Package leaflet: Information for the patient

[QR code to be included:]
https://www.medicines.org.uk/emc/product/324/rmms

▼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.

Episenta 150 mg prolonged-release capsule
Episenta 300 mg prolonged-release capsule
(sodium valproate)
(Referred to in this leaflet as Episenta)

WARNING

Episenta, 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 Episenta. 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 Episenta 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 Episenta, 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 seem the same as yours.
- If you get any 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 Episenta is and what it is used for
2. What you need to know before you take Episenta
3. How to take Episenta
4. Possible side effects
5. How to store Episenta
6. Contents of the pack and other information

1. What Episenta is and what it is used for

Episenta contains the active substance sodium valproate, which belongs to a group of medicines called antiepileptics which are used to control epileptic seizures and mania.

Episenta is used in the treatment of
- various types of epilepsy (seizures)
- mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder". Episenta can be used only if nothing else has worked for you.

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.

2. What you need to know before you take Episenta

Do not take Episenta
- if you are allergic to sodium valproate or any of the other ingredients of this medicine (listed in section 6)
- if you, or a member of your family, have or have had severe liver problems
- if you suffer from a disease called porphyria (a rare condition that affects the breakdown of components of red blood cells)
- if you have a known metabolic disorder, i.e. a urea cycle disorder
- if you have a genetic problem causing 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 Episenta if you are pregnant.
- For bipolar disorder, if you are a woman aged under 55 years who is able to have a baby, you must not take Episenta, 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) at all times during your entire treatment with Episenta. Do not stop taking Episenta 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 women").

Epilepsy
- For epilepsy, do not use Episenta 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 (see 'Pregnancy, breast-feeding and fertility – Important advice for women' below).
- For epilepsy, if you are a woman aged under 55 years who is able to have a baby, you must not take Episenta 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) at all times during your entire treatment with Episenta. Do not stop taking Episenta 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 women").

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 Episenta.

Warnings and precautions

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema have been reported in association with valproate treatment. Seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

The risk of liver damage is increased if Episenta 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 antiepileptics 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.

As with other antiepileptic drugs, 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 Episenta develops problems with balance and co-ordination, feeling lethargic or less alert, vomiting, tell your doctor immediately. This may be due to increased amount of ammonia in the blood.

Talk to your GP, specialist or pharmacist before taking Episenta if:
- you have a brain disease or a metabolic condition affecting your brain.
- you have problems with your pancreas.
- you have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests.
- 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.
- you are suspected to suffer from any metabolic disorders, particularly hereditary enzyme deficiency disorders such as “urea cycle disorder” because of a risk of increased ammonia level in the blood.
- you have a rare disorder named ‘carnitine palmitoyltransferase type II deficiency’, because you are at an increased risk of muscle disorders.
- you have impaired dietary intake in carnitine, found in meat and dairy products, especially in children less than 10 years old.
- you have a deficiency in carnitine and are taking carnitine.
- you have kidney problems. Your specialist may monitor your valproate level or adjust your dose.
- 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 have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking valproate.

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

Weight gain
Taking Episenta 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 before you start taking Episenta and during your treatment with this medicine. Episenta 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

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

Other medicines and Episenta
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 Episenta can affect the way some other medicines work. Also some medicines can affect the way Episenta works.

<u>The following medicines can increase the chance of you getting side effects, when taken with Episenta:</u>
- some medicines used for pain and inflammation (salicylates) such as aspirin
- some other medicines used to treat fits (epilepsy) – see section 3, 'Patients taking other medicines for fits'. This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, lamotrigine and felbamate.
- cannabidiol (used to treat epilepsy and other conditions).
- acetazolamide used to treat glaucoma, edema or fits
- some anti-infectives that contain pivalate (e.g., pivampicillin, adefovir dipivoxil).
- clozapine (to treat mental health conditions)

