# Episenta®▼ (Sodium Valporate) PROLONGED RELEASE CAPSULES Prescribing Information

| | Legal Category | NHS Price |
|---|---|---|
| Episenta 150mg prolonged-release capsule x 30 capsules | POM | £2.76 |
| Episenta 300mg prolonged-release capsule x 30 capsules | POM | £4.56 |
| Episenta 500mg prolonged-release granules x 30 sachets | POM | £6.30 |
| Episenta 1000mg prolonged-release granules x 30 sachets | POM | £12.30 |

For further information please contact Medical Information on MedInfo@desitin.co.uk.

Episenta is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reaction. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ . Adverse events should also be reported to Desitin

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# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1 NAME OF THE MEDICINAL PRODUCT

Episenta® 150 mg prolonged-release capsule

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release capsule contains 150 mg sodium valproate

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Female patients:

- For all female patients aged under 55 years: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all female patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

Male patients:

- For all male patients aged under 55 years initiating treatment with valproate: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all male patients established on treatment with valproate or male patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

For the treatment of manic episode in bipolar disorder only when there is no other effective or

tolerated treatment.
The continuation of treatment after manic episode could be considered in patients who have responded to sodium valproate for acute mania.

## 4.2 Posology and method of administration

Female children and women of childbearing potential aged under 55 years
No new female patients aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Valproate must be supervised by a specialist experienced in the management of epilepsy or bipolar disorder.
Valproate should not be prescribed in female children and women of childbearing potential aged under 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Where possible existing female children and women of childbearing potential aged under 55 years should be switched to another treatment unless two specialists independently consider and document there is no other effective or tolerated treatment. For those continuing to receive valproate, the benefits and risks of valproate should be carefully reconsidered at regular treatment reviews, at least annually (see section 4.4).
Valproate must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).
Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Male patients aged under 55 years
No new male children or men aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity are not applicable (see sections 4.4 and 4.6).
The specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the risk of infertility in males (see section 4.4, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

Posology

*Treatment in all forms of epilepsy:*
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.

Special populations

*Paediatric population*

*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. In children requiring doses higher than 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

*Children under 20kg*

20mg/kg body weight per day; in severe cases this may be increased up to 40mg/kg/day.

*Elderly*

Care should be taken when adjusting dosage in the elderly since the pharmacokinetics of 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.

*Renal impairment*

It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable (see section 4.9). Dosing should be modified according to clinical monitoring of the patient (see section 4.4).

*Hepatic impairment*

Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see section 4.4 and 4.8).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see section 4.3 and 4.4).

Salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with sodium valproate, concomitant use in children under 3 years of age can increase the risk of liver toxicity (see section 4.4).

*Combined Therapy (see section 4.5)*

When starting Episenta® in patients already on other anticonvulsants, these should be tapered slowly; initiation of Episenta® treatment should then be gradual, with target dose being reached after about 2 weeks. 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. 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.

N.B. In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2).

*Manic episodes in bipolar disorder*

*Adults*
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg sodium valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1,000 and 2,000 mg sodium valproate. Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored.
Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

*Paediatric population*
The efficacy of Episenta® in children below 18 years of age in the treatment of manic episodes in bipolar disorder has not been established. With respect to safety information in children see section 4.8.

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 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

Episenta® is contraindicated in the following situations:
- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Patients with known urea cycle disorders (see section 4.4).
- Porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).

Treatment of epilepsy
- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see

sections 4.4 and 4.6).

Treatment of bipolar disorder

- in pregnancy (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

## 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.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.

NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

The concomitant use of sodium valproate and carbapenem is not recommended (see section 4.5).

Aggravated convulsions:
As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

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 disorders including mitochondrial disorders such as carnitine deficiency, urea cycle

disorders, POLG mutations (see section 4.3 and 4.4) 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 years of age due to the risk liver toxicity (see also section 4.5). 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 (see section 4.4 Severe liver damage and also section 4.5).

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 for patients at risk and those with a prior history of liver disease.
Upon changes in concomitant medicinal products (dose increase or additions) that are known to impact the liver, liver monitoring should be restarted as appropriate (see section 4.5).
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) requires cessation of valproate 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.

Patients with known or suspected mitochondrial disease

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Urea cycle disorders and risk of hyperammonaemia
When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of risk of hyperammonaemia with sodium valproate (see sections 4.3 and 4.4).

Patients at risk of hypocarnitinaemia
Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 Patients with known or suspected mitochondrial disease and Urea cycle disorders and risk of hyperammonaemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.
Patients should be warned to report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed. Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative. In these patients, carnitine monitoring should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Episenta®. Carnitine supplementation should be considered in these patients. See also sections 4.5, 4.8 and 4.9.

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).

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 and 5.2).

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).

*Severe Cutaneous Adverse Reactions and Angioedema*

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

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).

Female children, women of childbearing potential aged under 55 years and pregnant women

**Pregnancy Prevention Programme**

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk (11 %) for congenital malformations and neurodevelopmental disorders (30–40 %) which may lead to permanent disability (see section 4.6).
Valproate must only be initiated by two specialists who independently consider and document that there is no other effective or tolerated treatment.

