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

Epival CR (sodium valproate) can seriously harm an unborn child when taken during pregnancy. If you are a female able to have a baby you must use effective method of birth control (contraception) without interruptions during your entire treatment with Epival CR. Your specialist will discuss this with you but you must also follow the advice in section 2 of this leaflet.

Schedule an urgent appointment with your general practitioner (GP) for a referral to a specialist if you want to become pregnant or if you think you are pregnant.

Do not stop taking Epival CR unless your specialist tells you to as your condition may become worse.

If you are a parent or caregiver of a female child treated with Epival CR, you must also read section 2 of this leaflet carefully and contact your child's GP once they experience their first period, the GP will refer your child to their specialist.

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 GP, specialist 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 effects talk to your GP, specialist or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Epival CR is and what it is used for
2. What you need to know before you take Epival CR
3. How to take Epival CR
4. Possible side effects
5. How to store Epival CR
6. Contents of the pack and other information

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

Epival CR belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down. This also belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.

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 can be used
- to treat epilepsy (fits) in adults and children.
  For male patients aged under 55 years not having used valproate before and for female patients aged under 55 years: this medicine is only used when two specialists have agreed that your condition does not respond to other treatments.
- to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).
  Epival CR can be used only if nothing else has worked for 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 of Epival CR (see section 6).
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- if you have liver problems, or you and your family have a history of liver problems, especially if caused by taking a medicine.
- if you have a rare illness called porphyria which affects your metabolism.
- if you have a known metabolic disorder, i.e. urea cycle disorders.
- if you have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).
- if you have a deficiency in carnitine (a very rare metabolic disease) that is untreated.

Bipolar disorder
- For bipolar disorder, you must not use Epival CR if you are pregnant (see 'Pregnancy, breast-feeding and fertility – Important advice for female patients aged under 55 years' below).
- For bipolar disorder, if you are a woman aged under 55 years who is able to have a baby, you must not take Epival CR, unless two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks and you use effective method of birth control (contraception) during your entire treatment with Epival CR. Do not stop taking Epival CR or your contraception, until you have discussed this with your specialist. Your specialist will advise you further (see below under "Pregnancy, breast-feeding and fertility – Important advice for female patients aged under 55 years").

Epilepsy
- For epilepsy, you must not use Epival CR if you are pregnant, unless two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks and (see 'Pregnancy, breast-feeding and fertility – Important advice for female patients aged under 55 years' below)..
- For epilepsy, if you are a woman aged under 55 years who is able to have a baby, you must not take Epival CR unless two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks and you use effective method of birth control (contraception) during your entire treatment with Epival CR. Do not stop taking Epival CR or your contraception, until you have discussed this with your specialist. Your specialist will advise you further (see below under "Pregnancy, breast-feeding and fertility – Important advice for female patients aged under 55 years").

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your GP, specialist or pharmacist before taking Epival CR.

Warnings and precautions

- The risk of liver damage is increased if Epival CR is taken by children under 3 years of age, in people taking other antiepileptic medicine at the same time or having other neurological or metabolic disease and severe forms of epilepsy.
- A small number of people being treated with medicines such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your GP or specialist.
- In patients with epilepsy, convulsions may become worse or happen more frequently whilst taking this medicine. If this happens contact your GP or specialist immediately.
- If you or your child taking Epival CR develops problems with balance and co-ordination, feeling lethargic or less alert, vomiting, tell your GP or specialist immediately. This may be due to increased amount of ammonia in the blood.

Talk to your specialist, GP or pharmacist before taking Epival CR

- if you have a **brain disease** or a metabolic condition affecting your brain.
- if you have **problems with your pancreas.**
- if you have **diabetes** or are being tested for diabetes. This medicine may affect the results of urine tests.
- if you know or your doctor suspects that there is a **genetic problem** caused by a mitochondrial disorder in your family, because of a risk of damage to your liver.
- if you are suspected to suffer from any metabolic disorders, particularly hereditary enzyme deficiency disorders such as a "urea cycle disorder" because of a risk of **increased ammonia level in the blood**.
- if you have a rare disorder named "**carnitine-palmitoyl transferase (CPT-)II deficiency**" because you are at an increased risk of muscle disorders.
- if you have **impaired dietary intake in carnitine**, found in meat and dairy products, especially in children less than 10 years old.
- if you have a **deficiency in carnitine** and are taking carnitine.
- if you have **kidney problems**. Your specialist may monitor your valproate level or adjust your dose.
- if you have an illness called 'systemic lupus erythematosus (SLE)' – a rare disease of the immune system which affects skin, bones, joints and internal organs.

