PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
The medicine is dispensed with a doctor's prescription only

Depalept Chrono 500 mg
Prolonged-release tablets

Active ingredients:
Each tablet contains:
Sodium valproate 333 mg
Valproic acid 145 mg
(equivalent to 500 mg Sodium valproate)

Inactive ingredients - see section 6 – "Further Information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

In addition to this leaflet, Depalept Chrono 500 mg also comes with a Patient Safety Information Card and Patient Booklet, to provide information on the risks. These accompanying materials contain important safety information, which you should know and adhere to before starting and during the course of treatment with Depalept Chrono. Read the Patient Safety Information Card, Patient Booklet, and the patient leaflet before starting treatment with the preparation. Keep them for later reference, if needed.

Warning

Valproate (Depalept Chrono 500 mg) can cause serious harm to an unborn child when taken during pregnancy. If you are a woman able to have a baby, you must use an effective method of birth control (contraception) without interruptions during the entire course of your treatment with Depalept Chrono 500 mg. Your doctor will discuss this with you, but you must also follow the recommendations in section 2 of this leaflet.

Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.

Do not stop taking Depalept Chrono 500 mg unless your doctor tells you to, as your condition may become worse.

1. WHAT IS THE MEDICINE INTENDED FOR?

This preparation is intended for treatment of partial, generalized or mixed epilepsy seizures. This preparation is intended to treat acute manic episode resulting from bipolar disorder when lithium cannot be used. The continuation of treatment may also be considered after manic episode, in patients who have responded to treatment with valproic acid.

Therapeutic group: anti-epileptic / fatty acid derivatives / anti-psychotics

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to valproate or to any of the additional ingredients contained in the medicine (listed in section 6),
- you, or a member of your family, has ever had a serious liver disease, or if you currently have serious liver disease or pancreatic disease,
- a member of your family has died from serious liver disease related to the use of valproic acid,
- you have a hereditary or acquired disease affecting the metabolism of hemoglobin (hepatic porphyria),
- you have a blood-clotting disorder,
- you have a genetic problem that causes a mitochondrial disorder (e.g., Alpers-Huttenlocher syndrome),
- you have a urea cycle disorder (a type of metabolic disorder),
- you have an untreated carnitine deficiency (a very rare metabolic disorder).

Bipolar disorder
- For bipolar disorder, you must not use Depalept Chrono 500 mg if you are pregnant.
- For bipolar disorder, if you are a woman able to have a baby, you must not take Depalept Chrono 500 mg, unless you use an effective method of birth control (contraception) during the entire treatment with Depalept Chrono 500 mg. Do not stop taking Depalept Chrono 500 mg or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see section "Pregnancy, breastfeeding and fertility").

Epilepsy
- For epilepsy, you must not use Depalept Chrono 500 mg if you are pregnant, unless no other treatment is effective for you.
- For epilepsy, if you are a woman able to have a baby, you must not take Depalept Chrono 500 mg, unless you use an effective method of birth control (contraception) during your entire treatment with Depalept Chrono 500 mg. Do not stop taking Depalept Chrono 500 mg or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see section "Pregnancy, breastfeeding and fertility").

Special warnings regarding use of the medicine

Inform your doctor immediately:
- In case of symptoms of liver or pancreatic damage (see "Tests and follow-up" below).
  The risk of liver damage is increased when Depalept Chrono 500 mg is used for children under 3 years of age, for people taking additional antiepileptic drugs at the same time, or with other neurological or metabolic disorders and severe forms of epilepsy.
- If you or your child develops problems such as balance or coordination disorders, fatigue or reduced alertness, or vomiting, tell your doctor immediately. This could be due to increased levels of ammonia in your blood.
- If your seizures worsen. As with other medicinal preparations used to treat epilepsy, treatment with Depalept Chrono 500 mg may increase the frequency or severity of seizures. If this happens, tell your doctor immediately.
- Self-destructive or suicidal thoughts have been observed in a smaller number of people treated with antiepileptics such as Depalept Chrono 500 mg. If you have these kinds of thoughts, contact your doctor immediately.

