PACKAGE LEAFLET: INFORMATION FOR THE USER

Epival CR 300 mg prolonged-release tablets
Epival CR 500 mg prolonged-release tablets

Active substance: sodium valproate

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

WARNING

Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment.
Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet.
Tell your doctor at once if you become pregnant or think you might be pregnant.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any of the side effectstalk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What Epival CR is and what it is used for

This medicine is an anticonvulsant (medication against epilepsy/fits). It is also used for the treatment of mania.

Sodium valproate, the active substance in Epival CR, is effective against certain types of convulsions. From the prolonged-release tablets, sodium valproate is released slowly into your body, thus acting over many hours.

Epival CR is used in the treatment of
- various forms of epilepsy (fits)
- mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called “bipolar disorder”. Epival CR can be used when lithium cannot be used.
- Epival CR must not be used by women who are trying to become pregnant or are pregnant as it can cause serious birth defects and developmental problems in the child, unless explicitly advised and agreed with your doctor to do so. All female patients who are capable of becoming pregnant will need

to consider this risk and follow the advice provided in section 2. Your doctor will discuss this with you.

2. What you need to know before you take Epival CR

Do not take Epival CR

- if you are allergic (hypersensitive) to sodium valproate or any of the other ingredients (see section 6.1 What Epival CR contains)
- if you have an active liver disease
- if close family-members have severe liver function disturbances or if there is a history of such disturbances in your family
- if you have a severe disturbance of the pancreas function
- if you suffer from hepatic porphyria (a rare metabolic disease).
- if you have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).

Warnings and precautions

Talk to your doctor or pharmacist before taking Epival CR

Special precautions are necessary

- if you suffer from "systemic lupus erythematosus" (a rare allergic condition which causes joint pain, skin rashes and fever): You should consult your doctor before you start taking Epival CR if you need to go in for surgery: Inform the treating physician before any type of surgery that you are taking Epival CR, because sodium valproate may prolong the bleeding time. Blood tests may have to be done.
- if there is a possibility that you suffer from "urea cycle enzymatic deficiency" (a rare metabolic disorder): You may have to undergo tests before starting treatment with Epival CR.
- if you know that there is a genetic problem caused by a mitochondrial disorder in your family.

A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor

Children and adolescents under 18 years of age:
Epival CR should not be used in children and adolescents under 18 years of age for the treatment of mania.

Other important things you should know before taking Epival CR:

- **Liver damage**
  In rare cases severe liver damage resulting in death has been reported. Patients most at risk are children under the age of three years who suffer from severe seizure disorders, particularly in association with mental retardation and/or congenital metabolic disorders. The frequency of such liver diseases generally decreases significantly in patients older than 10 years. Liver damage mostly occurred during the first 6 months of therapy, particularly between weeks 2 and 12 of treatment and usually when other anti-epileptic drugs were given at the same time.

  Especially during the first 6 months of treatment, patients at risk should therefore have their liver function checked regularly, and their treatment must be closely monitored.

  Signs of severe liver damage may include: increase in seizures, feeling unwell, weakness, loss of appetite, vomiting, pain in the upper abdomen, oedema (swelling of the fingers, legs and toes), lethargy, drowsiness, jaundice (yellowing of the skin or whites of the eyes). If you notice any such

symptoms, please consult a doctor immediately.
Similar symptoms may also occur in connection with a disease of the pancreas.

The risk of liver failure may increase if **salicylates** (e.g. aspirin) are taken at the same time. This risk is particularly high in infants and toddlers. Children under 12 years should not be given Epival CR in combination with acetylsalicylic acid at all. In adolescents, this combination should only be used after careful evaluation of the benefits and risks by their doctor, because it could increase the bleeding tendency and enhance the effects of Epival CR.

- Patients who suffered from **bone marrow damage** in the past may need special monitoring by their doctor during treatment.

- A **possible weight gain** during therapy was reported. Consult your doctor in order to discuss a suitable strategy against this risk.

- **Urine tests to diagnose diabetes** may be false-positive because of Epival CR. Please inform your doctor before such tests that you are taking Epival CR.

