SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Depalept 200 enteric coated tablets

Depalept 500 enteric coated tablets

Depalept Syrup

Depalept oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Depalept 200 enteric coated tablets:
Sodium valproate 200 mg/tab

Depalept 500 enteric coated tablets:
Sodium valproate 500 mg/tab

Depalept Syrup:
Each 5 ml contains: Sodium Valproate 200 mg/5ml

Depalept oral Solution:
Each ml contains: Sodium Valproate 200 mg/1ml

This medicinal product contains sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Depalept 200 enteric coated tablets

Depalept 500 enteric coated tablets

Depalept Syrup

Depalept oral Solution

Patient safety information Card

The marketing of Depalept is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Depalept is indicated for the treatment of generalized or partial epilepsy secondary generalized epilepsy and mixed forms of epilepsy.

4.2. Posology and method of administration

In female children, female adolescents, women of childbearing potential and pregnant women
Depalept should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see Section 4.4 and Section 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Depalept 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.

In view of the dosage strength this medicinal product is for use in adults and children weighing over than 17 kg only.
Depalept 500 mg and Depalept 200 mg enteric coated tablets are not suitable for children under the age of 6 years (risk of choking).

Posology

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 divided doses.
− In adults and adolscents, the usual dosage is 20 to 30 mg/kg per day in divided dose.
− In elderly patients, the dosage should be determined based on the control of seizures.
The daily dosage should 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).

Patients with renal insufficiency
It may be necessary to decrease the dosage in patients with renal insufficiency, and it may be necessary to increase the dosage in patients on dialysis. Sodium valproate is dialysable (see section 4.9). Dosage should be adjusted according to clinical monitoring of the patient (see section 4.4).

Method of administration.

Oral use.

The daily dose is to be administrered as 2 or 3 divided doses, preferably during meals:
• as 2 divided doses in patients under 1 year of age,
• as 3 divided doses in patients over 1 year of age.
The solution is to be ingested after diluting in a small quantity of non-fizzy drink.
Administer **only** the oral solution with the syringe for oral administration supplied in the box and the syrup with the measuring cup supplied in the box.

Initiation of Depalept therapy (oral administration):

- If the patient is already being treated and is taking other antiepileptics, begin administering sodium valproate 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).
- 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

- Pregnancy unless there is no suitable alternative treatment (see sections 4.4 and 4.6).
- Women of childbearing potential, unless the conditions listed in sections 4.4 and 4.6 are fulfilled (see sections 4.4 and 4.6).
- History of hypersensitivity to valproate, valproate semisodium, valpromide or to any of the excipients listed in section 6.1.
- Acute hepatitis.
- Chronic hepatitis.

- Patient or family history of severe hepatitis, especially drug-related.
- Hepatic porphyria.
- Patients with known urea cycle disorders (see section 4.4).
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase gamma (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under 2 years of age who are suspected of having a POLG-related disorder (see section 4.4).
- Combination with St John's Wort (see section 4.5).

4.4. Special warnings and precautions for use

Special warnings

Patient Card:

This product is marketed with patient safety information card (patient card). Please explain to the patient the implications of this treatment.

Female children/Female adolescents/Woman of childbearing potential/Pregnancy

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neuro-developmental disorders (see section 4.6). Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. If no other treatment is possible, the conditions below must be complied with.

Depalept is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- In women of childbearing potential, unless the conditions listed below are fulfilled (see sections 4.3 and 4.6).

Conditions

The prescriber must ensure that:

- individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimize the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neuro-developmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counseled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.
- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician in case of pregnancy.
- the patient has received the Patient Guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use.

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

Female children

- The prescriber must ensure that parents/caregivers of female children understand 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 neuro-developmental 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 listed should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach puberty or 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 result from a plasma pregnancy test with a sensitivity of at least 25 mIU/mL, confirmed by a healthcare provider, to rule out unintended use in pregnancy. This pregnancy test must be repeated at regular intervals during treatment.

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 1 effective method of contraception (preferably a user-independent form such as an intra-uterine device or implant) or 2 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 result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing estrogen-containing products.

