

Episenta

prolonged-release capsules and granules

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Episenta® 150 mg Prolonged-release Capsule and
Episenta® 300 mg Prolonged-release Capsule
Episenta® 500 mg Prolonged-release Granules and
Episenta® 1000mg Prolonged-release Granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release capsule contains sodium valproate 150 mg or 300 mg

Each sachet of prolonged-release granules contains sodium valproate 500 mg or 1000mg

For excipients see 6.1

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

150 mg - Blue and transparent capsule containing white or almost white, round, film-coated prolonged-release granules.

300 mg - Green and transparent capsule containing white or almost white, round, film-coated prolonged-release granules.

Prolonged-release granules.

White or almost white, round, film-coated prolonged-release granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sodium valproate is used in the treatment of all forms of epilepsy.

4.2 Posology and method of administration

Dosage requirements vary according to age and body weight and should be adjusted individually to achieve adequate seizure control. The daily dosage should be given in 1 – 2 single doses.

Monotherapy: usual requirements are as follows:

Adults: Dosage should start at 600mg daily increasing by 150-300mg at three day intervals until control is achieved. This is generally within the dosage range of 1000mg to 2000mg per day i.e. 20-30mg/kg body weight daily. Where adequate control is not achieved within this range the dose may be further increased to a maximum of 2500mg per day.

Children over 20kg: Initial dosage should be 300mg/day increasing until control is achieved. This is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body weight per day.

Children under 20kg: 20mg/kg body weight per day; in severe cases this may be increased up to 40mg/kg/day.
Use in the elderly: Care should be taken when adjusting dosage in the elderly since the pharmacokinetics of sodium valproate are modified. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels. Dosage should be determined by seizure control.

In patients with renal insufficiency: It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

Combined Therapy: In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with liver enzyme inducing drugs such as phenytoin, phenobarbital and carbamazepine. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

Method of administration

For oral administration.

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

When changing from sodium valproate enteric coated tablets to Episenta® it is recommended to keep the same daily dose.

4.3 Contraindications

Active liver disease.

Personal or family history of severe hepatic dysfunction, especially drug related.

Porphyria.

Hypersensitivity to valproate or any of the excipients.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the

available data do not exclude the possibility of an increased risk for sodium valproate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Hepatic dysfunction :

Conditions of occurrence:

Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsants therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age. The concomitant use of salicylates should be avoided in children under 3 due to the risk liver toxicity. Additionally, salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Episenta®, but the potential benefit of Episenta® should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: Conditions of occurrence):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures

These are an indication for immediate withdrawal of the drug.

Patients (or their carers), should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:

Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem at risk, and those with a prior history of liver disease. Amongst usual

investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decreases in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) require cessation of Episenta® therapy. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway. As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:

Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Episenta® should be discontinued.

Haematological:

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding. (see section 4.8 Undesirable effects).

Renal insufficiency:

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

Systemic lupus erythematosus:

Although immune disorders have only rarely been noted during the use of sodium valproate, the potential benefit of Episenta® should be weighed against its potential risk in patients with systemic lupus erythematosus (see section 4.8 Undesirable effects).

Hyperammonaemia:

When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of risk of hyperammonaemia with sodium valproate.

Weight gain:

Sodium valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable effects)

Pregnancy:

Women of childbearing potential should not be started on Episenta® without specialist neurological advice. Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see section 4.6 Pregnancy and lactation).

Diabetic Patients:

Sodium valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies: this may give false positive in the urine testing of possible diabetics.

Granules in Stools:

The prolonged-release granules are surrounded by an indigestible cellulose shell through which the sodium valproate is released and these shells will be seen as white residues in the stools of the patient. There are no safety issues concerning such residues.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Episenta® on other drugs

Like many other drugs, Episenta® may potentiate the effect of other psychotropics, such as antipsychotics, monoamine oxidase inhibitors, antidepressants and benzodiazepines. Therefore, clinical monitoring and the dosage of other psychotropics should be adjusted when appropriate.

Sodium valproate increases phenobarbital plasma concentrations and sedation may occur, particularly in children. Clinical monitoring is recommended throughout the first 15 days of combined treatment with an immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital levels when appropriate.

Sodium valproate increases primidone plasma levels causing an exacerbation of side effects, e.g. sedation. Clinical monitoring is recommended especially when initiating combined therapy with dosage adjustment as necessary.