- If you require a **blood test** to have your **thyroid function** checked, please inform your doctor about this, because treatment with Epival CR may lead to a false diagnosis of hypothyroidism (insufficient production of thyroid hormone).

- Occasionally **tablet parts may appear in the stools** as a visible white residue. However, this does not reduce the effect of the medicine, as the active substance is completely released from the tablet system (matrix) while the drug passes through the intestine.

Other medicines and Epival CR

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Epival CR and other medicines may influence each other in their effects:
- The effect of certain medicines for depression, medicines used to calm emotional and mental conditions (so-called neuroleptics, MAO-inhibitors, benzodiazepines such as lorazepam and diazepam) may be enhanced by Epival CR.
- The combination with clonazepam (for the treatment of epilepsy) may induce absence seizures: your doctor will adjust the dose of your medication and monitor your treatment carefully.
- Other medicines used to treat fits/epilepsy (e.g. phenobarbital, primidone, phenytoin, carbamazepine, lamotrigine, felbamate) and Epival CR may increase or reduce each other's effects.
- The effect of fluoxetine (an antidepressant) may be enhanced by Epival CR, whereas the effect of Epival CR may be reduced.
- Certain antibiotics (e.g. erythromycin) may increase the effect of Epival CR, others (e.g. meropenem, panipenem, imipenem) may reduce its effect.
- Cimetidine (used to treat stomach ulcers) may enhance the effect of Epival CR.
- Cholestyramine (used to treat high blood fat levels) may decrease the effect of Epival CR.
- The effect of certain anticoagulants (used to thin the blood, e.g. warfarin) may be increased by Epival CR.
- The effect of acetylsalicylic acid (e.g. aspirin) may be enhanced by Epival CR and vice versa.
- Medicines against malaria (mefloquine, chloroquine) may reduce the effect of Epival CR.
- The effect of zidovudine (used to treat HIV-infections) may be enhanced by Epival CR.
- The effect of temozolomide (for tumour treatment) may be increased by Epival CR.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
Carbapenem agents (antibiotic used to treat bacterial infections). The combination of valproic acid and carbapenems should be avoided because it may decrease the effect of sodium valproate.

The potential liver-damaging effect of Epival CR may be increased if you ingest alcohol or use other treatments that could have a negative effect on the liver.

Epival CR does not appear to influence the effect of oral contraceptives.

Taking Epival CR with food,drink and alcohol

You can take Epival CR with or after food.
During treatment with Epival CR you should not drink alcoholic beverages, as sodium valproate may potentiate the effects of alcohol.

Pregnancy, breast-feeding and fertility

Important advice for women

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It 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 malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- 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. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in ever 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. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.
- Ask your doctor about taking folic acid when trying for a baby. 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.

FIRST PRESCRIPTION
If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:
- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND NOT TRYING FOR A BABY
If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:
- Make sure you are using an effective method of contraception
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY
If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. 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 using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy/bipolar disorder is controlled and the risks to your baby are reduced.
- Tell your doctor at once when you know or think you might be pregnant.

UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT
Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your medicine until your doctor tells you to.

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:
- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

BREASTFEEDING
Very little Epival CR gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.

Driving and using machines

Use of this drug may affect reactivity and the patient's ability to drive, particularly if other medicines against epilepsy/fits or medicines with a calming effect are taken and in combination with alcohol.

Successful seizure control over a period of several months may enable patients to actively participate in road traffic. Your treating physician will inform you whether you may drive a vehicle.

3. How to take Epival CR

Always take Epival CR exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

DOSAGE AND DURATION OF TREATMENT
Dosage and duration of treatment are individually adjusted by your doctor.
In general, treatment is started with a lower dose, which is then gradually increased by your doctor until your optimal dose is reached.
The daily dose may be taken either once daily or in two divided doses.

If you have the feeling that the effect of Epival CR is too weak or too strong, please consult your doctor or pharmacist.
The duration of treatment and the dose may vary from one person to another; they will therefore be decided by your doctor depending on the course of your illness.