Before treatment with Depalept Chrono 500 mg, tell the doctor if:
- you have a blood system impairment (e.g., coagulation defect, etc.),
- you ever had or have a bone marrow disorder,
- you have systemic lupus erythematosus (a reaction where the body's immune system attacks its own connective tissue),
- you are suspected of having a metabolic disorder, especially hereditary enzyme deficiency diseases, such as a urea cycle disorder, as this carries a risk of increased ammonia levels in the blood.
- you have a rare medical condition called "carnitine palmitoyltransferase (CPT) type II deficiency", because you are at increased risk of muscle disorders,
- you have a known family history of or the doctor suspects a mitochondrial disorder in your family caused by a genetic problem, as this poses a risk of liver damage,
- you have a deficiency in the uptake of carnitine from food, such as meat and dairy products, especially in children under 10 years of age,
- you have a carnitine deficiency and you are taking carnitine,
- you have impaired kidney function and/or a protein deficiency in the blood,
- prior to any surgical or dental procedure (e.g., tooth extraction) or in the event of injury or spontaneous bleeding. Since there may be an increased tendency to bleed, you must inform the medical staff that you are taking Depalept Chrono 500 mg so that your blood clotting can be checked,
- you are concomitantly taking medicines that inhibit blood clotting (e.g., vitamin K antagonists); your tendency to bleed may be aggravated. Your blood clotting must therefore be regularly monitored,
- you are concomitantly taking acetylsalicylic acid (aspirin), as it may result in an increase in the valproic acid concentration (the active substance of Depalept Chrono 500 mg) in the blood.

Children and adolescents
This medicine is not intended for children weighing less than 17 kg.
This mode of administration is not intended for children under 6 years of age (a problem with swallowing the tablet, and consequently, a choking hazard).
Depalept chrono must not be used to treat manic episodes in children and adolescents under 18 years of age.

Take special care during treatment with Depalept Chrono 500 mg
- in young children who are taking other medicines for seizure disorders,
- in children and adolescents with multiple disabilities and serious types of seizures,
- Depalept Chrono 500 mg and acetylsalicylic acid must not be used at the same time to treat illnesses involving fever in infants and children. They may only be co-administered in adolescents and only if explicitly instructed to do so by a doctor.

Tests and follow-up
Liver and/or pancreatic damage:
Uncommon cases of severe liver damage and rare cases of pancreatic damage have been reported. Patients, especially infants, young children and children, must perform liver function tests before starting treatment, and during the first 6 months of treatment, especially patients in risk groups.
Liver or pancreatic damage can have non-specific signs and symptoms, generally with sudden onset, such as a recurrence of seizures, seizures worsening or becoming more frequent, consciousness disorders including confusion, restlessness, movement disorders, general malaise and feeling weak, loss of appetite, aversion to familiar foods, aversion to valproic acid, nausea, vomiting, pain in the upper abdomen, lethargy, drowsiness, abnormally frequent bruising (hematomas), jaundice (yellowing of the skin or the whites of the eyes), nosebleeds and/or a build-up of fluids (edema) in specific parts of the body or in the whole body. If these symptoms persist or get worse, you must refer to a doctor immediately, who will decide whether to continue your treatment with Depalept Chrono 500 mg.
• Early detection of liver or pancreatic damage
Before the start of treatment, your doctor should ask you detailed questions, perform a physical examination and request laboratory tests (particularly tests for metabolic disorders, liver or pancreas diseases and blood test or blood clotting problems). Laboratory tests should be performed again 4 weeks after the start of treatment.
In patients with no clinical signs but with abnormally high test values after 4 weeks, follow-up tests should be performed 3 times at intervals of no more than 2 weeks, then once a month until the 6th month of treatment.
Parents or caregivers must immediately inform the doctor of any clinical signs, regardless of this schedule.
In adolescents (starting from 15 years of age) **and adults**, monthly clinical and laboratory test monitoring is recommended during the first 6 months of treatment, as well as before the start of treatment.
After 12 months of treatment with no clinical signs, monitoring by a doctor is only needed 2 to 3 times per year.
• You may gain weight at the start of treatment. Check your weight regularly and talk to the doctor about suitable weight-control measures, if necessary.

