PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only
Depalept 500 mg enteric-coated tablets
Enteric-coated tablets, each tablet contains:
Sodium valproate 500 mg
Inactive and allergenic ingredients in the medicine – see section 6.

Warning
Children born to mothers that took Valproate during pregnancy have an increased risk for severe developmental disorders (about 30-40% of cases) and congenital malformations (about 11% of cases).
If you are a woman of childbearing age or if you are pregnant, the physician will prescribe Valproate for you only if other treatments are unsuitable.
Women of childbearing age should use effective contraceptives while taking this medicine. Do not discontinue taking this medicine without consulting your attending physician first. If despite using contraceptives you become pregnant unintentionally, contact your doctor immediately in order to discuss the options for alternative therapy, if possible.

In addition to the leaflet, there is a patient safety information card for Depalept. This patient safety information card contains important safety information that you must know before starting treatment with Depalept as well as during the treatment. Please review the patient safety information card and the patient leaflet before using the medicine. Please keep the patient safety information card for further review, if needed.
Read the entire leaflet carefully before using the medicine.
Keep this leaflet; you may need to read it again.
This leaflet contains concise information about the medicine. If you have any other questions, refer to the physician or the pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seemes to you that their medical condition is similar. This medicine is not intended for children who weigh less than 17 kg.

1. What is the medicine intended for?

This medicine is an anticonvulsant, and it is administered for treatment of certain kinds of epilepsy.
Therapeutic class: The active ingredient belongs to the anticonvulsants group.

2. Before using the medicine:

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient or one of the medicine's excipients (see section 6 – Additional information).
- You are sensitive to another medicine of the valproate family (Divalproate, Valpromide).
- You are suffering from a liver disease (such as acute or chronic hepatitis, or if you suffer from hepatic porphyria).
- You or a family member have suffered or currently suffer from acute liver disease, especially if caused by medicines.
- You are taking Mefloquine
- You are taking St. John's Wort (for treatment of depression).
- You are suffering from mitochondrial disorders due to a mutation in POLG gene, for example due to Alpers-Huttenlocher syndrome and in children under two years of age who are suspected for disorders associated with a mutation in POLG gene.
- You are suffering from urea cycle disorders.

Special warnings regarding the use of the medicine:

- **The medicine should not be given to girls, adolescent girls, women of childbearing age and pregnant women unless alternative treatments have been found to be unsuitable.**
- **Women of childbearing age who are treated with this medicine should use effective contraceptives. If a woman that takes this medicine plans to become pregnant, she should consult her doctor regarding the possibility to receive an alternative treatment.**

This medicine may cause abnormal blood count and bleedings, and in very rare cases, liver diseases (hepatitis) or pancreatic diseases (pancreatitis), which may be severe and life-threatening.
Your physician will refer you to perform blood tests for evaluation of liver function, especially during the first 6 months of treatment.
You should contact a physician immediately if the following effects appear:
Sudden tiredness, lack of appetite, fatigue, drowsiness, swelling in feet, weakness.
Recurrent vomiting, nausea, abdominal pain, jaundice (yellow eyes or skin).
Recurrence of epileptic seizures, even though you are taking the medicine properly.

- **Before treatment with Depalept, inform your doctor if:**
  - You suffer from hepatic impairment.
  - You suffer from hematologic impairment (such as coagulation etc.).
  - You suffer from kidney disease (renal insufficiency).
  - You suffer from Systemic Lupus Erythematosus.
  - You suffer from a metabolic disorder, especially a genetic disorder associated with enzyme deficiency, such as Urea cycle disorder, which may cause elevation of Ammonia blood levels.
  - Your family has a history of epilepsy, developmental impairment, neurological problems, severe migraines.
  - You suffer from Carnitine palmitoyltransferase (CPT) type II enzyme deficiency. In this case there is an increased risk for muscle breakdown when taking Depalept.
  - Your child is receiving another treatment for epilepsy or suffers from a neurologic or metabolic disease or from severe forms of epilepsy.
- Before performing any kind of surgery (dental procedure or another urgent treatment), you should inform the doctor that you are taking Depalept.
- Consult the doctor immediately if there is an increase in seizures frequency, or if you experience a different kind of seizures.
- This medicine may cause weight gain. Consult your doctor regarding methods for maintaining your body weight.
- Taking anticonvulsants may increase the risk for suicidal actions or thoughts. You and your family members must pay attention to changes in mood, behavior patterns and actions. Watch for signs indicating risk of suicide, such as: talking or thinking about wanting to hurt yourself, introversion and withdrawal from family and friends, depression or worsening of existing depression, preoccupation with the subject of death, abandoning or giving away prized possessions. If thoughts of this kind occur, refer to the doctor immediately.
- Children under the age of 3, especially those taking several medicines for treatment of epilepsy, are at a higher risk for: brain injury, mental retardation, genetic metabolic degenerative disease.
- Long-term use of Depalept is associated with a decrease in bone density, which may lead to osteoporosis, osteopenia and an increased risk for fractures.
- This medicine may cause an abnormal blood count and bleeding; the doctor will refer you (before starting this treatment and throughout it) to perform blood tests which will include blood count and coagulation function test.
- A severe allergic reaction that includes symptoms such as fever, lymph nodes enlargement and involvement of other body systems, with or without skin rash (called DRESS).