However, 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 hazards and necessary precautions associated with valproate use at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

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

In case of pregnancy

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate-exposed pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counseling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that

- the Patient Card is provided with every valproate dispensing and that the patients understand its content.
- 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, the Marketing Authorization Holder has provided educational materials to reinforce the warnings concerning the teratogenicity (congenital malformations) and fetotoxicity (neuro-developmental disorders) of valproate and provide guidance regarding use of valproate in women of childbearing potential. A Patient Card should be provided to all women of childbearing potential using valproate.

Exacerbation of seizures

As with other antiepileptics, administration of valproate may, instead of improvement, lead to a reversible exacerbation of seizure frequency and severity (including status epilepticus), or the onset of a new type of seizure. Patients should be advised to consult their physician immediately if exacerbation of seizures occurs (see section 4.8). These seizures should be differentiated from those that may occur due to a pharmacokinetic interaction (see section 4.5), toxicity (liver disease or encephalopathy - see sections 4.4 and 4.8) or overdose.

Since this medicinal product is metabolized into valproic acid, it should not be combined with other medicinal products undergoing the same transformation to avoid an overdose of valproic acid (e.g. valproate semisodium, valpromide).

Severe Liver damage

Conditions of occurrence

Severe liver damage resulting sometimes in fatalities has exceptionally been reported.

Patients most at risk are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disease. After the age of 3 years, the risk is significantly reduced and it progressively decreases with age.

In most cases, such liver damage occurred during the first 6 months of therapy, usually between the 2nd and 12th week and generally during antiepileptic polytherapy.

Suggestive signs

Clinical symptoms are essential for early diagnosis. In particular, the 2 conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see “Conditions of occurrence”):

- firstly, non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- secondly, recurrence of epileptic seizures despite proper treatment compliance.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.

Detection

Liver function tests should be performed before therapy and regularly during the first 6 months of therapy, especially in patients at risk.

If concomitant treatments known for their liver toxicity are changed (dose increase or new treatment), liver function tests must be carried out again [1](see also section 4.5 on the risk of liver damage with salicylates, other anticonvulsants including cannabidiol).

Among the usual investigations, tests which reflect protein synthesis particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases – "Precautions for use") requires cessation of therapy with this medicinal product (as a matter of precaution and in case they are taken concomitantly, salicylate derivatives should also be discontinued since they follow the same metabolic pathway).

Pancreatitis

Pancreatitis, which may result in fatalities, has been very rarely reported. Young children are at particular risk but this can be observed irrespective of age and treatment duration.

Pancreatitis with an unfavorable outcome is generally observed in young children or in patients with severe seizures, neurological impairment or anticonvulsant polytherapy.

Hepatic failure with pancreatitis increases the risk of fatal outcome.

In the event of acute abdominal pain or gastrointestinal signs such as nausea, vomiting and/or anorexia, a diagnosis of pancreatitis must be considered and, in patients with elevated pancreatic enzymes, treatment discontinued, and the necessary alternative therapeutic measures implemented.

Suicidal ideation and behaviour

Suicidal ideation and behavior have been reported in patients treated with antiepileptics in several indications. A meta-analysis of data from randomized, placebo-controlled trials of antiepileptic drugs has also shown a slight increase in risk of suicidal ideation and behavior. The causes of this risk are unknown and the available data do not make it possible to rule out an increased risk with valproate.

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

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, acute liver failure and liver-related deaths have been associated with valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the POLG gene, e.g. Alpers-Huttenlocher Syndrome.

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

Interaction with other medicinal products

Concomitant use of this medicinal product with lamotrigine and/or penems (carbapenems) is not recommended (see section 4.5).

Cognitive or extrapyramidal disorders

Cognitive or extrapyramidal disorders can be associated with imaging findings of cerebral atrophy. This type of clinical picture can thus be confused with dementia or Parkinson’s disease. These disorders are reversible on treatment discontinuation (see section 4.8).

Information related to excipients

Depalept 200, Depalept 500, Depalept Syrup and Depalept oral Solution contains 28 mg, 70mg, 29 mg and 28 sodium respectively per tablet, 5ml and 1 ml respectively equivalent to 1.4%, 3.5%, 1.5% and 1.4% respectively of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Depalept Syrup containes sorbitol and sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Precautions for use

Liver function tests should be performed before starting therapy (see section 4.3) and then periodically during the first 6 months, particularly in patients at risk (see section 4.4 "Severe liver damage - Detection").