Drug interactions

If you are taking, have recently taken, or might take other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist, especially if you are taking:

The effect, and sometimes side effects, of Depalept Chrono 500 mg are enhanced by the following medicines:
- Cimetidine (a medicine used to treat stomach ulcers),
- Erythromycin (a medicine used to treat bacterial infections),
- Acetylsalicylic acid (a medicine used to treat fever and pain): acetylsalicylic acid reduces the plasma protein binding of valproic acid. This can lead to an increase in the harmful effect of valproic acid on the liver. See also "Children and adolescents" in section 2 ("Before using the medicine").

The effect of Depalept Chrono 500 mg is weakened by the following medicines:
- Phenobarbital, primidone, phenytoin, carbamazepine (other medicines used to treat seizure disorders),
- Mefloquine (a medicine used to treat malaria),
- Rifampicin (a medicine used to treat tuberculosis),
- Carbapenems such as imipenem, panipenem and meropenem (antibiotics used to treat bacterial infections).
  Combined use of valproic acid and carbapenem-containing preparations should be avoided, as it may reduce the efficacy of valproic acid,
- Protease inhibitors such as lopinavir or ritonavir (medicines used to treat HIV),
- Estrogen-containing preparations (including some birth control pills),
- Metamizole (used to treat pain and fever).
- Methotrexate (used to treat cancer and inflammatory diseases).

The effect of Depalept Chrono 500 mg may be enhanced or weakened by the following medicine:
- Fluoxetine (medicine used to treat depression). Concentrations of valproic acid (the active ingredient of Depalept Chrono 500 mg) in the blood may increase, but certain cases of decreased concentrations have also been observed.

Depalept Chrono 500 mg enhances the effects, and sometimes side effects, of the following medicines:
- Phenobarbital, primidone, phenytoin, carbamazepine, lamotrigine (medicines used to treat seizure disorders),
- Neuroleptics (medicines used to treat psychological disorders), benzodiazepines (medicines used to treat stress and anxiety disorders), barbiturates (sedatives), MAO inhibitors (medicines used to treat depression) as well as other medicines used to treat depression,
- Codeine (a medicine used to treat coughing),
- Zidovudine (a medicine used to treat HIV),
- Medicines that reduce blood clotting (e.g., vitamin K antagonists or acetylsalicylic acid). These medicines may cause an increased tendency to bleed,
- Rufinamide (a medicine used to treat seizure disorders) (extra caution must be taken in children),
- Propofol (a medicine used as an anesthetic).

In children, the levels of phenytoin (another medicine used to treat seizure disorders) in the blood can increase if taken at the same time as clonazepam (a benzodiazepine used to treat states of stress and anxiety, and seizure disorders) and valproic acid.
In patients with a history of absence seizures (a particular type of generalized seizure starting in both sides of the brain), cases of absence status epilepticus (a prolonged semi-conscious state) were reported during simultaneous treatment with clonazepam (a medicine used to treat seizure disorders) and medicines containing valproic acid.
In one patient with schizoaffective disorder (a psychological disorder), the combination of valproic acid, sertraline (an antidepressant) and risperidone (a neuroleptic) led to a catatonic state (a condition characterized by immobility accompanied by rigidity that does not respond to external stimuli).

Other interactions
- Depalept has no effect on blood lithium levels,
- Depalept does not reduce the effect of hormonal contraceptives (e.g., birth control pill),
- In patients with diabetes, tests for ketones in the urine may yield false positive results, as valproic acid is partially metabolized into ketones. Other medicinal preparations, such as cannabidiol (used to treat epilepsy and other disorders), that strain hepatic metabolism may increase the risk of liver damage.
- Signs of brain damage (encephalopathy) and/or increased levels of ammonia in the blood (hyperammonemia) have been reported when valproic acid is combined with topiramate (a medicine used to treat seizure disorders),
- If Depalept is used with acetazolamide (a medicine used to treat glaucoma), there can be an increase in ammonia levels in the blood resulting in a risk of brain damage (encephalopathy),
- If valproic acid is used at the same time as phenobarbital or phenytoin, there can be an increase in ammonia levels in the blood. Therefore, your doctor will monitor you carefully for this,
- If valproic acid is used with quetiapine (a medicine used to treat psychiatric disorders), the risk of a drop in the number of white blood cells (leukopenia, neutropenia) may increase,
- Depalept can lower the concentration of olanzapine (medicine used to treat psychiatric disorders) in the blood,
- Some medicinal preparations used to treat infections that contain pivalates (e.g., pivampicillin, adevofir dipivoxil) may increase the risk of carnitine deficiency when concomitantly administered with valproate.