If you are taking or have recently taken other medicines including non-prescription medicines and food supplements, tell the physician or the pharmacist.
Do not take Depalept if you are taking the following medicines:
- Mefloquine – a medicine for treatment of Malaria.
- St. John's Wort - an herb for treatment of depression.

You should inform your doctor if you are taking Lamotrigine (another medicine for treatment of epilepsy) or medicines of the penem family (a group of antibiotics for treatment of bacterial infections, such as Meropenem, Imipenem, Panipenem).
Avoid use of Aspirin-containing medicines while using this medicine, especially in children under the age of 3.
Inform the doctor or pharmacist if you are taking any of the following medicines:
- Medicines affecting the central nervous system.
  - Sedative and hypnotic medicines, such as benzodiazepines.
  - Medicines for treatment of Parkinson's disease.
  - Anti-depressant medicines such as Imipramine, Monoamine oxidase inhibitors.
  - Cough and cold medicines.
  - Medicines for treatment of epilepsy such as Phenobarbital, Phenytoin, Fosphenytoin, Carbamazepine, Primidone, Felbamate, Topiramate, Rufinamide.
- Antibiotics such as: Aztreonam, Rifampicin, Erythromycin.
- Vitamin K dependent anticoagulants such as Warfarin.
- Zidovudine, Lopinavir, Ritonavir – for treatment of patients with HIV infection.
- Cimetidine – against gastric acidity.
- Nimodipine – used against venous constriction during cerebral bleeding.
- Quetiapine, Olanzapine – for treatment of psychiatric diseases.
- Colestyramine – a cholesterol-lowering medicine.
- Acetazolamide.

Using the drug, food and alcohol consumption
If you are sensitive to any type of food or medicine, inform your doctor before starting treatment with this medicine.
Drinking alcoholic beverages is not recommended during treatment with this drug.
The medicine should be taken with or after a meal.
Pregnancy and breastfeeding
If you are a woman of childbearing age, the doctor will prescribe this medicine for you only if alternative treatments were found unsuitable.

- Valproate may harm the fetus if taken during pregnancy. The risk increases with the dosage, **but it exists with all dosages.**
- **Children exposed to Valproate in the womb are at high risk for severe congenital malformations and developmental disorders.** Congenital malformations reported include spina bifida (a developmental malformation in which the spine does not develop properly), facial, upper lip, palate and skull malformations; cardiac, renal, urinary and genital malformations; limbs deformities.
- It has been found that in women taking Valproate, around **11 babies out of 100 are born with congenital malformations, compared with 2-3 babies out of 100 in the general population. About 30-40% of kindergarten-age children of mothers who took Valproate in pregnancy may suffer from developmental issues, such as: walking retardation, memory impairment, lower cognitive abilities, language and speaking difficulties.**
- Autistic Spectrum Disorders are diagnosed more frequently (3-5 times more) in children exposed to Valproate.
- Some data exist which show that children who were exposed to Valproate in the womb have a greater tendency to develop symptoms of Attention Deficit and Hyperactivity Disorder (ADHD).

Before giving you the medicine, the doctor will explain to you the possible risks to your baby in case of Valproate exposure during pregnancy. If later you decide that you wish to become pregnant, do not stop taking the drug before consulting with the doctor and considering the option of changing your therapy, if possible.
- Consult your doctor regarding taking folic acid while trying to become pregnant. Taking folic acid before pregnancy can reduce the risk for malformations in the spine closure and early miscarriages, which exists in all pregnancies. Folic acid's ability to prevent congenital malformations, which may occur as a result of taking Valproate, has not been proven.

If this is the first time Valproate has been prescribed for you, the doctor will explain to you the possible risks for your baby in case of Valproate exposure during pregnancy. **If you are a woman of childbearing age, you should use effective contraceptives while using the medicine.** Consult your gynecologist regarding effective contraceptives.
Important issues:
- Make sure that you are using effective contraceptives.
- Immediately consult the doctor if you are pregnant or think you might be pregnant.