If you are not sure if any of the above apply to you, talk to your GP, specialist or pharmacist before taking Epival CR.

Weight gain
Taking Epival CR may make you put on weight. Talk to your GP, specialist or pharmacist about how this will affect you.

Blood tests
Your GP and/or specialist may request blood tests and liver function tests before and during your treatment with this medicine. Epival CR can change the levels of liver enzymes shown in blood tests. This can mean that your or your child's liver is not working properly.

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 medicines and Epival CR

Tell your GP, specialist or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epival CR can affect the way some other medicines work. Also, some medicines can affect the way Epival CR works.

Please tell your GP, specialist or pharmacist if you are taking any of the following:

- Some medicines used for pain and inflammation (salicylates), e.g. aspirin.
- Some other medicines used to treat fits (epilepsy) – see section 3. This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate.
- Cannabidiol (used to treat epilepsy and other conditions).
- Medicines used to calm emotional and mental health disorders (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine).
- Monoamine oxidase inhibitors (MAOIs) such as moclobemide (used to treat depression and anxiety), selegiline (used to treat Parkinson's disease), linezolid (used to treat infections).
- Anticoagulants, used to thin the blood and prevent clots (e.g. warfarin). Your GP, specialist or pharmacist may change your dose of the blood thinning medicine and monitor your treatment closely.
- Zidovudine and protease inhibitors such as lopinavir and ritonavir - used to treat HIV infection and AIDS.
- Carbapenem agents (antibiotic used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of valproic acid and carbapenems should be avoided because it may decrease the effect of your medicine.
- Some anti-infectives that contain pivalate (e.g., pivampicillin, adefovir dipivoxil).
- Some medicines used to treat or prevent malaria such as mefloquine and chloroquine.
- Temozolomide, used to treat cancer.
- Cimetidine, used to treat stomach ulcers.
- Cholestyramine, used to lower blood fat (cholesterol) levels.
- Nimodipine, used to treat bleeding in the brain (subarachnoid haemorrhage).
- Propofol – used for anaesthesia.
- Oestrogen-containing products (including some birth control pills)
- Metamizole - used to treat pain and fever.
- Methotrexate – used to treat cancer and inflammatory diseases.

Taking Epival CR with food, drink and alcohol

You can take Epival CR with or after food.
Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

Important advice for female patients aged under 55 years

Bipolar disorder

- For bipolar disorder, you must not use Epival CR if you are pregnant.
- For bipolar disorder, if you are a female patient aged under 55 years, you must not take Epival CR unless two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks. If you are able to have a baby, you must use an effective method of birth control (contraception) during your entire treatment with Epival CR.
- Do not stop taking Epival CR or your contraception, until you have discussed this with your specialist. Your specialist will advise you further.

Epilepsy

- For epilepsy, you must not use Epival CR if you are pregnant, unless two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks.
- For epilepsy, if you are a female patient aged under 55 years, you must not take Epival CR unless two specialists have agreed that your condition does not respond to other treatments

and the benefits of treatment outweigh the risks. If you are able to have a baby, you must use an effective method of birth control (contraception) during your entire treatment with Epival CR.
- Do not stop taking Epival CR or your contraception, until you have discussed this with your specialist. Your specialist will advise you further.