Use of the medicine and food
It is preferable to take the medicine with food.

Use of the medicine and alcohol consumption
The effects of Depalept Chrono 500 mg can be enhanced or weakened, and the side effects stronger, if you consume alcohol during treatment. Therefore, avoid drinking alcohol during the course of treatment.

Pregnancy, breastfeeding and fertility

Important information for women
Also see section 2 "Do not use the medicine if:".
The risks of valproate when taken during pregnancy (irrespective of the disease for which valproate is used)
• Talk to your doctor immediately if you are planning to have a baby or are pregnant.
• Valproate carries a risk if taken during pregnancy. The higher the dosage, the higher the risks, but all dosages carry a risk, including use of valproate in combination with other medical preparations to treat epilepsy.
• The medicine may cause serious birth defects and impair the baby's physical and mental development after birth. The most commonly reported birth defects include *spina bifida* (where the bones of the spine are not properly developed), facial and skull defects, heart, kidney, urinary tract and sexual organ defects, limb defects and several defects that occur together and affect many organs and body parts. Birth defects may lead to disabilities that can be seriously debilitating.
• Cases of hearing disorders and deafness have been reported in children exposed to valproate during pregnancy.
• In children exposed to valproate during pregnancy, eye malformations associated with other congenital malformations have been identified. These eye defects can affect vision.
• If you take valproate during pregnancy, you have a higher risk than other women of having a child with birth defects that require medical treatment. Among women who take valproate, around 11 babies in every 100 will have birth defects. This is in comparison to 3 babies in every 100 born to women who don't have epilepsy.
• It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Affected children can suffer from slow development in walking and talking, from a lower intellectual level than other children, and from language and memory difficulties.
• Autistic spectrum disorders are more often diagnosed in children who were exposed to valproate. There is some evidence that children exposed to valproate during pregnancy are at increased risk of developing attention deficit hyperactivity disorder (ADHD).
• Before prescribing this medicine to you, your doctor will explain what might happen to your baby if you become pregnant while taking valproate. If you decide later that you want to get pregnant, do not stop taking your medicine or your method of contraception until you have discussed this with your doctor.
• If you are a parent or a caregiver of a female child treated with valproate, refer to the doctor once the child experiences her first menstruation.
• Some birth control pills (estrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of contraception that is the most appropriate for you.
• Ask your doctor about taking folic acid when you are trying to become pregnant. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects ascribed to use of valproate.
• If you have taken medicines containing valproic acid during pregnancy, the blood clotting parameters (platelet and fibrinogen levels) and coagulation factors of your newborn baby must be checked for any potential blood clotting disorders.
• Newborn babies of mothers who were treated with medicinal preparations containing valproic acid during the last trimester of pregnancy may show signs of withdrawal syndrome (such as restlessness, excessive movements, tremor, seizures or feeding disorders).
• Cases of low blood sugar levels have been reported in newborn babies of mothers who were treated with valproate during the last trimester of pregnancy.
• Cases of underactive thyroid function have also been reported in newborn babies of mothers who received valproate to treat epilepsy during pregnancy.

Please choose and read the situations which apply to you from the situations described below:
○ I AM STARTING TREATMENT WITH DEPALEPT CHRONO 500 MG
○ I AM TAKING DEPALEPT CHRONO 500 MG AND AM NOT PLANNING TO GET PREGNANT
○ I AM TAKING DEPALEPT CHRONO 500 MG AND PLAN TO GET PREGNANT
○ I AM PREGNANT AND AM TAKING DEPALEPT CHRONO 500 MG

I AM STARTING TREATMENT WITH DEPALEPT CHRONO 500 MG
If this is the first time you have been prescribed Depalept Chrono 500 mg, your doctor will explain to you the risks to the unborn child if you become pregnant. Once you are capable of conceiving, you will need to make sure you use an effective method of contraception without interruption throughout the entire course of your treatment with Depalept Chrono 500 mg. Talk to your doctor if you need advice on contraception.