Phenytoin total plasma levels are decreased by sodium valproate acid; the free form of phenytoin is increased leading to possible overdosage symptoms. Therefore, clinical monitoring is recommended with the free form of phenytoin being measured.

The toxic effects of carbamazepine may be potentiated by sodium valproate requiring clinical monitoring and dosage adjustment particularly at initiation of combined therapy.

Sodium valproate may reduce lamotrigine metabolism and increase its mean half-life. The dosage of lamotrigine should be decreased as necessary. The risk of rash is increased in combined therapy with lamotrigine.

Sodium valproate may raise zidovudine plasma concentrations leading to increased zidovudine toxicity. The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from the plasma protein binding site by valproate. The prothrombin time should be closely monitored.

4.5.2 Effects of other drugs on Episenta®

Antiepileptics with enzyme inducing effects e.g. phenytoin, phenobarbital, carbamazepine, decrease valproate plasma levels. Plasma levels should be monitored and dosage adjusted accordingly. Mefloquine and chloroquine increases valproate metabolism and therefore epileptic seizures may occur in combined therapy. The dosage of sodium valproate may need adjustment.

Free valproate levels may be increased in the case of concomitant use with highly protein bound agents e.g. acetylsalicylic acid. Valproate plasma levels may also be increased when used concomitantly with cimetidine or erythromycin as a result of reduced hepatic metabolism.

Carbapenem antibiotics such as imipenem and meropenem decrease plasma valproate levels. If administering these antibiotics with sodium valproate close monitoring of valproate plasma levels is recommended.

Colestyramine may decrease the absorption of valproate.

The effect of hormonal contraceptives (“the pill”) is not reduced by sodium valproate.

Caution is advised when using Episenta® in combination with newer antiepileptics whose pharmacodynamics may not be well established.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

Risk associated with epilepsy and antiepileptics

In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3%) reported in the general population. Although an increased number of children with malformations have been reported in cases of multiple drug therapy, the respective role of treatments and disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardiovascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Developmental delay has been reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

Risks associated with valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: valproate is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. An increased incidence of major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers with epilepsy treated with valproate. Some data from studies of women with epilepsy, have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.

In view of the above data

When a woman is planning pregnancy, this provides an opportunity to review the need for antiepileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, woman should be advised to start taking folic acid supplementation (5 mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsants monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000 mg daily. The administration in several divided doses over the day and the use of a prolonged release

formulation is preferable in order to avoid high peak plasma levels.

During pregnancy, Episenta® antiepileptic treatment should not be discontinued if it has been effective.

Nevertheless, specialist prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation.

Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special warnings and special precautions for use).

Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenaemia; afibrinogenaemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other antiepileptic enzyme inducing drugs. Therefore platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of valproate in breast milk is low, with a concentration between 1% to 10% of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contraindications to breast feeding by patients on Episenta®.

4.7 Effects on ability to drive and use machines

Use of Episenta® may provide seizure control such that the patient may be eligible to hold a driving licence. At the start of treatment with sodium valproate, at higher dosages or with a combination of other centrally acting drugs, reaction time may be altered to an extent that affects the ability to drive or to operate machinery, irrespective of the effect on the primary disease being treated. Patients should be warned of the risk of transient drowsiness. This is especially the case when taken during anticonvulsant polytherapy, concomitant use of benzodiazepines or in combination with alcohol.

4.8.1 Undesirable effects

Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and lactation)

Hepato-biliary disorders:

Rare cases of hepatic dysfunction (see section 4.4 Special warnings and precautions for use). Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been reported (see sections 4.2 (Posology and method of administration, 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Increased liver enzymes are common, particularly early

in treatment, and may be transient (see section 4.4 Special warnings and precautions for use).

Gastro-intestinal disorders: (nausea, gastralgia, diarrhoea)

Frequently occur at the start of the treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Episenta® with or after food.

Very rare cases of pancreatitis, sometimes fatal, have been reported (see section 4.4 Special warnings and precautions for use).

Nervous system disorders:

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with a too high starting dose or a too rapid dose escalation or concomitant use of other anticonvulsants, notably phenobarbital. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur, this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders:

Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Episenta® should be discontinued. Very rare cases of hyponatraemia have been reported. Hyperammonaemia associated with neurological symptoms have also been reported (see section 4.4 Special warnings and precautions for use). In such cases further investigation should be considered.