The risks of valproate when taken during pregnancy (irrespective of the disease for which valproate is used)
hich valproate is used)
- Contact your GP immediately if you are planning to have a baby or are pregnant. Your GP will urgently refer you to your specialist.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk, including when valproate is used in combination with other medicines to treat epilepsy.
- It can cause serious birth defects and can affect the physical and mental development of the child as it grows after birth and may lead to permanent disability. 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 11 babies in every 100 will have birth defects. This compares to 2 to 3 babies in every 100 born to women from the general population.
  - The most frequently reported birth defects 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 and multiple associated malformations affecting several organs and parts of the body. Birth defects may result in disabilities which may be severe and/or permanent.
  - Hearing problems or deafness have been reported in children exposed to valproate during pregnancy.
  - Eye malformations have been reported in children exposed to valproate during pregnancy in association with other congenital malformations. These eye malformations may affect vision.
- 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).
- Before prescribing this medicine to you, two specialists will have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks, and your specialists 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 baby you must not stop taking your medicine or your method of contraception until you have discussed this with your specialist.
- If you are a parent or a caregiver of a female child treated with valproate, you must contact their GP once your child using valproate experiences their first period (menarche). Their GP will refer your child to their specialist who will decide with another specialist whether valproate is the only possible treatment or whether another medicine should be prescribed.
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your GP, specialist or sexual health and contraception clinic about the method of birth control (contraception) that is the most appropriate for you.
- Ask your specialist 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.

Please choose and read the situations which apply to you from the situations described below:

O I AM STARTING TREATMENT WITH Epival CR
O I AM TAKING Epival CR AND NOT PLANNING TO HAVE A BABY
O I AM TAKING Epival CR AND PLANNING TO HAVE A BABY
O I AM PREGNANT AND I AM TAKING Epival CR

I AM STARTING TREATMENT WITH Epival CR
If you are a female patient aged under 55 years who is able to have a baby, this medicine can only be prescribed for you if two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks. If this is the first time you have been prescribed Epival CR, your specialist will have explained the risks to an unborn child if you become pregnant. If you are able to have a baby, you must use an effective method of birth control (contraception) without interruption throughout your treatment with Epival CR. Talk to your GP, specialist or sexual health and contraception clinic if you need advice on birth control (contraception).

Key messages:
- Pregnancy must be excluded before start of treatment with Epival CR with the result of a pregnancy test, confirmed by your specialist.
- You must use an effective method of birth control (contraception) during your entire treatment with Epival CR.
- You must discuss the appropriate methods of birth control (contraception) with your GP or specialist. Your GP or specialist 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 the management of bipolar disorder or epilepsy. During this visit your specialist will reassess whether you should continue receiving treatment with valproate or whether another medicine should be prescribed. The specialist will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your specialist if you want to have a baby.
- Tell your specialist immediately if you are pregnant or think you might be pregnant.

I AM TAKING Epival CR AND NOT PLANNING TO HAVE A BABY
If you are a female patient aged under 55 years who is able to have a baby, this medicine can only be prescribed for you if two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks. If you are continuing treatment with Epival CR and you are not planning to have a baby make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with Epival CR. Talk to your GP, specialist or sexual health and contraception clinic if you need advice on birth control (contraception).

Key messages:
- You must use an effective method of birth control (contraception) during your entire treatment with Epival CR.
- You must discuss contraception (birth control) with your GP or specialist. They 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 the management of bipolar disorder or epilepsy. During this visit your specialist will reassess whether you should continue receiving treatment with valproate or whether another medicine should be prescribed. They will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your GP or specialist if you want to have a baby.
- Tell your specialist, or GP to be urgently referred to your specialist, immediately if you are pregnant or think you might be pregnant.

I AM TAKING Epival CR AND PLANNING TO HAVE A BABY

If you are planning to have a baby, first schedule an appointment with your GP. Your GP will urgently refer you to your specialist.

Do not stop taking Epival CR or your contraception, until you have discussed this with your specialist. Your specialist will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development (behaviour and learning disorders) which can be seriously debilitating and/or permanent. Your GP will refer you to a specialist experienced in the management of bipolar disorder or epilepsy, so that other treatment options can be evaluated early on. Your specialist 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.