Episenta® is contraindicated in the following situations:

Treatment of epilepsy
- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see

sections 4.3 and 4.6).

Treatment of bipolar disorder

- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The specialist must ensure that

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion, to support her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability, including the magnitude of these risks for children exposed to valproate in utero.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorders.
- the patient understands the need to consult her general practitioner (GP) for referral to a specialist as soon as she is planning a pregnancy to ensure timely discussion and switching to another treatment prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her GP for urgent referral to a specialist in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also apply to women who are not currently sexually active unless the specialist considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The specialist must ensure that

- the parents/caregivers of female children understand the need to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist.
- the parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability including the magnitude of these risks for children exposed to valproate in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider other treatment options. If valproate is the only effective and tolerated treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to another treatment before they reach menarche.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to support her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

*Oestrogen-containing products*

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing oestrogen-containing products.
On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist

The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss and complete the annual risk acknowledgement form with the patient and/or carer, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider other treatment options. Every effort should be made to switch to an appropriate treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to another treatment prior to

conception, and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must immediately contact her GP to be referred to a specialist to re-evaluate treatment with valproate and consider switching to other treatment options. The patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that
- the patient card is provided with every valproate pack dispensation and that the patients understand its content.
- the patients are advised not to stop valproate medication and to immediately contact their GP to be referred to a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.
An annual risk acknowledgement form needs to be discussed and completed with the patient and/or carer at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy or bipolar disorder.

Male children and men
All male patients and/or their carers should be made aware of the potential risk to children born to men treated with valproate in the 3 months before conception (see also section 4.6), of the risk of infertility in men (see section 4.2, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk (see section 4.6) and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation.

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

For males aged under 55 years, at initiation of treatment, the specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

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

Alcohol
Alcohol intake is not recommended during treatment with valproate.

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.

Excipient with known effect
This medicinal product contains sodium, but less than 1 mmol sodium (23 mg) per capsule, i.e. it is essentially “sodium-free”.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of Episenta® on other drugs

*Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines*
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. In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

*Lithium*
Episenta® has no effect on serum lithium levels.

*Olanzapine*

Valproic acid may decrease the olanzapine plasma concentration.

*Phenobarbital*
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.

*Primidone*
Sodium valproate increases **primidone** plasma levels causing an exacerbation of side effects, e.g. sedation; these signs cease with long term treatment. Clinical monitoring is recommended especially when initiating combined therapy with dosage adjustment as necessary.

*Phenytoin*
Episenta® decreases phenytoin total plasma concentration. and increases the free form of phenytoin leading to possible overdosage symptoms. Therefore, clinical monitoring is recommended with the free form of phenytoin being measured,when phenytoin plasma levels are determined.

*Carbamazepine*
Clinical toxicity has been reported when Episenta® was administered with carbamazepine as Episenta® may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

*Lamotrigine*
Episenta® reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

*Felbamate*
Valproic acid may decrease the felbamate mean clearance by up to 16%.

*Rufinamide*
Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

*Propofol*
Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

*Zidovudine*
Episenta® may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

*Nimodipine*
In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

*Vitamin K-dependent anticoagulants*
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproate The prothrombin time should be closely monitored.

*Temozolomide*
Co-administration of **temozolomide** and Episenta® may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on Episenta®
*Antiepileptics*
Antiepileptics with enzyme inducing effects e.g. **phenytoin, phenobarbital, carbamazepine,** decrease valproate plasma levels. Plasma levels should be monitored and dosage adjusted accordingly.

Valproic acid metabolite levels may be increased in the case of concomitant use with **phenytoin** or **phenobarbital**. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of felbamate and Episenta® decreases valproic acid clearance by 22 %–50 % and consequently increase the valproic acid plasma concentrations. Episenta® dosage should be monitored.

*Anti-malaria agents*
**Mefloquine** and **chloroquine** increases valproate metabolism and therefore epileptic seizures may occur in combined therapy. The dosage of sodium valproate may need adjustment.

*Highly protein bound agents*
Free valproate levels may be increased in the case of concomitant use with highly protein bound agents e.g. **acetylsalicylic acid**.

*Cimetidine or erythromycin*
Valproate plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

*Carbapenem antibiotics (such as imipenem, panipenem and meropenem)*
Decreases in blood levels of valproic acid have been reported when it is co-administered with **carbapenem agents** resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

*Colestyramine*
**Colestyramine** may decrease the absorption of valproate.

*Rifampicin*
**Rifampicin** may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co- administered with rifampicin.

*Protease inhibitors*
Protease inhibitors such as **lopinavir** and **ritonavir** decrease valproate plasma level when co-administered.

*Oestrogen-containing products, including oestrogen-containing hormonal contraceptives*
**Oestrogens** are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in

decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.
On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

**Metamizole** may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

*Methotrexate*
Some case reports describe a significant decrease in valproate serum levels after **methotrexate** administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Other interaction
*Risk of liver damage*
The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section 4.4). Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4). Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be exercised when valproate is concomitantly used with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

*Newer anti-epileptics (including topiramate and acetazolamide)*
Caution is advised when using Episenta® in combination with newer **antiepileptics** whose pharmacodynamics may not be well established.