Epilepsy:

Epival CR treatment must be started and supervised by a doctor specialised in the treatment of epilepsy or bipolar disorders.

In general, the treatment of epilepsy is a long-term treatment.

Monotherapy

Adults
The recommended dose is between 1000 and 2000 mg daily; if necessary, a higher daily dose (up to 2500 mg per day) may be prescribed by your doctor.

Use in children and adolescents
Children over 20 kg body weight:
The dose is based on the child's weight. In general, 20 to 30 mg sodium valproate per kg body weight per day are administered (for example in case of 30 kg body weight and an average dose of 25 mg/kg: 2½ tablets of 300 mg per day).
If necessary, the doctor may prescribe daily doses higher than 30 mg per kg body weight.

For children under 20 kg body weight, other presentations of Epival CR (for example an oral solution or a syrup) are available and may be prescribed instead of tablets.

The following table serves as a general dosage guideline for orientation:

Age	Body Weight	Average Dose
3 - 6 months	approx. 5.5 - 7.5 kg	150 mg per day
6 - 12 months	approx. 7.5 - 10 kg	150 - 300 mg per day
1 - 3 years	approx. 10 - 15 kg	300 - 450 mg per day
3 - 6 years	approx. 15 - 20 kg	450 - 600 mg per day
7 - 11 years	approx. 20 - 40 kg	600 - 1200 mg per day
12 - 17 years	approx. 40 - 60 kg	1000 - 1500 mg per day
Adults (including elderly patients)	approx. 60 kg and higher	1200 - 2100 mg per day

Patients with disturbed kidney and/or liver function:
Your doctor may prescribe a lower dose.

Combination therapy
If you are also taking other medicinal products to treat your illness, your doctor will adjust the dose accordingly.

Mania:

The daily dosage should be established and controlled individually by your doctor.
Initial dose
The recommended initial daily dose is 750 mg.

Average recommended maintenance daily dose
The recommended daily doses usually range between 1000 mg and 2000 mg.

Use in children and adolescents
Epival CR is not recommended for the use in children and adolescents for the treatment of mania.

ADMINISTRATION
Take the tablets whole with sufficient amounts of fluid.
If gastro-intestinal side-effects (e.g. nausea) occur at the beginning of treatment, you should take the tablets during or after meals.
The tablets may be divided into halves, but must not be chewed or crushed.

If you take more Epival CR

Symptoms of an acute overdose may include nausea, vomiting, dizziness, sometimes also serious, or even fatal, side-effects affecting the central nervous system and breathing. If you take more tablets than you should or if a child has taken the medicine by accident, consult your doctor or go to the nearest accident and emergency department immediately. Take this leaflet and any remaining tablets with you so the doctor will know what you have taken.

If you forget to take Epival CR

If you forgot to take a dose at the right time, take it as soon as you remember. However, if you are already nearing the time for your next scheduled dose, you should skip the forgotten dose and then continue treatment as prescribed. Do not take a double dose to make up for a forgotten dose.

If you stop taking Epival CR

Do not interrupt or stop the treatment with Epival CR without consulting your doctor. This could have a negative effect on your treatment and might induce more seizures. Please discuss any signs of intolerance or changes in the course of your illness with your treating physician.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Please note that the following list includes all reported side effects – even those that occur very rarely.

Tell your doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:
- Allergic reaction: Signs may include rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. In a very small number of patients, serious skin reactions may occur and may sometimes even be life-threatening and may include blistering or bleeding of the skin around the

lips, nose, eyes and genitals, or skin lesions affecting also the palms or the soles of your feet. These skin reactions may be accompanied by a feeling of being generally unwell, flu-like symptoms, fever and aching muscles.
- Increased amount of ammonia in the blood: Signs may be vomiting, problems with balance and coordination and feeling lethargic or less alert.
- Deep loss of consciousness (coma) may occur in very few patients.
- Liver problems and problems of the pancreas: These may show as a sudden illness with signs including feeling sick, being sick repeatedly, being very tired and weak, stomach pain, jaundice (yellowing of the skin or whites of the eyes), loss of appetite, or a general feeling of being unwell.
- Increased tendency to bleed, or if you seem to get bruises or infections more easily. This could be due to certain conditions affecting the blood cells, e.g. a severe reduction in the number of white blood cells (possibly causing frequent infections, fever, severe chills, sore throat or mouth ulcers), reduction in the number of red blood cells or in the total number of blood cells (which can make you feel tired, short of breath or look pale), or conditions inhibiting blood clotting (coagulation) thus leading to more frequent bruises or to bleeding more or longer than usual.