It should be emphasized that, as with most antiepileptic drugs, a moderate, transient and isolated increase in liver enzymes may be noted without any clinical signs, particularly at the beginning of the therapy.

More extensive biological investigations (including prothrombin rate) are recommended in this case; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

Blood tests (blood cell count, including platelet count, bleeding time and coagulation parameters) are recommended prior to treatment, then after 15 days and at the end of treatment or before surgery, and in case of spontaneous bruising or 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.

This medicinal product is contraindicated in patients with urea cycle enzyme deficiencies. A few cases of hyperammonemia with stupor or coma have been described in these patients (see section 4.3).

Although immune disorders have been noted only exceptionally during the use of this medicinal product, its potential benefit should be weighed against its potential risk in patients with systemic lupus erythematosus.

Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimize the risk.

Since valproate is excreted mainly in the urine partly in the forms of ketone bodies, ketone body excretion test may give false positive results in diabetic patients.

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

Alcohol intake is not recommended during treatment with Depalept.

Children

Monotherapy is recommended in children under the age of 3 years when prescribing valproate, but the potential benefit should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see section 4.4 "Severe liver damage" and also section 4.5).

The simultaneous prescription of salicylates should be avoided in children under 3 years due to the risk of hepatotoxicity (see also section 4.4) and the risk of bleeding.

In children with a history of unexplained hepatic and gastrointestinal disorders (anorexia, vomiting, acute episodes of cytolysis), episodes of lethargy or coma, mental retardation or with a family history of neonatal or infant death, metabolic tests and, in particular, fasting and post-prandial blood ammonia tests must be performed prior to any valproate treatment.

Use in male patients

see section 4.6 (Fertility, pregnancy and lactation)

4.5. Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

+ St. John's Wort

There is a risk of decreased plasma concentrations and reduced efficacy of the antiepileptic.

Inadvisable combinations

+ Lamotrigine

There is a higher risk of serious skin reactions (toxic epidermal necrolysis).

Furthermore, an increase in lamotrigine plasma concentrations may occur (decreased hepatic metabolism by sodium valproate).

If coadministration proves necessary, close clinical monitoring is required.

+ Penems (carbapenems)

There is a risk of seizures due to a rapid decrease in valproic acid plasma concentrations, which may become undetectable.

Co-administration of valproic acid and carbapenems has led to decreases in plasma concentrations of valproic acid of approximately 60 to 100% in around two days. Due to the rapid onset and the extent of

the decreased plasma concentrations, simultaneous administration of carbapenems in patients stabilised on valproic acid who cannot be monitored should therefore be avoided (see section 4.4).

Combinations requiring precautions for use

+ Acetazolamide

Increased hyperammonemia with increased risk of encephalopathy may occur.

Regular monitoring of clinical and laboratory parameters is required.

+ Aztreonam

There is a risk of seizures due to a decrease in valproic acid plasma concentrations.

Clinical monitoring, plasma assays and possible dose adjustment of the anticonvulsant are required during treatment with the anti-infective agent and after its discontinuation.

+ Carbamazepine

Increased plasma concentrations of the active metabolite of carbamazepine with signs of overdose may occur. In addition, reduced valproic acid plasma concentrations may occur due to its increased hepatic metabolism by carbamazepine.

Clinical monitoring, plasma assays and dose adjustment of both anticonvulsants are required.

+ Felbamate

Increased serum valproic acid concentrations with a risk of overdose may occur.

Clinical monitoring and monitoring of laboratory parameters and possible valproate dose adjustment are required during treatment with felbamate and after its discontinuation.

+ 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 valproate clearance, which in turn is thought to cause a decrease in serum valproate concentrations and to potentially reduce valproate efficacy (see section 4.4). Consider monitoring valproate serum levels.

Conversely, valproate has no enzyme-inducing effect; as a consequence, valproate does not reduce the efficacy of estro-progestative agents in women receiving hormonal contraception.

+ Metamizole

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.

+ Nimodipine (oral route and, by extrapolation, by injection)

There is a risk of a 50% increase in plasma nimodipine concentrations. Therefore, nimodipine dose reduction is necessary in hypotensive patients.

