

EPISENTA® SOLUTION FOR INJECTION

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Episenta® solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium valproate 100mg/ml

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Episenta® solution for injection may be used for epileptic patients who would normally be maintained on oral sodium valproate but for whom oral therapy is temporarily not possible.

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. Episenta® solution for injection is ready to use by intravenous infusion. The total daily dose should be divided in three to four single slow intravenous injections or should be given by continuous infusion.

Monotherapy:

Adults: Dosage should start at 400 – 800mg 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 per day. Where adequate control is not achieved within this range the dose may be further increased to a maximum of 2500mg per day.

Children: 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 40 mg/kg bodyweight per day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg body weight per day clinical chemistry and haematological parameters should be monitored.

Use in 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 decreasing 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 response as monitoring of plasma concentration may be misleading.

Combined Therapy: When starting Episenta® in patients already on other anticonvulsants these should be tapered slowly. Initiation of Episenta® therapy should then be gradual, with target dose reached after about two weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with liver enzymes inducing drugs such as phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Episenta®.

When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturates should be reduced.

Method of administration: Episenta® solution for injection may be given by slow intravenous injection over 3 – 5 minutes or

by infusion in 0.9% saline or 5% dextrose. Episenta® solution for injection should not be administered via the same intravenous line with other drugs. Patients already treated with oral sodium valproate may be continued at their current daily dose. The intravenous administration of Episenta® solution for injection should be replaced by oral therapy as soon as practicable. Close monitoring of plasma levels and – if necessary – dosage adjustments have to be performed during the change-over to a parenteral therapy, during parenteral therapy and during the switch back to oral therapy, in particular in such patients receiving higher doses of valproate or in patients receiving drugs potentially influencing the metabolism of valproate. For instructions on preparation and dilution of Episenta® solution for injection before administration see section 6.6 Special Precautions for Disposal.

4.3 Contraindications

Liver disease, family history of severe hepatic dysfunction, particularly drug related. Porphyria. Hypersensitivity to valproate.

4.4 Special warnings and precautions for use

Sodium valproate very commonly causes weight gain which may be marked and progressive. All patients should be warned of this risk at the initiation of therapy and appropriate strategies adopted to minimise weight gain. Monitor body weight during sodium valproate therapy.

Clinical symptoms are a more sensitive indicator in the early stages of hepatic failure than laboratory investigations. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur.

Routine measurement of liver function should be undertaken in those at risk before and during the first six months of therapy including children under three years, especially those with mental retardation, organic brain damage or metabolic disorder.

There have been reports of severe pancreatitis, which may be fatal, in patients receiving valproic acid or valproate not only during the first six months of therapy but also after several years of use. Patients experiencing symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting) should undergo medical evaluation including estimation of serum amylase; if pancreatitis is diagnosed, valproate should be discontinued. Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (See section 4.8 Undesirable Effects).

The drug should be discontinued if signs of liver damage occur or if serum amylase are elevated. Valproic acid inhibits the second stage of platelet aggregation. If spontaneous bruising or bleeding occurs medication should be withdrawn. It is recommended that patients receiving sodium valproate be monitored for platelet function and clotting time before major surgery. Withdrawal of sodium valproate or transition to another antiepileptic should be made gradually to avoid precipitation of an increase in seizure frequency. Sodium valproate may give false positives for ketone bodies in the urine testing for diabetics.