For epilepsy: You must not use Epival CR if you are pregnant, unless two specialists have agreed that your condition does not respond to other treatments and the benefits of treatment outweigh the risks. Your specialist may decide to change the dose of Epival CR, switch you to another medicine and stop treatment with Epival CR, a long time before you become pregnant – this is to make sure your illness is stable.

For bipolar disorder: You must not use Epival CR if you are pregnant. Your specialist may decide to switch you to another medicine and stop treatment with Epival CR, a long time before you become pregnant – this is to make sure your illness is stable.

Ask your specialist about taking folic acid when planning to have 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 taking Epival CR unless your specialist tells you to.
- Do not stop using your methods of birth control (contraception) before you have talked to your specialist 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 specialist. During this visit your specialist will reassess whether you should continue receiving treatment with valproate or whether another medicine should be prescribed They will make sure you are well aware and have understood all the risks and advices related to the use of valproate during pregnancy.
- Your specialist will try to switch you to another medicine or stop treatment with Epival CR a long time before you become pregnant.
- Schedule an urgent appointment with your GP to be urgently referred to your specialist, immediately if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING Epival CR

Do not stop taking Epival CR, unless your specialist tells you to as your condition may become worse. Schedule an urgent appointment with your GP. Your GP will refer you immediately to your specialist if you are pregnant or think you might be pregnant. Your specialist will then advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development (behaviour and learning disorders) which can be seriously debilitating and/or permanent.

Your GP will refer you to your specialist experienced in the management of bipolar disorder or epilepsy, so that other treatment options can be evaluated.

For epilepsy only: In the exceptional circumstances when two specialists have agreed that Epival CR is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing. You and your partner could receive counselling and support regarding the valproate exposed pregnancy.

Ask your specialist 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 GP. Your GP will refer you immediately to your specialist, if you are pregnant or think you might be pregnant. Your specialist will then advise you further.
- Do not stop taking Epival CR unless your specialist 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 other treatment options.
- You must get thorough counselling on the risks of Epival CR during pregnancy, including malformations and physical and mental development disorders in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

Make sure you read the patient guide that you will receive from your specialist, GP or pharmacist. If you are a female of childbearing potential, your specialist will discuss and complete the Annual Risk Acknowledgement Form with you and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

Newborn babies of mothers who took valproate during pregnancy may have:
- Blood clotting problems (such as blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar).
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

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

Important advice for male patients
- If you are a male aged under 55 years, before prescribing this medicine to you for the first time, two specialists will have agreed that your condition does not respond to other treatments or the risk to fertility does not apply to you.
- Your specialist will have explained to you the known risk of male infertility (see section 4) and the potential risk in children born to fathers treated with valproate.
- If you are a parent or a caregiver of a male child treated with valproate, a specialist will explain to you that there are studies showing toxic effects of valproate on the testes of animals receiving the medicine and it is unclear what this means for humans.

Potential risks related to taking valproate in the 3 months before conception of a child

A study suggests a possible risk of mental and movement related developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known. The study has limitations and therefore it is not clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. The study was not

large enough to show which particular type of movement and mental developmental disorder children may be at risk of developing.

As a precautionary measure, your GP or specialist will discuss with you:
- The potential risk in children born to fathers treated with valproate
- The need to use effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment
- The need to consult your specialist when you are planning to conceive a child and before stopping contraception (birth control)
- The possibility of other treatments that can be used to treat your disease, depending on your individual situation

Do not donate sperm when taking valproate or for 3 months after stopping valproate.

Talk to your GP or specialist if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your GP or specialist. Do not stop your treatment without talking to your GP or specialist. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your GP. During this visit your GP will discuss with you the precautions associated with valproate use. They will refer you to a specialist to discuss the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the Patient Guide that you will receive from your specialist, GP or pharmacist. If you are a male aged under 55 years starting treatment with valproate, your specialist will discuss and complete a risk acknowledgement form with you and will ask you to sign it and keep it.

Driving and using machines
You may feel sleepy when taking Epival CR. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

Epival CR contains sodium

Epival CR 300 mg prolonged-release tablets
This medicine contains 42 mg sodium (main component of cooking/table salt) in each prolonged-release tablet. This is equivalent to 2.1 % of the recommended maximum daily dietary intake of sodium for an adult.