Key messages:
• Pregnancy must be ruled-out before starting treatment with Depalept Chrono 500 mg by the result of a pregnancy test, confirmed by your doctor,
• You must use an effective method of birth control (contraception) during your entire course of treatment with Depalept Chrono 500 mg,
• You must discuss the appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control,
• You must have regular (at least annual) appointments with a specialist experienced in treating bipolar disorder or epilepsy. During this visit, your doctor will make sure you are well aware and understand all the risks and recommendations related to the use of valproate during pregnancy,
• Tell your doctor if you want to become pregnant,
• Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING DEPALEPT CHRONO 500 MG AND AM NOT PLANNING TO GET PREGNANT
If you are continuing treatment with Depalept Chrono 500 mg but are not planning to get pregnant, make sure you are using an effective method of contraception without interruption during your entire treatment with Depalept Chrono 500 mg. Talk to your doctor if you need advice on contraception.

Key messages:
• You must use an effective method of birth control (contraception) during your entire treatment with Depalept Chrono 500 mg,
• You must discuss contraception (birth control) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control,
• You must get regular (at least annual) appointments with a specialist experienced in treating bipolar disorder or epilepsy. During this visit, your doctor will make sure you are well aware of and understand all the risks and recommendations related to the use of valproate during pregnancy,
• Tell your doctor if you want to become pregnant,
• Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING DEPALEPT CHRONO 500 MG AND PLAN TO GET PREGNANT
If you are planning to get pregnant, first schedule an appointment with your doctor.
Do not stop taking Depalept Chrono 500 mg or using your contraception until you have discussed this with your doctor. Your doctor will advise you further.
Babies born to mothers who have been treated with valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the treatment of bipolar disorder or epilepsy, so that alternative treatment options can be evaluated at an early stage. The specialist can take a number of measures so that the course of your pregnancy is as smooth as possible and that any risk to you and your unborn child is reduced as much as possible.
The specialist may decide to change the dosage of Depalept Chrono 500 mg or switch you to another medicine, or stop treatment with Depalept Chrono 500 mg a long time before you become pregnant – this is to make sure your illness is stable.
Ask your doctor about taking folic acid when planning to become pregnant. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects ascribed to the use of valproate.

Key messages:
• Do not stop taking Depalept Chrono 500 mg unless your doctor tells you to,
• Do not stop using your methods of birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced,
• First, schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and recommendations related to the use of valproate during pregnancy,
• Your doctor will try to switch you to another medicine, or stop treatment with Depalept Chrono 500 mg a long time before you become pregnant,
• Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM TAKING DEPALEPT CHRONO 500 MG
Do not stop taking Depalept Chrono 500 mg unless your doctor tells you to, as your condition may become worse. Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.
Babies born to mothers who have been treated with valproate are at serious risk of birth defects and problems with development which can be seriously debilitating.
You will be referred to a specialist experienced in the treatment of bipolar disorder or epilepsy, so that alternative treatment options can be evaluated.
In the exceptional circumstances when Depalept Chrono 500 mg is the only available treatment option during pregnancy, you will be monitored very closely, both for the management of your underlying disease and to check the development of your unborn child. You and your partner can receive counseling and support regarding the valproate-exposed pregnancy.
Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
• Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant,
• Do not stop taking Depalept Chrono 500 mg unless your doctor tells you to,
• Make sure you are referred to a specialist experienced in the treatment of epilepsy or bipolar disorder to evaluate the need for alternative treatment options,
• You must request thorough counseling on the risks of Depalept Chrono 500 mg during pregnancy, including teratogenicity (birth defects) and physical and mental developmental disorders in children,
• Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrence of malformations.

In all cases, make sure you read the patient booklet and Patient Safety Information Card that you will receive from your doctor.

Breastfeeding
Small amounts of valproic acid pass into breast milk. If you are breastfeeding, consult your doctor before taking this medicine.

Fertility
This medicine can impair your fertility. Case reports showed that these effects can usually be reversed after discontinuing treatment with the active ingredient or reducing the dosage. Do not stop your treatment unless you have discussed it with your doctor.

Driving and operating machinery
Do not drive or operate machinery without consulting your doctor.
At the start of treatment with Depalept Chrono 500 mg, if you take high dosages or also take another medicine that affects the central nervous system, you might have central nervous system effects such as drowsiness or confusion, which can impair your reaction times. This means that your ability to drive or use machines will be impaired.

