

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

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, Checklist for information on risks 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 who is able to conceive, you must use an effective method of birth control 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. Regardless of your medical condition, never stop taking Depalept Chrono 500 mg before talking about it with the doctor, 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 and/or prevent acute manic episodes resulting from bipolar disorder.

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 someone from your family, has ever suffered from a severe liver disease, or if you currently suffer from severe 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).

Bipolar disorder

- For bipolar disorder, do not use Depalept Chrono 500 mg if you are pregnant.
- For bipolar disorder, if you are a woman who is able to conceive, do not take Depalept Chrono 500 mg, unless you use an effective method of birth control throughout the entire course of your treatment with Depalept Chrono 500 mg. Do not stop taking Depalept Chrono 500 mg or your birth control until you have discussed this with your doctor. Your doctor will advise you further (see section “Pregnancy, breastfeeding and fertility”).

Epilepsy

- For epilepsy, do 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 who is able to conceive, do not take Depalept Chrono 500 mg, unless you use an effective method of birth control throughout the entire course of your treatment with Depalept Chrono 500 mg. Do not stop taking Depalept Chrono 500 mg or using your birth control 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

Before treatment with Depalept Chrono, 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 (Lupus disease; a reaction where the body’s immune system attacks its own connective tissue),
- you have a metabolic problem, especially a hereditary enzyme deficiency. Treatment with medicines containing valproic acid can cause an increase in the levels of ammonia in the blood (hyperammonemia). Inform your doctor if you have symptoms such as exhaustion, tiredness, vomiting, decrease in blood pressure or increase in seizures. Your doctor will monitor the levels of ammonia and valproic acid in your blood and decide whether to reduce your dosage of Depalept Chrono 500 mg. If an enzyme deficiency of the urea cycle is suspected, your blood ammonia levels should be checked before you begin treatment with valproic acid (see “Do not use the medicine if.” in section 2).
- If you have a metabolic disease caused by a carnitine palmitoyltransferase type II (CPT-II) deficiency, the risk of developing serious muscle problems (rhabdomyolysis) is higher when using medicines containing valproic acid,
- you have a known family history of a mitochondrial disorder caused by a genetic problem,
- you have a kidney disease and/or a protein deficiency in the blood,
- you are scheduled to undergo surgery or a dental procedure (e.g., tooth extraction), or if you are injured or have spontaneous bleeding. As this medicine can cause 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 taking other medicines that can reduce blood clotting (e.g., vitamin K antagonists); your tendency to bleed may be increased. Your blood clotting must therefore be regularly monitored,
- you are also taking acetylsalicylic acid (aspirin); there might be an increase in concentrations of valproic acid (the active ingredient of Depalept Chrono 500 mg) in your blood,
- your seizures worsen. As with other epilepsy medicines, treatment with **Depalept Chrono 500 mg** can cause your seizures to worsen or become more frequent. If this happens, consult your doctor immediately,
- Self-destructive or suicidal thoughts have been observed in a small number of people treated with antiepileptics such as Depalept Chrono 500 mg. If you have these kinds of thoughts, contact your doctor immediately.

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).

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,
- Do not use Depalept Chrono 500 mg and acetylsalicylic acid at the same time to treat illnesses involving fever in infants and children. This combined treatment can only be given to adolescents and only if explicitly instructed to do so by a doctor.

Tests and follow up

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), nosebleeds and/or a build-up of liquid (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 problems with blood tests or blood clotting).

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**, clinical follow-up and follow-up with laboratory tests once a month during the first 6 months of treatment, as well as before the start of treatment, are recommended.

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, or have recently taken, other medicines, including non-prescription medicines or 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).

The effect of Depalept Chrono 500 mg may be enhanced or weakened by the following medicine:

- Fluoxetine (a 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 anxiety or stress 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 may increase if taken at the same time as clonazepam (a benzodiazepine used to treat anxiety, stress 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 stiffness 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., oral contraceptives),
- In patients with diabetes, tests for ketones in the urine may yield false positive results, as valproic acid is partially metabolized into ketones,
- Other medicines that impair liver 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 may be an increase in blood ammonia levels leading to 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 zetiapine (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 (a medicine used to treat psychiatric disorders) in the blood.

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:

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 become pregnant or are pregnant,
- Taking valproate during pregnancy carries a risk. The higher the dosage, the higher the risks, but all dosages carry a risk,
- The medicine can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported 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. Cases of hearing problems and deafness have been reported in children exposed to valproate during pregnancy,
- 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 10 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 the pregnancy may have problems with early childhood development. Children affected 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 the 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 using your contraceptive 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 birth control that is the most appropriate for you,
- Ask the 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 associated with valproate use,
- 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 with the result of a pregnancy test, confirmed by your doctor,
- Use an effective method of birth control during the entire course of your treatment with Depalept Chrono 500 mg. You must discuss the appropriate methods of 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 have regular (at least one per year) 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 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 the entire course of your 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 during the entire course of your treatment with Depalept Chrono 500 mg,
- You must discuss 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 one per year) 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 associated with valproate use.

Key messages:

- Do not stop taking Depalept Chrono 500 mg unless your doctor tells you to,
- Do not stop using your contraceptives 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 AM TAKING DEPALEPT CHRONO 500 MG
Do not stop taking Depalept Chrono 500 mg unless your doctor tells you so, 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 the unborn child. You and your partner can receive counselling 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 get thorough counselling on the risks of Depalept Chrono 500 mg during pregnancy, including teratogenicity activity and developmental effects in children,
- Make sure you are referred to a specialist for prenatal monitoring in order to identify 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. However, individual case reports show that this effect is reversible after treatment is stopped.

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.

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.

Do not exceed the recommended dose.

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/she can immediately take the 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 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

Benign, malignant and unspecified tumors (including cysts and polyps)

Rare: blood cell precursors do not develop properly in the spinal cord (myelodysplastic syndrome).

Blood and lymphatic system disorders

Common: a decrease in the number of red blood cells (anemia), platelets (thrombocytopenia) or white blood cells (leukopenia). Uncommon: a decrease in the 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), impaired development of red blood cells (aplasia) or the development of unusually large red blood cells in normal (macrocytosis) or reduced (macrocytic anemia) numbers.

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: impaired thyroid function.

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 (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 lack of appetite, decreased sodium levels in the blood (hyponatremia) that can lead to confusion.

Rare: obesity.

Psychiatric disorders

Common: confused state, hallucinations, 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: tremor.

Common: extrapyramidal disorders (movement disorders affecting how the brain controls muscles, partially irreversible), dazed state (stupor)*, drowsiness, seizures (convulsions)*, memory disorders, headache, rapid and uncontrollable eye movements (nystagmus), dizziness and numbness or pricking (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), 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 decline in mental function (cognitive disorder).