+ Phenobarbital, and by extrapolation primidone

Increased hyperammonemia with increased risk of encephalopathy may occur.

Regular monitoring of clinical and laboratory parameters is required.

+ Phenytoin, and by extrapolation fosphenytoin

Increased hyperammonemia with increased risk of encephalopathy may occur.

Regular monitoring of clinical and laboratory parameters is required.

+ Propofol

A possible increase in propofol blood levels may occur. When coadministered with valproate, a reduction in propofol dose should be considered.

+ Rifampicin

There is a risk of seizures due to increased hepatic metabolism of valproate by rifampicin.

Clinical monitoring and monitoring of laboratory parameters and possible anticonvulsant dose adjustment are required during treatment with rifampicin and after its discontinuation.

+ Rufinamide

A possible increase in rufinamide concentrations may occur, in particular in children weighing less than 30 kg.
In children weighing less than 30 kg: the total dose of 600 mg/day after dose titration should not be exceeded.

+ Topiramate

Increased hyperammonemia with increased risk of encephalopathy may occur.

Regular monitoring of clinical and laboratory parameters is required.

+ Zidovudine

There is a risk of increased adverse effects of zidovudine, particularly hematological effects, due to decrease in its metabolism by valproic acid.

Regular monitoring of clinical and laboratory parameters is required. A blood count should be performed to test for anemia during the first 2 months of the combination.

+ Zonisamide

Increased hyperammonemia with increased risk of encephalopathy may occur.

Regular monitoring of clinical and laboratory parameters is required.

Other forms of interaction

+ Lithium

Depalept has no effect on serum lithium levels.

+ Risk of liver damage

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity (see section 4.4).

Concomitant use of valproate and other anticonvulsants increases the risk of liver damage, especially in young children (see section 4.4).

Concomitant use with cannabidiol increases the incidence of raised transaminases. In patients of all ages receiving concomitantly cannabidiol at doses of 10 to 25 mg/kg and valproate, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19% of patients. Appropriate liver monitoring should be exercised when valproate is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol. Dose reductions or therapy cessation should be considered in case of significant anomalies of liver parameters (see section 4.4).

4.6. Fertility, pregnancy and lactation

Valproate is contraindicated (see sections 4.3 and 4.4):

- during pregnancy unless there is no suitable alternative treatment.
- in women of childbearing potential, unless the conditions listed in section 4.4 are fulfilled.

Pregnancy

Teratogenicity and neuro-developmental effects

Both valproate monotherapy and valproate polytherapy including other antiepileptics are frequently associated with abnormal pregnancy outcomes. 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). In animals, 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 2-3%).

The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic 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 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 types of malformations include neural tube defects (approximately 2-3%), facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects (in particular, hypospadias), 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/loss 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 had not resolved.

In utero exposure to valproate may result in congenital eye disorders (including coloboma and microphthalmia), which were reported in association with other congenital anomalies. These congenital eye disorders may affect visual ability.

- **Neuro-developmental disorders**

Studies have shown that exposure to valproate *in utero* increases the risk of neuro-developmental disorders in exposed children. The risk of neurodevelopmental disorders (including that of 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 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 pre-school 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 (aged 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate *in utero* that the decrease in IQ 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 autism spectrum disorders (approximately 3-fold) and childhood autism (approximately 5-fold) compared with the unexposed study population.

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

Women of childbearing potential

Depalept should not be used in women of childbearing potential unless other treatments are ineffective or not tolerated. If no other treatment is possible, Depalept can only be initiated if the conditions listed in section 4.4 is complied with (see section 4.4), in particular:

- the patient is not pregnant (plasma pregnancy test with a sensitivity of at least 25 mIU/mL negative at the start of treatment and at regular intervals during treatment).
- the patient is using at least 1 effective method of contraception.
- and the patient is informed of the risks associated with using valproate during pregnancy.

In women of childbearing potential, the benefit-risk balance must be carefully reevaluated at regular intervals during treatment (at least annually).

Estrogen-containing products

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

If a woman plans a pregnancy

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counseling regarding the valproate risks for the unborn child to support her informed decision-making regarding family planning.