Pregnancy

Women of childbearing potential should not be started on sodium valproate without specialist neurological advice. Sodium valproate is the antiepileptic of choice in patients with

certain types of epilepsy such as generalised epilepsy +/- myoclonus/photosensitivity. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

4.5 Interaction with other medicinal products and other forms of interaction

Like many other drugs, Episenta® may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other antidepressants. The effect of hormonal contraceptives ("the pill") is not reduced by valproic acid. Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Aspirin may displace valproate from binding sites resulting in higher free levels of valproate. Phenytoin levels may be affected by Episenta® and should be monitored, particularly the free form which may increase following an initial decrease in total levels. Valproic acid inhibits the metabolism of lamotrigine, the dosage of which should therefore be adjusted as necessary. Co-administration of lamotrigine and Episenta® might increase the risk of rash. Zidovudine plasma concentration may be raised leading to increased zidovudine toxicity. Dosage of Episenta® may require adjustment when used in combination with other anticoagulants (see Dosage, Combined Therapy). Mefloquine increases the breakdown of valproic acid and also has potentially spasmogenic effects. Concomitant administration can therefore lead to epileptic attacks. The serum concentration of valproic acid can be elevated by the concomitant administration of cimetidine and erythromycin. Cholestyramine may decrease the absorption of valproate. Since valproic acid is partially metabolised to ketone bodies, the possibility of a false positive reaction of a test for ketone body elimination should be taken into account in diabetics with suspected ketoacidosis.

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 anti-epileptic 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. 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 antiepileptic 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: an increased incidence of congenital abnormalities (including cases of facial dysmorphism, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate. Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.

- In view of the above data

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic 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, women should be advised to start taking folic acid supplementation (5 mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsant 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, valproate anti-epileptic 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 phenobarbitone and other anti-epileptic 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 valproate.

4.7 Effects on ability to drive and use machines

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. This is especially the case when taken during anticonvulsant polytherapy, concomitant use of benzodiazepines or in combination with alcohol.

4.8 Undesirable effects

Sodium valproate very commonly causes weight gain which may be marked and progressive (see section 4.4 Special Warnings and Precautions for Use). Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children, particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. In the majority of cases, liver damage was observed within the first 6 months of treatment, particularly between weeks 2 and 12, and mostly associated with concomitant use of other antiepileptics. In most cases, symptoms (loss of appetite, nausea, vomiting, stomach-ache, dislike of usual food, dislike of valproate, tiredness, lack of energy, increase in the frequency/severity of seizures, haematomas/epistaxis, oedema of the eyelids/lower extremities, icterus) appear even before the change in laboratory values. Therefore, clinical monitoring of the patients is more important than the laboratory findings. The above mentioned clinical signs are indication for immediate withdrawal of the drug.

Measures to be taken for the early detection of liver damage:

Before the beginning of treatment and periodically during the first six months especially in those who seem most at risk and those with a prior history of liver disease, comprehensive clinical examination (especially with regard to metabolic disorders, hepatopathy, pancreatic and coagulation disorders) and laboratory determination of the blood count, including platelets, bilirubin, SGOT, SGPT, gamma-GT, lipase, alpha-amylase in the blood, blood sugar, total protein, Quick's time, PTT, fibrinogen, factor VIII and associated factors. The patients must be closely monitored (particularly in the event of fever), the parents/guardians must be told about possible signs of liver damage (see above) and must be included in the monitoring process. The patient should be instructed to report any signs of liver damage to clinician for investigation. Raised liver enzymes are not uncommon during treatment with Episenta® and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including results of blood coagulation should be monitored until they return to normal. However an abnormally prolonged Quick's time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicyclates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Episenta® should be discontinued. Oedema has been reported rarely. When abnormality of the urea cycle is suspected, pretreatment ammonia levels should be measured. Pancreatic: Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as haemorrhage with

a rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use (see section 4.4 Special Warnings and Precautions for Use). Patients experiencing acute abdominal pain should have their serum amylase estimated. If these levels are elevated treatment should be discontinued.

Renal: 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 valproate therapy, but the mode of action is yet unclear.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication. Red cell hypoplasia, pancytopenia and leucopenia have been reported rarely. The blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects. 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.

Coma has rarely been observed. These cases have often been associated with too high a starting dose or to a rapid dose escalation or concomitant use of other anticonvulsants. They have usually been reversible on withdrawal of treatment or reduction of dosage. Very rare cases of reversible dementia associated with reversible cerebral atrophy have been reported.