Epival CR 500 mg prolonged-release tablets
This medicine contains 70 mg sodium (main component of cooking/table salt) in each prolonged-release tablet. This is equivalent to 3.5 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Epival CR

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

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

Your specialist will decide how much Epival CR to give you or your child depending on your or your child's body weight. If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your GP or specialist.

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

Epilepsy:

Monotherapy *(epilepsy treatment with sodium valproate only)*

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 specialist.

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, or 1½ tablets of 500 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 kidney problems
Your specialist may decide to adjust your or your child's dose.

Patients taking other medicines for fits (epilepsy)
You or your child may be taking other medicines for epilepsy at the same time as Epival CR. If so, your specialist should gradually initiate treatment depending on your or your child's condition. Your doctor may increase the dose of Epival CR by 5–10 mg for each kg of body weight each day depending on which other medicines you are taking.

Mania:

The daily dosage should be established and controlled individually by your specialist.

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.

Patients with kidney problems
Your specialist may decide to adjust your dose.

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 than you should

If you or your child take more tablets than you should, contact your GP or specialist urgently or go to a hospital casualty department immediately. Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: feeling sick or being sick, headache, blurred vision due to pupil of the eye becoming smaller, dizziness, poor reflexes, confusion, memory loss and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Epival CR

If you or your child forgot to take a dose, 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 stop taking Epival CR or alter your or your child's dose without consulting your specialist. If you or your child stop taking Epival CR without your specialist's advice, your condition may get worse.

Tests
Make sure you or your child keep your regular appointments for a check-up. They are very important as your or your child's dose may need to be changed. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epival CR.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Tell your GP, specialist or go to a hospital straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:

- Signs including 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.
- Vomiting, problems with balance and coordination and feeling lethargic or less alert may be signs of an increased amount of ammonia in the blood.
- Deep loss of consciousness (coma) may occur in very few patients.
- 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 may be signs of Liver problems and problems of the pancreas.
- Increased tendency to bleed, or if you seem to get bruises or infections more easily.

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).
- Double vision (rare).

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.

The following side effects have been reported:

Very common (may affect more than 1 in 10 people):
- uncontrolled trembling or shaking movements in one or more parts of your body (tremor)
- nausea

Common (may affect up to 1 in 10 people):
- isolated, moderate hyperammonaemia (increased levels of ammonia in the blood without abnormal liver test values)
- especially in case of excessively high doses, treatment with valproate may cause transitory anomalies of the blood count or blood clotting disturbances
- lack of enough red blood cells (anaemia)
- weight gain
- decreased sodium levels in the blood (hyponatraemia)
- seeing or sensing things that aren't there while a person is awake and conscious (such as hearing voices)
- confusional state
- aggression
- agitation
- disturbance in attention
- tickling/tingling sensation or numbness, trembling
- movement disorders due to impaired regulation of muscle coordination in the brain (so-called extrapyramidal symptoms; stupor)
- sleepiness, the state of feeling drowsy, ready to fall asleep
- trouble with memory
- convulsions (fits)
- headache
- twitching of the eyes (nystagmus)
- partly reversible tinnitus and partly reversible impairment of hearing
- increased bleeding
- vomiting, diarrhoea, lack of appetite or constipation may occur at the beginning of treatment
- gingival disorder, especially gingival hyperplasia
- stomach ache (gastralgia)
- swelling of gums or mouth, sore mouth, mouth ulcers and burning feeling of mouth (stomatitis)
- hypersensitivity reactions
- nail and nail bed disorders
- transient hair loss
- severe abdominal cramps during a women's period
- urinary incontinence (unintentional passing of urine)
- liver injury