Folate supplementation before pregnancy and at the beginning of pregnancy may decrease the risk of neural tube defects common to all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure**.**

Pregnant women

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:

- the lowest effective dose must be used
- the daily dose of valproate should be divided 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 specialist experienced in teratology for evaluation and counseling regarding the exposed pregnancy.

- Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations.

Before delivery

Coagulation tests should be performed in the mother before delivery, including in particular a platelet count, fibrinogen levels and coagulation time (activated partial thromboplastin time: aPTT).

Risk in the neonate

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Normal hemostasis test results in the mother do not make it possible to rule out hemostasis abnormalities in the neonate. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates at birth.
- Cases of hypoglycemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Post-natal monitoring/monitoring of children

Close monitoring of the neuro-developmental behavior must be implemented in children exposed to valproate during pregnancy and suitable treatment initiated as early as possible if necessary.

Breast-feeding

Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in 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 therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women treated with valproate (see section 4.8). In men, the administration of valproate may also impair fertility (reduced sperm motility in particular) (see section 4.8). In some cases, these fertility disorders are reversible after discontinuing treatment for at least 3 months. In a limited number of cases, it was reported that a significant reduction in dosage can improve fertility. However, in other cases, the reversibility of this male infertility is not known.

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A large nationwide retrospective cohort study by Christensen et al., including more than 1.2 million children of whom 1,336 were exposed to paternal valproate during spermatogenesis, with a median follow-up of about 10 years, found no increased risk of major congenital malformations (ARR 0.89, 95% CI 0.67-1.18) or neurodevelopmental disorders including ASD (AHR 1.10, 95% CI 0.88-1.37; ASD AHR 0.92, 95% CI 0.65-1.30) in exposed offspring.

Additionally, a retrospective observational study in 3 Nordic countries suggests an increased risk of 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 a new spermatogenesis without valproate exposure).

Due to the limited data, methodological limitations, and conflicting findings, no recommendations can be made until further data become available.

4.7. Effects on ability to drive and use machines

The attention of patients, particularly those who drive or use machines, must be drawn to the risk of drowsiness, especially in patients receiving anticonvulsant polytherapy or concomitant administration with other medicinal products that may increase drowsiness.

4.8. Undesirable effects

Classification of expected frequencies:

Very common (≥ 10%); common (≥ 1% to < 10%); uncommon (≥ 0.1% to < 1%); rare (≥ 0.01% to < 0.1%); very rare (< 0.01%); not known (cannot be estimated from the available data).

Congenital, familial and genetic disorders

- Congenital malformations and neuro-developmental disorders (see sections 4.4 and 4.6).

Blood and lymphatic system disorders

- Common: anemia, thrombocytopenia.
  Cases of dose-dependent thrombocytopenia have been reported, generally discovered systematically and without any clinical repercussions.
  In patients with asymptomatic thrombocytopenia, if possible, given the platelet level and control of the disease, simply reducing the dose of this medicinal product usually leads to resolution of thrombocytopenia.
- Uncommon: leukopenia, pancytopenia.
- Rare: bone marrow aplasia or pure red cell aplasia, agranulocytosis, macrocytic anemia, macrocytosis.

Investigations

- Common: weight gain*.
- Rare: decrease in at least 1 coagulation factor, abnormal coagulation tests (such as prolonged prothrombin time, prolonged activated partial thromboplastin time, prolonged thrombin time, prolonged INR) (see sections 4.4 and 4.6), vitamin B8 (biotin) deficiency/biotinidase deficiency.

*as weight gain is a risk factor for polycystic ovary syndrome, patient weight must be carefully monitored (see section 4.4).

Nervous system disorders

- Very common: tremor
- Common: extrapyramidal disorders**, stupor*, sedation, seizures*, memory impairment, headache, nystagmus, nausea or dizziness.
- Uncommon: coma*, encephalopathy*, lethargy*, reversible parkinsonism**, ataxia, paresthesia,
- Rare: diplopia, cognitive disturbances of insidious and progressive onset (which may progress as far as complete dementia) and which are reversible a few weeks to a few months following treatment withdrawal**

*Cases of stupor and lethargy, sometimes leading to transient coma (encephalopathy), have been observed with valproate; they 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 valproate doses.