An increase in alertness may occur. Occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Hearing loss, either reversible or irreversible has rarely been reported, though a causal relationship has not been established.

Gastrointestinal: Increase in appetite and an increase in weight is not uncommon. Minor gastric irritation may occur in some patients at the start of treatment.

Dermatological: Transient hair loss with regrowth of curly hair has been reported in some patients. Cutaneous reactions such as exanthematous rash have rarely been reported. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea, acne and hirsutism. Very rarely gynaecomastia has occurred.

Other: In individual cases, taking sodium valproate led to changes in immunological defence mechanism (vasculitis, lupus erythematosus-like symptoms).

4.9 Overdose

Cases of accidental and suicidal 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 there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in presence of very high plasma levels. A number of deaths have occurred following large overdoses. Hospital management of overdose including induced vomiting, gastric lavage, assisted ventilation and other supportive measures is recommended. 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

ATC no: N03AG01

The mode of action of valproic acid in epilepsy 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

Per definition, with intravenous injection the bioavailability amounts to 100%. The half-life is 8 – 20 h in most patients but can in exceptional cases be considerably lower. It is usually shorter in children. In infants under 2 months the half-life can be prolonged up to 60 hours. In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

Steady-state concentration is normally achieved after treatment in 3 - 5 days. A satisfactory effect is most often achieved at 40 – 100mg/litre (278 – 694 micromol/litre), but the patient's overall situation must be considered. The reported range may depend on time of sampling and presence of co-medication. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Episenta® may not be clearly correlated with the total or free (unbound) plasma valproic acid levels. The CSF concentration is up to 10% of the plasma concentration. The percentage of free (unbound) drug is usually between 6 and 15% of the total plasma levels. 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 in 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

Acute toxicity

Depending on the species of the animal and mode of administration the LD₅₀ is between 0.5 – 1.5g/kg body weight. The symptoms observed included, for example, ataxia, sedation, hypothermia, catelapsy, co-ordination disorders and vomiting.

Chronic toxicity

Testicular atrophy, degeneration of the vas deferens and insufficient spermatogenesis as well as lung and prostate gland changes have been observed in chronic toxicity studies at dosages of more than 250 mg/kg in rats and 90 mg/kg in the dog. In rats, at 200 mg/kg p.o., morphological

hepatocytes changes were seen. At 750 mg/kg i.p., functional liver disorders and, among other things, hyperammonaemia, occurred.

Carcinogenic and mutagenic potential

Carcinogenic studies have been conducted in the rat and mouse. At very high doses, increased subcutaneous fibrosarcoma was observed in male rats.

Studies of mutagenic potential have shown no mutagenic effect.

Reproduction toxicology

Valproic acid has been found to be teratogenic in mice, rats, hamsters, monkeys and rabbits. The effects occur primarily as skeletal (palatal cleft, costal and vertebral fusion) and renal malformations, in mice also as encephalocele and malformation of the neural tube. Malformations have also been observed in neurulation studies in chicken embryo in vitro.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edentate, Water for injections

6.2 Incompatibilities

Episenta® solution for injection should not be administered via the same intravenous line with other drugs.

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale: 24 months. Shelf life after dilution or reconstitution according to the directions: Chemical and physical in-use stability has been demonstrated for 3 days at 20 - 22°C.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Glass ampoule containing 3 ml or 10 ml solution for injection.

6.6 Instructions for Use/Handling

From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be not longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. For infusion of Episenta® solution for injection it may be diluted in 0.9% saline or 5% dextrose. Tests with the recommended infusion solutions over three days at 20 - 22°C show compatibility. Prior to use Episenta® solution for injection and the diluted solution should be visually inspected. Only clear solutions without particles should be used.

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Ltd., 85, High Street, Tunbridge Wells, Kent TN11 1YG, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 18157/0027.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28th July 2006.

10 DATE OF REVISION OF THE TEXT

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