Blood and lymphatic system disorders:

Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation).

Spontaneous bruising or bleeding is an indication of withdrawal of medication pending investigations (see section 4.6 Pregnancy and lactation).

Skin and subcutaneous disorders:

Cutaneous reactions such as exanthematous rash rarely occur with sodium valproate. In very rare cases, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported. Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within 6 months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders:

Amenorrhoea and irregular periods have been reported. Very rarely gynaecomastia has occurred

Vascular disorders:

The occurrence of vasculitis has occasionally been reported.

Ear disorders:

Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders:

There have been isolated reports of reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with sodium valproate therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders:

Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders:

Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special warnings and precautions for use).

4.9 Overdose

Cases of accidental and deliberate overdosage with oral therapy 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. In massive overdose, 10 to 20 times the maximum therapeutic levels, there may be serious CNS depression or coma with muscular hypotonia, hyperflexia, miosis, impaired respiratory function, metabolic acidosis. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported. A number of deaths have occurred following large overdoses. Hospital management of

overdose includes induced vomiting, gastric lavage, assisted ventilation and other supportive measures. Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Fatty acid derivatives
ATC no: N03AG01

The mode of action of valproic acid is not fully understood but may involve an elevation of gamma-amino butyric acid levels in the brain.

In certain in-vitro studies, it was reported that sodium valproate could stimulate HIV replication, but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed, the effect of sodium valproate on HIV replication ex-vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

With peroral administration 90-100% of the dose is rapidly absorbed.

Maximal plasma concentration is achieved with Episenta® within 6.5 ±3.3 hours. The half-life is 12-16 h in most patients but can in exceptional cases be considerably lower. Impaired renal function prolongs the half-life. In infants under 2 months the half-life can be prolonged up to 60 hours but in older children it is the same as in adults.

Steady-state concentration is normally achieved after treatment in 3-5 days. A satisfactory effect is most often achieved at 50 – 100 µg/ml, but the patient's overall situation must be considered.

The relation between the dose and effect, and between plasma concentrations and effect, has not been fully clarified. The CSF concentration is up to 10% of the plasma concentration. About 90% of sodium valproate is bound to plasma protein, which may entail a risk of clinically significant interactions with other antiepileptics, primarily phenytoin. Sodium valproate is metabolised to a great extent and is excreted in the urine as conjugated metabolites. Sodium valproate crosses the placental barrier and concentrations of foetal plasma are comparable to those in the mother.

Valproic acid passes into breast milk but is not likely to influence the child when therapeutic doses are used.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Prolonged –release granule: calcium stearate, silicon dioxide (methylated), ammonio methacrylate copolymer type B, sodium lauryl sulphate, polysorbate 80.
Granule coating: ethylcellulose, dibutylsebacate, oleic acid.

150 mg Capsule shell: gelatine, indigo carmine (E132), sodium lauryl sulphate.

300 mg Capsule shell: gelatine, indigo carmine (E132), quinoline yellow (E104), sodium lauryl sulphate.

Prolonged–release granule: calcium stearate, silicon dioxide (methylated), ammonio methacrylate copolymer type B, sodium lauryl sulphate, polysorbate 80.

Granule coating: ethylcellulose, dibutylsebacate, oleic acid

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container. Keep the container tightly closed.

6.5 Nature and contents of container

Capsules: Polypropylene container with polyethylene stopper or polyethylene container with polypropylene screw cap containing 50, 100 or 200 prolonged-release capsules

Sachets: 50, 100 or 200 Clay coated kraftpaper/Aluminium/PE sachets.

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Limited, 85 High Street, Tunbridge Wells, Kent, TN1 1YG UK

8 MARKETING AUTHORISATION NUMBER(S)

Episenta 150 mg prolonged-release capsule
PL18157/0021

Episenta 300mg prolonged-release capsule
PL18157/0022

Episenta® 500 mg Prolonged-release granules
PL18157/0023

Episenta® 1000 mg Prolonged-release granules
PL18157/0024

9 DATE OF FIRST

AUTHORISATION/RENEWAL OF THE AUTHORITY

6 October 2006

10 DATE OF REVISION OF THE TEXT

7 July 2009