<u>Episenta may increase the effect of the following medicines:</u>
- medicines used for thinning the blood (such as warfarin)
- zidovudine used to treat HIV infection
- temozolomide used to treat cancer
- medicines for depression
- monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine
- nimodipine
- propofol – used for anaesthesia

<u>The following medicines can affect the way Episenta works:</u>
- oestrogen-containing products (including some birth control pills)
- some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- cimetidine used for stomach ulcers
- protease inhibitors such as lopinavir and ritonavir – used for HIV infection and AIDS
- antibiotics e.g. erythromycin, carbapenem agents (antibiotics used to treat bacterial infections). The combination of valproic acid and carbapenems should be avoided because it may decrease the effect of sodium valproate.
- rifampicin used to treat tuberculosis and other infections
- cholestyramine used to lower blood fat (cholesterol) levels
- metamizole – used to treat pain and fever
- methotrexate – used to treat cancer and inflammatory diseases.

It may still be possible for you to take Episenta; your doctor will advise you on what is suitable for you.

Taking Episenta with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Important advice for female patients aged under 55 years

Bipolar disorder

- For bipolar disorder, you must not use Episenta if you are pregnant.
- For bipolar disorder, if you are a female patient aged under 55 years, you must not take Episenta, 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) at all times during your entire treatment with Episenta. Do not stop taking Episenta or your birth control (contraception), until you have discussed this with your specialist. Your specialist will advise you further.

Epilepsy

- For epilepsy, you must not use Episenta 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 Episenta 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) at all times during your entire treatment with Episenta. Do not stop taking Episenta or your birth control (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)

- 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 2–3 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 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.
    - Autism and related disorders are more often diagnosed in children exposed to valproate during pregnancy, and there is some evidence that children exposed to valproate during pregnancy are at increased risk of developing Attention Deficit Hyperactivity Disorder (ADHD).

- If you take valproate during pregnancy, your baby may have a lower weight than expected for their age at birth.
- 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 birth control (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 should contact the 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 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.

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

0 I AM STARTING TREATMENT WITH EPISENTA

0 I AM TAKING EPISENTA AND NOT PLANNING TO HAVE A BABY

0 I AM TAKING EPISENTA AND PLANNING TO HAVE A BABY

0 I AM PREGNANT AND I AM TAKING EPISENTA

I AM STARTING TREATMENT WITH EPISENTA

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 Episenta, 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) at all times during your entire treatment with Episenta. 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 Episenta 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 Episenta.
- 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.
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.
- 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 of 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 EPISENTA 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 Episenta and you are not planning to have a baby, you must use an effective method of birth control (contraception) at all times during your entire treatment with Episenta. 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 Episenta.
- You must discuss appropriate and effective methods of birth control (contraception) 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 (contraception).
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.
- 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 advices 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 EPISENTA 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 Episenta or your birth control (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 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 are 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 Episenta 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 Episenta, switch you to another medicine and stop treatment with Episenta, a long time before you become pregnant – this is to make sure your illness is stable.

For bipolar disorder: You must not use Episenta if you are pregnant. Your specialist may decide to switch you to another medicine and stop treatment with Episenta 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 Episenta 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 Episenta 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 EPISENTA

Do not stop taking Episenta, 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 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 Episenta 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 Episenta 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 Episenta 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.

Breast-feeding
Very little Episenta 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 Possible side effects) and the potential risk in children born to fathers treated with valproate.
- If you are a parent or 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 Episenta. If this happens, 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.

Episenta contains sodium
Episenta 150 mg: This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.
Episenta 300 mg: This medicine contains 41.4 mg sodium (main component of cooking/table salt) in each capsule. This is equivalent to 2 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Episenta

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

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

Dosage

Epilepsy
Your specialist will decide the number of capsules you should take. This will depend on your age and weight and will be adjusted to achieve adequate control of your seizures.
The daily dosage may be taken as one single or two divided doses (half in the morning and half in the evening).