**These symptoms can be associated with imaging findings of cerebral atrophy.

Ear and labyrinth disorders

- Common: hearing loss.

Respiratory, thoracic and mediastinal disorders

- Uncommon: pleural effusion.

Gastrointestinal disorders

- Very common: nausea.
- Common: vomiting, gingival disorders (mainly gingival hyperplasia), stomatitis, upper abdominal pain, diarrhea that may occur in some patients at the start of treatment, but usually disappearing after a few days without discontinuing the treatment.
- Uncommon: pancreatitis with possibly fatal outcome requiring early treatment discontinuation (see section 4.4).

Renal and urinary disorders

- Common: urinary incontinence.
- Uncommon: renal failure.
- Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome.

Skin and subcutaneous tissue disorders

- Common: transient and/or dose-related alopecia, nail and nail bed disorders.
- Uncommon: angioedema, skin reactions, hair disorders (such as abnormal hair texture, hair color changes, abnormal hair growth).

- Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) or drug hypersensitivity syndrome.

Endocrine disorders

- Uncommon: inappropriate antidiuretic hormone secretion syndrome (IADHS), hyperandrogenism (hirsutism, virilism, acne, androgenetic alopecia and/or increase in androgen hormone levels).
- Rare: hypothyroidism (see section 4.6).

Metabolism and nutrition disorders

- Common: hyponatremia.
- Rare: hyperammonemia* (see section 4.4), obesity.

*Cases of isolated and moderate hyperammonemia without change in liver function tests may occur, especially during polytherapy, and should not cause treatment discontinuation.

However, cases of hyperammonemia associated with neurological symptoms (which may progress to coma) have also been reported, and require further investigations (see section 4.4).

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

- Rare: myelodysplastic syndrome.

Vascular disorders

- Common: hemorrhage (see sections 4.4 and 4.8).
- Uncommon: cutaneous vasculitis, mainly leukocytoclastic vasculitis.

General disorders and administration site conditions

- Uncommon: hypothermia, non-severe peripheral edema.

Hepatobiliary disorders

- Common: liver disorders (see section 4.4).

Reproductive system and breast disorders

- Common: irregular menstruation.
- Uncommon: amenorrhea.
- Rare: male infertility (see section 4.6), polycystic ovaries.

Musculoskeletal and connective tissue disorders

- Uncommon: decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with Depalept. The mechanism of action of Depalept on bone metabolism is not known.
- Rare: acute systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4).

Psychiatric disorders

- Common: confusional state, hallucinations, aggressiveness*, agitation*, attention disorders*.
- Rare: abnormal behavior*, psychomotor hyperactivity*, learning disabilities*.

*These effects are mainly observed in the paediatric population.

Paediatric population

The safety profile of valproate in the paediatric population is comparable to adults, but some adverse 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 events reactions after authorization 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

Signs of acute massive overdose usually include a calm coma, which may be more or less deep, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis, hypotension and circulatory collapse/shock.

A few cases of intracranial hypertension related to cerebral edema have been described.

Patient management in a hospital setting includes: gastric lavage if indicated, maintenance of effective diuresis, cardiorespiratory monitoring. In very serious cases, renal replacement therapy may be performed if necessary.

The prognosis for such poisoning is generally favorable. However, a few deaths have been reported.

The sodium content in valproate-containing medicinal products can lead to hypernatremia in the event of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIEPILEPTICS, ATC code: N03AG01.

Valproate is pharmacologically active primarily on the central nervous system.

The drug has an anticonvulsant effect on a very wide range of seizures in animals and epilepsy in humans.

Experimental and clinical studies on valproate suggest 2 types of anticonvulsant effect.

The first is a direct pharmacological effect related to valproate concentrations in the plasma and the brain.

The second appears to be indirect and is probably related to the metabolites of valproate, which remain in the brain, or to changes in neurotransmitters or direct membrane effects. The most widely accepted hypothesis is that of gamma-aminobutyric acid (GABA) levels, which increase following valproate administration.

Valproate reduces the duration of intermediate stages of sleep, with a concomitant increase in slow sleep.