Continuing Valproate treatment when you are not planning pregnancy
Make sure you are using effective contraceptives throughout the treatment period. Consult your gynecologist regarding effective contraceptives.
Important issues:
- Make sure that you are using effective contraceptives.
- Consult the doctor if you are pregnant or think you might be pregnant.

In case you are planning to become pregnant: Do not stop using the medicine before consulting with the attending physician.
Consult your doctor before becoming pregnant, if possible, in order to reduce the risk to your baby. Your doctor may decide to reduce the dosage of Valproate or to put you on a different treatment before you will try to become pregnant.
If you become pregnant, you should be under close medical supervision due to your medical condition and in order to monitor the fetus' development. Consult your doctor regarding taking folic acid while trying to become pregnant. Taking folic acid before pregnancy can reduce the risk for malformations in the spine closure and early miscarriages, which exists in all pregnancies. Prevention of congenital malformations with folic acid in women who take Valproate has not been proven to this day.
Important issues:
- Do not stop using contraceptives before consulting the doctor and finalizing a plan for your future treatment which will allow keeping the epilepsy under control and reducing the risk to the fetus.
- Consult the doctor if you are pregnant or think you might be pregnant.

An unplanned pregnancy during Valproate treatment
Children exposed to Valproate in the womb are at high risk for severe congenital malformations and developmental disorders. If you are taking Valproate and you think that you might be pregnant, contact your doctor immediately.
Consult your doctor regarding taking folic acid while trying to become pregnant. Taking folic acid before pregnancy can reduce the risk for malformations in the spine closure and early miscarriages, which exists in all pregnancies. Prevention of congenital malformations with folic acid in women who take Valproate has not been proven to this day.
Important issues:
- Consult your doctor immediately if you are pregnant or think you might be pregnant.
- Do not stop taking Valproate until the doctor will order you to.

Make sure you've read and understood the patient information provided by the doctor. In case you have questions, consult the doctor or pharmacist.
Breastfeeding
Do not breastfeed while taking Depalept, unless the doctor recommends otherwise. Consult the doctor or pharmacist before starting treatment with any medicine.

Driving and operating machinery
Using this medicine may impair alertness, especially if taken alongside other medicines for epilepsy or medicines that cause drowsiness.
If you experience this effect or if your epilepsy is not yet under control and you continue to suffer from seizures, do not drive or operate dangerous machinery.
Children should be cautioned against riding a bicycle or playing near a road etc.
Important information about some ingredients of the medicine:
Sodium content in each tablet: about 70 mg

3. How should you use the medicine?

Always use according to the doctor's instructions.
Consult with the doctor or pharmacist if you are unsure.
The dosage and treatment regimen will be determined by the doctor only.
The doctor may recommend to divide the required dose to twice a day. It is best to take the drug during meals.
Do not exceed the recommended dose
This medicine is not intended for children who weigh less than 17 kg.
Tests and follow-up:
Before starting the treatment and during the first 6 months of treatment with this medicine, you should perform blood tests and liver function tests.
If you accidentally took a higher dose or if a child accidentally swallowed the medicine, immediately contact a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.
You might suffer from the following effects: coma, muscle weakness, loss of some reflexes, miosis, impaired breathing, metabolic acidosis, lowering of blood pressure and shock.
If you forgot to take this medicine at the required time, do not take a double dose. Take the next dose at the scheduled time and consult a doctor.
Follow the treatment as recommended by the doctor. This medicine should be used at set intervals as determined by the attending physician.
If you stop taking Depalept
Do not stop treatment with Depalept without consulting a doctor, even if your health has improved. Discontinuation of treatment should be done gradually.
In case you discontinue Depalept treatment abruptly or not according to your physician's instruction, you might be in an increased risk for seizures.
Do not take medicines in the dark! Check the label and the dosage every time you take the medicine. Wear glasses if you need them.
If you have any other questions regarding the use of the medicine, consult the physician or the pharmacist.

4. Side effects

As with any medicine, use of Depalept may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.
Contact the doctor immediately if you experience the following side effects –
- This medicine can cause liver diseases (hepatitis) or pancreatic diseases (pancreatitis), which may be severe and life-threatening. These effects are uncommon and may appear suddenly accompanied by weakness, tiredness, loss of appetite, fatigue, drowsiness, which may sometimes be associated with vomiting and abdominal pain.
- In rare cases, appearance of a rash on the skin, which may sometimes be accompanied by papules which may involve the mouth area (erythema multiforme), the appearance of papules with skin detachment that can quickly spread all over the body and be life-threatening (toxic epidermal necrolysis, Steven-Johnson syndrome).
- An allergic reaction which includes:
  - Sudden swelling of the face and/or neck which causes breathing difficulty and is life-threatening (angioedema).
  - A severe allergic reaction which includes symptoms such as fever, skin rash, lymph nodes enlargement, renal impairment, abnormal blood tests results, such as an increase in a type of white blood cells (eosinophils).
- Strange behavior – especially if this medicine is taken together with Phenobarbital or if the dosage of this medicine was increased suddenly.
- Spontaneous appearance of bruises or bleedings, blood coagulation problems.