Dose for adults including the elderly
The recommended starting dose is 600 mg daily increasing by 150–300 mg every three days until the seizures are controlled.
This dose is usually within the range of 1,000 mg to 2,000 mg daily, but can be increased to a maximum of 2,500 mg daily if necessary. Your specialist may alter your dose if you are taking other antiepileptic drugs, have poor kidney function or you are an elderly patient.

Dose for children and adolescents
The dose for children will depend on their weight:
For children over 20 kg the recommended starting dose is 300 mg daily. This can be increased up to a maximum of 35 mg for each kg of bodyweight daily to control the seizures.
For children under 20 kg the usual dose is 20 mg for each kg of bodyweight which can be increased up to a maximum of 40 mg for each kg of bodyweight daily.

Manic episodes in bipolar disorder

Adults

The daily dosage should be established and controlled individually by your specialist. Initial dose: The recommended initial daily dose is 750 mg. Mean daily dose: The recommended daily doses usually range between 1,000 mg and 2,000 mg.

Method of administration
The capsules should be swallowed whole without chewing with plenty of liquid, e.g. a full glass of water. If you have difficulty in swallowing, the contents of the capsule may be sprinkled or stirred into soft food or drinks and swallowed immediately without chewing or crushing the granules. The food or drink should be cold or at room temperature. A mixture of the granules with liquid or soft food should not be stored for future use. If the granules are taken in a drink, some may stick to the glass after the drink has been finished, you should rinse the glass with a small amount of water and drink this as well. The granules should not be given in babies' bottles as they can block the teat.

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

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

If you take more Episenta than you should
If you or your child take more Episenta 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 Episenta
If you or your child forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Episenta
Do not stop taking Episenta or alter your or your child's dose without checking with your specialist. If you or your child stop stop taking Episenta 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. Episenta can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Episenta.

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

4. Possible side effects

Like all medicines this medicine can cause side effects, although not everybody gets them.

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:

- You have an allergic reaction which may manifest as:
  - Blisters with skin detachment (blistering, peeling or bleeding on any part of your skin (including your lips, eyes, mouth, nose, genitals, hands or feet) with or without rash), sometimes with flu-like symptoms such as fever, chills, or aching muscles. These may be signs of conditions named 'Toxic epidermal necrolysis' or 'Stevens-Johnson Syndrome'.
  - Skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These may be signs of a condition named 'erythema multiforme'.
  - Allergy-triggered swelling with painful itchy welts (most often around the eyes, lips, throat and sometimes hands and feet) and swallowing or breathing problems. These may be signs of 'angioedema' or an anaphylactic reaction.
  - Syndrome with skin rash, fever, lymph node enlargement and possible impairment of other organs. These may be signs of a condition named 'Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)'.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Episenta. It includes feeling sick (nausea) and being sick (vomiting) many times; extreme tiredness, drowsiness and weakness; stomach pain including severe upper stomach pain; yellowing of the skin or whites of the eyes (jaundice); loss of appetite; swelling of the legs and feet (may include other parts of the body); worsening of your fits or a general feeling of being unwell. Your doctor may tell you to stop taking Episenta immediately if you have these symptoms.
- Blood disorders that can be shown in blood tests. Signs may include:
  - Spontaneous bruising or bleeding due to blood clotting problems or decreased platelet count, or getting more infections than usual (thrombocytopenia).
  - Severe decrease of white blood cells or bone marrow failure, sometimes revealed by fever and breathing difficulty (agranulocytosis).
  - Decreased red blood cell count (anaemia) or abnormally increased red blood cell size (macrocytosis).
  - Bone marrow disorders that affect red blood cells, white blood cells and platelets (pancytopenia).
- Drowsiness, change in consciousness level (including coma), confusion, loss of memory, abnormal behaviour including changes in attention, concentration and mood. This could also be associated with hallucinations or more frequent or severe fits. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Episenta starting dose is high or has been suddenly increased.
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism).
- Difficulty breathing, pain or pressure in the chest chest (especially when breathing in), shortness of breath and dry cough due to buildup of fluid around the lungs (pleural effusion)
- An increase in the number and severity of convulsions.
- Muscle pain and weakness (rhabdomyolysis).
- Joint pain, fever, fatigue or rash. These may be signs of systemic lupus erythematosus (SLE).
- Problems with balance and co-ordination, feeling lethargic or less alert, associated with being sick (vomiting). This may be due to an increased amount of ammonia in your blood.
- Shakiness (tremor), jerky muscle movements, unsteadiness when walking (parkinsonism, extrapyramidal disorder, ataxia).
- Rapid, uncontrollable movement of the eyes.
- Kidney disease or kidney problems (renal failure, tubulointerstitial nephritis and Fanconi syndrome) which may manifest as reduced urinary output or blood in the urine.