5.2. Pharmacokinetic properties

The various pharmacokinetic studies conducted on valproate have shown that:

- The bioavailability in the blood following oral administration is close to 100%.
- The volume of distribution is mainly limited to the blood and to the rapid-exchange extracellular fluids. Valproate circulates in the CSF and in the brain.
- Placental transfer (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.
- The half-life is 15 to 17 hours.
- Therapeutic efficacy usually requires a minimum serum concentration of 40 to 50 mg/L, with a wide range from 40 to 100 mg/L. If higher plasma levels prove necessary, the expected benefits must be weighed against the risk of occurrence of adverse effects, particularly dose-dependent effects. However, levels remaining above 150 mg/L require a dose reduction.
- The steady-state plasma concentration is reached in 3 to 4 days.
- Valproate is highly protein-bound. Protein binding is dose-dependent and saturable.
- The major metabolic pathway of valproate is glucuronidation (approximately 40%), mainly via UGT1A6, UGT1A9 and UGT2B7.
- Valproate is excreted mainly in the urine, following metabolization by glucuronide conjugation and beta-oxidation.
- Valproate can be dialyzed, but hemodialysis only affects the free fraction of blood valproate (approximately 10%).

- Valproate does not induce enzymes involved in the metabolic system of cytochrome P 450, in contrast with most other antiepileptics. It therefore does not accelerate its own degradation or that of other substances, such as estrogen-progestogens and oral anticoagulants.

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

5.3. Preclinical safety data

Animal studies have demonstrated that valproate exposure *in utero* results in physical and functional abnormalities in the auditory systems of rats and mice.

In vitro, valproate was not mutagenic in bacteria, or in mouse lymphoma assays, and did not induce DNA repair activity in primary culture of rat hepatocytes. However, in vivo, 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 either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal aberrations in rodents. Furthermore, an increase in sister-chromatid exchange in epileptic patients exposed to valproate was reported in published studies compared with untreated healthy subjects. However, contradictory results were obtained when comparing the data for epileptic patients treated with valproate with the data for untreated epileptic patients. The clinical significance of these conclusions on DNA/chromosomes is unknown.

Non-clinical data from conventional carcinogenicity studies reveal no particular risk for humans.

Reproductive toxicity

Valproate 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. In mice, certain behavioural changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation at teratogenic doses of valproate. The underlying mechanisms and the clinical relevance of these findings are unknown.

In repeated dose toxicity studies, testicular degeneration/atrophy, abnormal spermatogenesis and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 1 250 mg/kg/day and 150 mg/kg/day, respectively.

In juvenile rats, the 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 to be more susceptible than adults to testicular disorders. Relevance of the testicular findings to paediatric population is unknown.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Depalept 200 enteric coated tablets:
Purified talc, povidone (K25), maize starch, cellulose acetate phtalate, calcium silicate, polyethylene glycol 400, diethyl phthalate, povidone (K90), titanium dioxide micronized ,magnesium stearate.

Depalept 500 enteric coated tablets:
Purified talc, povidone (K25), cellulose acetate phthalate, maize starch, calcium silicate, povidone (K90), polyethylene glycol 400, diethyl phthalate, titanium dioxide micronized, magnesium stearate, Iron yellow oxide E172.

Depalept Syrup:
Sucrose, sorbitol solution 70%, sodium methyl hydroxybenzoate, saccharin sodium, ponceau 4R, cherry flavour, sodium propyl hydroxybenzoate, purified water.

Depalept oral Solution:
Urea, diluted hydrochloric acid or sodium hydroxide, purified water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life and Special precautions for storage

The expiry date of the product is indicated on the packaging materials.
Depalept tablets must be kept in a cool, dry, dark place, at room temperature (below 25^0C). Can be used up to 2 months from opening.
Depalept syrup should be stored at 25ºC . Can be used up to 2 months from opening.
Depalept oral solution should be stored at 25ºC. Can be used up to 60 days from opening.

6.4. Nature and contents of container

Depalept Enteric-Coated tablets 200 mg: 40 tablets
Depalept Enteric-Coated tablets 500 mg: 40 tablets
Depalept Solution: Bottles of 50 ml
Depalept Syrup: Bottles of 110 ml

7. Manufacturer

CTS Chemical Industries Ltd., Kiryat Malachi

Revised in 01/2026 according to the MoH guidelines.