Tell your doctor as soon as possible, if you have any of the following side effects:
- Changes in mood (depression), confusion (occasionally followed by disturbed consciousness or associated with hallucinations or convulsions (fits)), lethargy, feeling less responsive than normal, twitching of the eyes, or loss of brain function (usually temporary)
- Disturbance or lack of coordination affecting balance and manner of walking, limb or eye movements and / or speech; dizziness/spinning sensation
- Drowsiness: this is often experienced when other medication used to treat epilepsy is given at the same time.
- Dementia and memory loss (usually reversible)
- Trembling, particularly at higher dosages
- Pins and needles (tingling or numbness of the hands and feet)
- Parkinson-like symptoms (such as reduced capacity of movement, trembling, increased muscular tension), or involuntary movements
- Increased alertness, hyperactivity, aggression and inappropriate behaviour
- Porphyria (a rare metabolic disease which may be associated with red coloration of the urine, abdominal spasms and pain as well as vomiting).

Tell your doctor or pharmacist, if any of the following side effects get serious or last longer than a few days, or if you notice any side effects not listed in this leaflet:
- Vasculitis (inflammation of the blood vessels), which may present as pain, reddening or itching
- Menstruation disorders, e.g. irregular periods or missed periods, cysts on the ovaries, breast enlargement in men, increased growth of face or body hair, acne
- Oedema (swelling of the hands, ankles and feet)
- Nystagmus (rapid, uncontrollable movements of the eyes)
- Tinnitus (buzzing, hissing, whistling, ringing or other persistent noise in the ears), hearing loss
- Headache
- Increased appetite leading to weight gain
- Lack of appetite, weight loss, constipation, increased saliva
- Feeling sick, stomach ache or diarrhoea, especially at the beginning of treatment; this can usually be helped by taking the tablets with or after food (see under 3: “Administration”).
- Temporary hair loss has been noted in some patients. Regrowth normally begins within six months, although the hair may become curlier than before.
- Kidney problems leading to sugar/glucose in the urine and other abnormalities, bedwetting in children, or increased need to pass urine
- Skin changes, e.g. rash.

Other side effects:
- Changes in liver function may occur at the beginning of treatment – detected by a blood test.
- Obesity may rarely occur.
- Nail and nail bed disorders may occur commonly.

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epival CR

Keep out of the sight and reach of children.

Tightly close the container after each use.
Do not use Epival CR after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Epival CR contains

- The active substance is sodium valproate. 1 prolonged-release tablet contains 300 / 500 mg sodium valproate.
- The other ingredients are:
  Tablet core: citric acid monohydrate, ethylcellulose, ammonio methacrylate copolymer (type B) (contains sorbic acid), purified talc, colloidal hydrated silica, magnesium stearate.
  Film-coating: ammonio methacrylate copolymer (type A & B) (contains sorbic acid), purified talc, carmellose sodium, titanium dioxide (E 171), triethyl citrate, vanillin.

What Epival CR looks like and contents of the pack
White, oval-shaped prolonged-release tablets, with score line and engraving "CC3" / “CC5” on one side. The tablets can be divided into equal halves.
Epival CR is available in tablet container of 50 or 100 tablets.

Marketing Authorisation Holder and manufacturer
G.L. Pharma GmbH
Schlossplatz 1
A-8502 Lannach

This leaflet was last updated on 30.12.2015

Reg.no.: PL 21597/0005 (300 mg)
PL 21597/0006 (500 mg)