Important information about some of the ingredients of the medicine
This medicine contains 47.21 mg sodium (the main ingredient in table salt) in each prolonged-release tablet.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.
The dosage and treatment regimen will be determined by the doctor only. Treatment with **Depalept Chrono** 500 mg must be started and supervised by a doctor specialized in the management of epilepsy or bipolar disorder.
The doctor may recommend that the required dose be divided to twice a day. It is preferable to take the medicine at mealtimes.
If your illness is well controlled by the treatment, your doctor may recommend treatment once a day.
If you have kidney disease and/or a protein deficiency in the blood, the levels of the active ingredient of **Depalept Chrono** 500 mg (valproic acid) in your blood can be increased. Your doctor will reduce your daily dose if necessary.

Do not exceed the recommended dose.
When switching to Depalept Chrono 500 mg from previous tablets which are not prolonged-release, it must be ensured that the levels of valproic acid in the blood are high enough. This switch will be done according to your doctor's instructions.

Always take the tablets with a full glass of water. Do not take the prolonged-release tablets with a carbonated drink such as sparkling water.
Do not chew or crush the tablet, as it may affect the way the medicine is absorbed into the body.
The tablet can be halved when a dosage of 250 mg (half a tablet) is needed.
Depalept Chrono are tablets that gradually release the active ingredient. Some of the inactive ingredients are not absorbed by the digestive system and can be seen in the stools.

If you accidentally take a higher dosage
If you took an overdose or if a child has accidentally swallowed the medicine, consult your doctor immediately so he can take any necessary emergency measures, or proceed to a hospital emergency room, and bring the package of the medicine with you.
The undesirable effects listed under "Side effects" may become stronger, i.e., both adults and children may be more likely to have seizures or behavioral disorders. Isolated cases of death following massive overdose have been reported.

If you forget to take the medicine
If you forgot to take this medicine at the designated time, do not take a double dose. Take the next dose at the usual time and consult the doctor.
Adhere to the treatment regimen as recommended by the doctor.

If you stop taking the medicine
Do not change dosages, interrupt or stop your treatment with Depalept Chrono 500 mg without consulting your doctor. Talk to your doctor beforehand if you think you have developed an intolerance or a change in your medical condition. Otherwise, you may jeopardize your treatment and start having seizures again.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Depalept Chrono 500 mg may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.
The frequency of side effects is classified as follows:

Very common: occur in more than 1 in 10 patients
Common: occur in 1 to 10 in 100 patients
Uncommon: occur in 1 to 10 in 1,000 patients
Rare: occur in 1 to 10 in 10,000 patients
Very rare: occur in less than 1 in 10,000 patients
Frequency unknown: frequency cannot be estimated from the available data

Tell your doctor or pharmacist if one or more of the following side effects are severe or last for more than a few days; you may need medical treatment.

Neoplasm benign, malignant and unspecified tumors (including cysts and polyps)
Rare: blood cell precursors do not develop properly in the bone marrow (myelodysplastic syndrome, detected in blood count).

Blood and lymphatic system disorders
Common: a decrease in the number of red blood cells (anemia), platelets (thrombocytopenia) or a very low number of white blood cells (leukopenia).
Uncommon: a very low number of all blood cells (pancytopenia).
Rare: impaired bone marrow function with a decrease in the number of all white blood cells (lymphopenia, neutropenia) or with a significant decrease in a particular type of white blood cell (agranulocytosis), abnormal development of red blood cells (aplasia) or development of unusually large red blood cells in normal (macrocytosis) or reduced (macrocytic anemia) numbers. This can be seen in the blood counts and sometimes manifests through signs such as fever and difficulty breathing.

Endocrine disorders
Uncommon: increased levels of antidiuretic hormone in the blood (syndrome of inappropriate antidiuretic hormone secretion - SIADH), excessive hair growth in women, virilism, acne, male-pattern hair loss and/or hyperandrogenism.
Rare: hypothyroidism, which may cause tiredness or weight gain.

Metabolism and nutrition disorders
Very common: isolated and moderate increase in the amount of ammonia in the blood (hyperammonemia), with no effect on liver function, but occasionally with central nervous system symptoms such as impaired balance and coordination, fatigue or decreased alertness, accompanied by vomiting. Tell your doctor immediately if you experience these symptoms. You may need urgent medical attention (also see "Special warnings regarding use of the medicine" in section 2).
Common: weight gain (a risk factor for the onset of polycystic ovary syndrome) or weight loss, increased appetite or appetite loss, decreased sodium levels in the blood (hyponatremia) that can lead to confusion.
Rare: obesity.
Frequency unknown: decreased carnitine levels (in blood or muscle tests).