Additional possible side effects:
Congenital malformations and mental and physical development disorder (see section "pregnancy and breastfeeding").
Additional side effects:
Very common side effects – side effects that occur in more than one out of ten patients:
- Tremor, nausea.

Common side effects – side effects that occur in 1-10 out of 100 patients:
- Decrease in red blood cells count (anemia) and platelets (thrombocytopenia).
- Weight gain.
- Motor nervous system disturbances (symptoms include: tremor, limbs rigidity and difficulty walking), sometimes irreversible. In some cases Parkinson-like effects may be reversible.
- Drowsiness, dizziness, memory impairment, headaches.
- Quick and involuntary eye movements.
- Seizures.
- Deafness.
- In the beginning of the treatment: diarrhea, vomiting, abdominal pain
- Gum problems, especially their enlargement (gingival hyperplasia).
- Pain and swelling in the mouth, wounds and burning sensation (stomatitis).
- Hypersensitivity, hair loss.
- Low levels of blood sodium (hyponatremia, a symptom of improper secretion of antidiuretic hormone).
- Severe pains during menstruation period.
- Confusion, hallucinations (seeing or hearing non-existing things), aggresiveness, irritability, attention problems.
- Hepatic impairment.
- Bleeding.

Uncommon side effects – side effects that occur in 1-10 out of 1000 patients:
- Decrease in blood cells count (general and white blood cells).
- Alertness impairment which may develop into a temporary coma, with remission after dose reduction or treatment cessation.
- Encephalopathy.
- A tingling/numbness sensation in the limbs.
- Difficulty in movement synchronization.
- Breathing difficulties and pains due to an inflammation of protective tissues in the lungs (pleural effusion).
- Skin rash.
- Hair problems (changes in the hair structure, color or growth).
- Cases of metabolic impairment in the bones, such as bones that become more fragile (Osteopenia), bone mass reduction (osteoporosis) and fractures. Consult the doctor or pharmacist if you are taking a long-term treatment of anti-epileptic drugs, if you suffer or have suffered in the past from osteoporosis or if you are taking corticosteroids.
- Hyperandrogenism (signs including excessive hairiness, development of masculine features in a woman, acné, male hair loss and rise in androgen).
- Decrease in body temperature (hypothermia).
- Non-severe edemas in the limbs.
- No menstrual period.
- Blood vessels inflammation.

Rare side effects – side effects that occur in up to 1 of 1,000 patients:
- Bone marrow function failure, including a decrease in red and white blood cells counts, macrocytic anemia.
- Decrease in coagulation factors which cause abnormal coagulation tests (such as: increase in prothrombin time and INR time).
- Deficiency in vitamin B8 – Biotin/Biotinidase.
- Dementia and cognitive impairment which appear gradually and remiss several weeks to several months after stopping the treatment.
- Kidney problems, difficulty or inability to control urination (wetting and bed-wetting).
- Kidney damage (tubulointerstitial nephritis).
- An autoimmune reaction with joint pains, skin rash and fever (systemic lupus erythematosus).
- Muscle pains, muscle weakness which may be severe (rhabdomyolysis).
- Hypothyroidism.
- A bone marrow damage classified as a myelodysplastic syndrome.
- Polycystic ovaries, male fertility impairment.
- Increased psychomotor activity, learning disabilities, abnormal behavior.

If a side effect occurs, or if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor. Side effects may be reported to the Ministry of Health by clicking on the link "report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdverseEffectMedic@moh.gov.il

5. How to store the medicine?

Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the physician.
Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
Store in a dry place, at a temperature below 25ºC.
Can be used for up to two months from opening.

6. Additional information

In addition to the active ingredient the medicine also contains:
(Note: the supervising pharmacist is responsible to match an inactive ingredient list to the updated quality certificates).
Purified talc, povidone (K25), maize starch, cellulose acetate phthalate, Calcium silicate, polyethylene glycol 400, diethyl phthalate povidone (K90), titanium dioxide micronized, magnesium stearate. Iron yellow oxide E172
What does the medicine look like and what are the contents of the package:
A glass jar containing 40 white, round, coated tablets.
Manufacturer/license holder and address: CTS Chemical Industries Ltd., 3 Hakidma St., Kiryat Malachi.
This leaflet was checked and approved by the Ministry of Health in November 2015.
Registration number of the medicine in the National Drug Registry of the Ministry of Health: 337122348