Uncommon (may affect up to 1 in 100 people):
- reduced number of blood platelets (especially in children), transitorily severely reduced number of white blood cells (leucopenia)
- severe reduction in all blood cells which can cause weakness, bruising or make infections more likely (pancytopenia)
- increased formation of “antidiuretic” hormone (leading to increased build-up of fluid in tissue) (Syndrome of inappropriate antidiuretic hormone secretion (SIADH))
- excessive levels of androgens in the female body (hyperandrogenaemia)
- acne and excessive growth of facial or body hair
- hair disorder (e.g. altered hair texture, change of hair colour, abnormal hair growth), transient hair loss
- unconscious state
- continual tightening and contraction of certain muscles resulting in problems walking and talking

- loss of muscle coordination; awkward, uncoordinated walking unsteadiness when walking
- abnormal brain function
- lethargy (occasionally followed by disturbed consciousness and sometimes associated with hallucinations or convulsions)
- reversible parkinsonism (tremor, stiffness and shuffling)
- aggravated convulsions
- pain, reddening or itching of the skin, which may be signs of an inflammation of the blood vessels (vasculitis)
- collection of fluid around the lungs in the chest cavity, which can cause shortness of breath and may require treatment
- inflammation of the pancreas, which may take a life-threatening course (see section 2. under "Other things you should know before taking Epival CR").
- severe liver damage, sometimes taking a fatal course (see section 2. "Other things you should know before taking Epival CR")
- rash
- bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your GP, specialist or pharmacist if you are on long-term anti-epileptic medication, have a history of osteoporosis, or take steroids.
- kidney disorder (renal insufficiency)
- absence of menstrual period in women
- low body temperature
- peripheral oedema (accumulation of fluid in tissue)

Rare (may affect up to 1 in 1,000 people):
- decreased production of blood cells by the bone marrow (including pure red cell aplasia, agranulocytosis, macrocytic anaemia, macrocytosis)
- abnormally low level of thyroid gland hormone
- vomiting, disturbed coordination of movements and progressive clouding of consciousness may be signs of increased ammonia levels in the blood. If such symptoms occur, consult a doctor immediately.
- obesity
- hyperactivity
- abnormal behavior
- learning disorder
- reversible dementia
- loss of neurons and the connections between them
- cognitive impairment
- double vision
- potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer; Stevens-Johnson syndrome)
- life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer; Toxic Epidermal Necrolysis)
- severe reaction of the skin and gut lining that may include rash and shedding or death of tissue (erythema multiforme)
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)
- systemic lupus erythematosus (a rare immune disorder)
- allergic painful swelling of skin and mucous membranes, particularly in the face
- breakdown of damaged skeletal muscle (rhabdomyolysis)
- enuresis (involuntary discharge of urine)
- inflammation of the spaces between renal tubules (tubulo-interstitial nephritis)
- reversible failure of the tubules in the kidney to reabsorb small molecules, passing a lot of urine and feeling thirsty (Fanconi syndrome)
- male infertility
- changes on the ovaries and menstrual irregularities in women (polycystic ovarian syndrome)

- abnormal blood clotting
- abnormal coagulation tests
- porphyria (a rare metabolic disease)

Very rare (may affect up to 1 in 10,000 people):
- increased breast growth in men
- transient brain affection or loss of consciousness; if you notice any of these or similar symptoms, contact a specialist as quickly as possible.

Not known (frequency cannot be estimated from the available data):
- depressed states
- increase in alertness
- decrease in carnitine levels (shown in blood or muscular tests)

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

Tests
Epival CR can change levels of liver enzymes, blood clotting factors, salts or sugars shown up on blood and urine tests.

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), bedwetting (enuresis), renal disfunction (Fanconi Syndrome), overgrowth of gum tissue, aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity and learning disorder.

Reporting of side effects
If you get any side effects, talk to your GP, specialist or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 30, 50 or 100 tablets.

Not all pack sizes may be marketed.

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

This leaflet was last updated in July 2024.

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

The following information is intended for healthcare professionals only:

Overdose

Symptoms
Cases of accidental and deliberate valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However, some deaths have occurred following massive overdose.

However, the symptoms may be variable and seizures have been reported in the presence of very high plasma levels in patients with epilepsy (see section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Epival CR formulations may lead to hypernatraemia when taken in overdose.

Management
Hospital management of overdose should be symptomatic, including cardio-respirato-gastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalize ammonia levels.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.