Psychiatric disorders
Common: confusion, hallucinations (seeing, feeling or hearing things that are not real), aggressiveness*, restlessness*, attention disorders*.
Uncommon: irritability, hyperactivity.
Rare: abnormal behavior*, learning disabilities*, mental and physical (psychomotor) hyperactivity*.
*These side effects are primarily observed in children.

Nervous system disorders
Very common: shaking (tremor).
Common: extrapyramidal disorders (movement disorders affecting how the brain controls muscles, such as uncontrollable muscle contractions; partially reversible), dazed state (stupor)*, drowsiness, seizures (convulsions)*, memory disorders, headache, rapid and uncontrollable eye movements (nystagmus), dizziness and numbness or prickling (paresthesia).
Uncommon: coma*, brain damage (encephalopathy)*, lethargy*, Parkinson's syndrome which is reversible when treatment with valproic acid is stopped, increased muscle stiffness (spasticity), difficulty coordinating movements (ataxia), such as an unsteady gait, worsening of seizures (see "Special warnings regarding use of the medicine" in section 2).
Signs of brain damage (encephalopathy) have been described shortly after use of medicines containing valproic acid. These signs were reversible upon discontinuation of treatment. In some cases, these signs were associated with an increase in blood ammonia levels, as well as an increase in blood phenobarbital levels in the case of combined treatment with phenobarbital.
Rare: double vision; a marked decrease in mental capacity (dementia), which is reversible upon discontinuation of treatment, and sometimes associated with a decrease in brain size; slight decrease in mental function (cognitive disorder).
There have been rare reports of brain disease (chronic encephalopathy) with impaired brain function and mental capacity, particularly with high dosages or in the case of combined treatment with other medicines used to treat seizure disorders.
Frequency unknown: drowsiness.
*Cases of a dazed state (stupor) and lethargy leading to consciousness disorders, including transient coma or brain damage (encephalopathy) have been reported, sometimes associated with more frequent seizures, particularly in the case of combined treatment with phenobarbital or topiramate or following a sudden dosage increase. These symptoms are reversible when the dosage is reduced or treatment stopped.
During **long-term treatment** with Depalept Chrono 500 mg, particularly if combined with phenytoin (another medicine to treat epilepsy), signs of brain damage (encephalopathy) may occur: an increase in the number of seizures, lack of motivation, dazed state (stupor), decreased muscle tone (muscular hypotonia) and significant changes in the electrical activity of the brain (EEG).

Ear and labyrinth (inner ear) disorders
Common: hearing loss (sometimes permanent).
Frequency unknown: tinnitus (ringing in the ears).

Vascular disorders
Common: spontaneous bruising or bleeding (see "Special warnings regarding use of the medicine" and "Pregnancy, breastfeeding and fertility" in section 2).
Uncommon: inflammation of blood vessels (vasculitis).

Respiratory, thoracic and mediastinal disorders
Uncommon: breathing difficulty and pain due to inflammation of the envelope of the lungs or build-up of fluid between the lungs and the chest (pleural effusion).

Gastrointestinal disorders
Very common: nausea.
Common: vomiting, gum disorders (mainly gingival hyperplasia (enlargement)), inflammation of the mucous membrane in the mouth (sores, swelling, ulcers and a burning sensation in the mouth), diarrhea particularly at the start of treatment, and pain in the upper abdomen which usually regresses within a few days without stopping treatment.
Uncommon: damage to the pancreas, sometimes fatal (see "Do not use the medicine if:" in section 2), increased saliva production (particularly at the start of treatment).

Hepatobiliary disorders
Common: serious (sometimes fatal) liver damage that is not dependent on the dosage (see "Do not use the medicine if:" in section 2).