- Confusion, that could be due to decreased levels of sodium in your blood, identified by a blood test, or to a condition named 'Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion'.

Tell your GP, specialist or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:

- Feeling sick (nausea), being sick (vomiting), stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the capsules with food.
- Overgrowth of gums (gingival hypertrophia), swelling of gums, sore mouth, mouth ulcers and burning feeling of mouth (stomatitis)
- Headache
- Hearing loss, hearing problems or deafness
- Double vision
- Nail and nail bed disorders
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine.
- Transient hair loss, abnormal hair growth, abnormal hair texture, changes in hair colour
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest (particularly in women), acne or thinning hair.
- Skin rash caused by inflammation of small blood vessels (vasculitis)
- Irregularity or absence of women's period, pain during women's period, cysts in the ovaries (polycystic ovaries)
- Breast enlargement in men, male infertility (usually reversible after treatment discontinuation and may be reversible after dose reduction. Do not stop your treatment without speaking to your specialist first.)
- Swelling of the feet and legs (oedema)
- Obesity, weight gain – as your appetite may be increased
- Kidney disease, kidney problems, blood in the urine, bedwetting or increased need to pass urine, unintentional passing of urine (urinary incontinence)
- Passing a lot of urine and feeling thirsty (Fanconi syndrome)
- Decrease in carnitine levels (shown in blood or muscular tests)
- Seeing, feeling or hearing things that are not there (hallucinations)
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, memory impairment, or cognitive or learning disorder
- Tingling or numbness in the hands and feet
- Lowering of normal body temperature
- Darker areas of skin and mucosae (hyperpigmentation)

<u>Bone disorders</u>
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.

<u>Tests</u>
Episenta can change levels of liver enzymes, blood clotting factors, salts or sugars shown up on blood and urine tests.

You may notice the remains of the white shells of the granules in your stools (faeces). This is normal and the active part of the medicine will already have been released from the granule.

<u>Additional side effects in children</u>

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 dysfunction (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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search 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 Episenta

Keep this medicine out of the sight and reach of children.
Store the capsules in the original package.
Store below 25 °C.
Keep the container tightly closed.
Do not use this medicine after the expiry date which is stated on the container label and carton after "Expiry date:". The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater. 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 Episenta contains
- The active substance is sodium valproate.
- The other ingredients are calcium stearate, colloidal anhydrous silicon dioxide (methylated), ammonio methacrylate copolymer type B, sorbic acid, sodium hydroxide, ethyl cellulose, dibutyl sebacate, oleic acid, gelatin, sodium lauryl sulfate, indigo carmine (E 132) and (for 300 mg capsules only) quinoline yellow (E104).

What Episenta looks like and contents of the pack
Episenta 150 mg capsules are blue/transparent hard gelatine capsules containing white granules.
Episenta 300 mg capsules are green/transparent hard gelatine capsules containing white granules.
Each pack contains 30, 50, 100 or 200 capsules.
Not all pack sizes may be marketed.

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