as ester glucuronide in the urine after renal excretion. There are more than 20 metabolites, whereby those of omega-oxidation are regarded as hepatotoxic. Less than 5 % of the valproic acid dose appears unchanged in the urine.

The main metabolite is 3-keto-valproic acid, of which 3–60 % is found in the urine. This metabolite has an anticonvulsive effect in mice. In humans, the effect has not yet been clarified.

In contrast to other anti-epileptics, valproic acid has no liver enzyme-inducing effect and thus does not promote its own metabolism.

Elimination
In one study, plasma clearance was 12.7 ml/min in patients with epilepsy. In healthy subjects, it is 5–10 ml/min. If enzyme-inducing anti-epileptics are taken, it increases.

In healthy subjects, the plasma half-life of valproic acid in healthy subjects is 17.26 ± 1.72 hours.
In combination with other medicinal products (e.g. primidone, phenytoin, phenobarbital and carbamazepine), the half-life falls to between 4 and 9 hours depending on enzyme induction. Newborn infants and children up to 18 months old exhibit a plasma half-life of between 10 and 67 hours. The longest half-lives have been observed immediately after delivery. Over the age of 2 months, the results become more like those of adults.

Linearity/non-linearity
There is an almost linear relationship between the dose of Depalept Chrono and the serum concentration.

Specific patient groups
In patients with liver disease, the half-life is prolonged. In cases of overdose, half-lives of up to 30 hours have been observed.

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

When the volume of distribution increases in the third trimester of pregnancy, hepatic and renal clearance increase, with a potential fall in the serum concentration despite a constant dose.

It should also be noted that plasma protein binding can change and the proportion of free (therapeutically active) valproic acid can increase during the course of a pregnancy.

Placental transfer/Excretion into breast milk (see section 4.6)
Valproate crosses the placental barrier in animal species and in humans.
- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Valproate is excreted in human milk with a concentration ranging from 1 % to 10 % of maternal serum level.

Bioavailability
A bioavailability study in 12 healthy subjects (20–45 years old, male) conducted in 1985 compared a dose of two Depalept Chrono 500 mg prolonged-release tablets in the morning with a dose of one Depalept 500 mg film-coated tablet in the morning and one in the evening, and produced the following results at steady state (day 10):

	Depalept Chrono 500 mg prolonged-release tablets (1 x 1000 mg/day)	Depalept Chrono 500 mg gastro-resistant film-coated tablets (2 x 500 mg/day)
Minimum plasma concentration (C_{min}):	44.7 ± 9.6 µg/ml	54.3 ± 16.0 µg/ml
Peak plasma concentration (C_{max}):	81.6 ± 15.8 µg/ml	95.2 ± 15.8 µg/ml
Time to peak plasma concentration (t_{max}):	6.58 ± 2.23 h	3.08 ± 0.5 h
Area under concentration time curve (AUC):	1486 ± 249 µg·h/ml	1572 ± 286 µg·h/ml

Values are given as mean values and ranges.

5.3 Preclinical safety data

Acute toxicity
Acute toxicity tests with sodium valproate on various animal species have produced LD_{50} values of between 1200 and 1,600 mg/kg of body weight after oral administration and between 750 and 950 mg/kg of body weight after intravenous administration.

Chronic toxicity
Chronic toxicity tests found testicular atrophy (degeneration of the ductus deferens and inadequate spermatogenesis) and lung and prostate changes at doses of 250 mg/kg of body weight and above in rats and doses of 90 mg/kg of body weight and above in dogs.

Mutagenic and carcinogenic potential
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 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 epileptic patients exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in epileptic patients treated with valproate with those in untreated epileptic patients. The clinical relevance of these DNA/chromosome findings is unknown.
Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Toxicity to reproduction
Valproate has induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.
Behavioural abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have been also observed in the 2nd 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.
Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

In repeat-dose toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs (*no observed adverse effect levels*) for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs.
The safety margin comparisons based on extrapolated AUC (*area under the curve*) in rats and dogs indicate that there may be no safety margin.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Based on these data, juvenile animals were not considered more susceptible to testicular findings than adult. Relevance of the testicular findings to the paediatric population is unknown.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance. However, male infertility has been identified as an undesirable effect in humans (see sections 4.6 and 4.8).

HIV replication

Several studies have shown that sodium valproate stimulates the replication of human immunodeficiency viruses *in vitro*. This *in vitro* effect is mild and depends on the experimental models used and/or individual reactions to valproic acid on a cellular level. There are no known clinical consequences of these observations. Nevertheless, these results should be included in the assessment of routine viral load test results in HIV-positive patients taking sodium valproate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, hydrated colloidal silica, polyacrylate 30% dispersion, ethylcellulose, saccharin sodium, macrogol 6000, talc, colloidal anhydrous silica, titanium dioxide.

6.2 Incompatibilities

Depalept Chrono 500 mg should not be taken with carbonated drinks such as mineral water or similar.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

No special storage conditions, however, it is recommended to store in a cool and dry place.

6.5 Nature and contents of container

Aluminium/PVC-aluminium blister packs of 30 prolonged release tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Israel Ltd., Greenwork Park, P.O box 47, Yakum.

8. MARKETING AUTHORISATION NUMBERS

119-33-27953

Revised in March 2024 according to MOHs guidelines.