Skin and subcutaneous tissue disorders
Common: hypersensitivity, transient and/or dose-dependent hair loss; nail and nail bed disorders.
Uncommon: swelling (angioedema) with painful, itchy hives, mostly around the eyes, lips, throat and larynx, sometimes also on the hands, feet and genitals; skin rash, hair changes (such as change in hair texture, change in hair color, abnormal hair growth).
Rare: serious skin reactions: blistering, peeling or bleeding of the skin (including the lips, eyes, mouth, nose, genitals, hands, or feet) with or without a rash, sometimes with flu-like symptoms such as fever, chills or aching muscles (Stevens-Johnson syndrome or toxic epidermal necrolysis or Lyell syndrome); rash (especially on the palms of the hands and soles of the feet) or skin lesions with a pink/red periphery and pale center which may be itchy, flaky, or filled with fluid (erythema multiforme); syndrome with rash, fever and swollen lymph nodes and an increase in certain white blood cells (eosinophils), and with possible impairment of other organs caused by the medicine (DRESS).

Musculoskeletal and connective tissue disorders
Cases of decreased bone mineral density (osteopenia and osteoporosis) leading to fractures have been reported. Consult your doctor or pharmacist if you are receiving long-term treatment with an antiepileptic drug, if you have a history of osteoporosis or if you are also taking cortisone or other steroid hormones.
Rare: reactions of the body's defense systems against its own connective tissue, with signs such as joint pain, fever, fatigue and skin rash (systemic lupus erythematosus), also see "Special warnings regarding use of the medicine" in section 2); severe muscle breakdown accompanied by muscle weakness and pain (rhabdomyolysis).

Renal and urinary disorders
Common: urinary incontinence (unintentional urination).
Uncommon: renal failure, signs may include a reduced amount of urine.
Tell your doctor immediately if this serious side effect occurs. You may need urgent medical help.
Rare: urinary incontinence or increased urgency to urinate, inflammatory kidney disorder (tubulointerstitial nephritis), excretion of large amounts of urine accompanied with thirst (Fanconi syndrome).

Reproductive system and breast disorders
Common: menstrual pains (dysmenorrhea).
Uncommon: irregular or missing periods (amenorrhea).
Rare: male infertility, which is usually reversible after treatment discontinuation or may be reversible after reduction of the dosage. Do not stop your treatment without first speaking to your doctor.
High levels of the sex hormone testosterone in the blood and abnormal function of the ovaries (polycystic ovary syndrome).

Congenital (hereditary), familial and genetic disorders
(See section "Pregnancy, breastfeeding and fertility").

General disorders
Uncommon: lower body temperature (hypothermia), build-up of fluid in the arms and/or legs (peripheral edema).

Side effects in investigation
Rare: blood clotting disorders, recognizable by changes in blood clotting-related lab values (see also "Special warnings regarding use of the medicine" and "Pregnancy, breastfeeding and fertility" in section 2). Decreased levels of vitamin B7 in the body (biotin deficiency).

Additional effects
Inform your doctor immediately if you suffer from side effects that **are not dosage-dependent**, such as possible signs of liver or pancreatic damage (see section 2 "Before using the medicine"). He will decide whether to continue treatment with Depalept Chrono 500 mg.

Additional side effects in children
Some side effects of valproate occur more frequently in children or are more severe compared to adults. These include liver damage, inflammation of the pancreas (pancreatitis), aggression, agitation, attention deficit disorders, abnormal behavior, mental and physical (psychomotor) hyperactivity and learning difficulties.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult the doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il), that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
Do not use the medicine after the expiry date (exp. date) that appears on the box and blister.
The expiry date refers to the last day of that month.

Storage conditions
There are no special storage conditions. It is recommended to store at room temperature.
Do not dispose of medicines via the wastewater (e.g., the toilet or sink). Ask the pharmacist how to dispose of medicines that are not in use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredients, the medicine also contains:
Hypromellose, hydrated colloidal silica, polyacrylate 30% dispersion, ethylcellulose, saccharin sodium, macrogol 6000, talc, colloidal anhydrous silica, titanium dioxide
Each tablet contains 47.21 mg sodium.
What the medicine looks like and contents of the package:
Oblong and film-coated white tablets with a score line. 30 tablets in a blister package.
Registration holder and its address: Sanofi Israel Ltd., Greenwork Park P.O. box 47 Yakum.
Revised in August 2023 according to MOH guidelines.
Registration number of the medicine in the National Drug Registry of the Ministry of Health: 1193327953.