Concomitant administration of valproate and **topiramate** or **acetazolamide** has been associated with encephalopathy and/or hyperammonaemia. careful monitoring of signs and symptoms is advised in particularly at- risk patients such as those with pre-existing encephalopathy.

*Pivalate-conjugated medicines*
Concomitant administration of valproate and pivalate-conjugated medicines (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4 Patients at risk of hypocarnitinaemia). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

*Quetiapine*
Co-administration of Episenta® and **quetiapine** may increase the risk of neutropenia/leucopenia.

*Clozapine*
Concomitant treatment of valproate and clozapine may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of valproate with clozapine is necessary, careful monitoring for both events is required.

## 4.6 Fertility, pregnancy and lactation

- Episenta® is contraindicated as treatment for bipolar disorder in pregnancy.
- Episenta®is contraindicated as treatment for epilepsy in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see section 4.3 and 4.4).
- Episenta®is contraindicated for use in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and Developmental Effects

*Pregnancy Exposure Risk related to valproate*

In females, both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neuro-developmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate

Valproate was shown to cross the placental barrier in both animal species and humans (see section 5.2).

In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

*Congenital malformations from in utero exposure*

A meta-analysis (including registries and cohort studies) showed that approximately 11 % of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2–3 %).

The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.

The risk is dose dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

*In utero* exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

*In utero* exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

*Neuro-developmental disorders from in utero exposure*

Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neuro-developmental disorders which may lead to permanent disability (including that of autism) seems to be dose-dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists cannot be established based on available data. When valproate is administered in polytherapy

with other antiepileptic drugs during pregnancy, the risk of neuro-developmental disorders which may lead to permanent disability in the offspring were also significantly increased as compared with those in children from the general population or born to untreated women with epilepsy.
The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
When valproate is administered in monotherapy, studies in children exposed *in utero* to valproate show that up to 30-40 % experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics during pregnancy, although the role of confounding factors related to intellectual disability cannot be excluded. There is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data from a population-based study show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.
Available data from another population-based study show that children exposed to valproate *in utero* are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

*Female children and women of childbearing potential aged under 55 years (see above and section 4.4)*

*Oestrogen-containing products*
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

*If a woman plans a pregnancy*
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

*Pregnant women*
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy.
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).
If a woman using valproate becomes pregnant, she must be immediately referred by their GP to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper- excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding

Valproate is excreted in human milk with a concentration ranging from 1 % to 10 % of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Episenta® therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8).
Valproate administration may also impair fertility in men (see sections 4.2, 4.4 and 4.8). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception.

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. The study was not large enough to investigate associations

with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4).

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

## 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 Undesirable effects

Frequency categories are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

<u>Congenital, familial and genetic disorders</u>
Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

<u>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</u>
*Rare:* myelodysplastic syndrome

*Not known:* acquired Pelger-Huet anomaly

Hepato-biliary disorders

*Common:* liver injury (see section 4.4); increased liver enzymes, particularly early in treatment, and may be transient (see section 4.4)

*Not known:* severe liver damage, including hepatic failure sometimes resulting in fatalities (see sections 4.2, 4.3 and 4.4)

Gastro-intestinal disorders

*Very common:* nausea

*Common:* vomiting, gingival disorder, (mainly gingival hyperplasia), stomatitis gastralgia, diarrhoea
The above three adverse events frequently occur at the start of the treatment, but usually disappearing after a few days without discontinuing treatment. These problems can usually be overcome by taking Episenta® with or after food.

*Uncommon:* pancreatitis, sometimes lethal (see section 4.4)

Psychiatric disorders

*Common:* confusional state, hallucinations, aggression*, agitation*, disturbance in attention*

*Rare:* abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Nervous system disorders

*Very common:* tremor

*Common:* extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

*Uncommon:* coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia, aggravated convulsions (see section 4.4)

*Rare:* reversible dementia associated with reversible cerebral atrophy, cognitive disorder

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 occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have uncommonly been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.
An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Endocrine disorders

*Uncommon:* Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased)

*Rare:* hypothyroidism (see section 4.6)

Metabolism and nutrition disorders

*Common:* hyponatraemia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary

syndrome (see section 4.4).

*Rare* hyperammonaemia* (see section 4.4), obesity
*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, 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.
Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see sections 4.3 and 4.4).
*Not known:* hypocarnitinaemia (see section 4.3 and 4.4)

Blood and lymphatic system disorders
*Common:* anaemia, thrombocytopenia (see section 4.4)
*Uncommon:* pancytopenia, leucopenia
*Rare:* bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis
The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Episenta® has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6).).

Skin and subcutaneous tissue disorders
*Common:* hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within 6 months, although the hair may become more curly than previously.
nail and nail bed disorders
*Uncommon:* angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)
*Rare:* toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome
*Not known:* hyperpigmentation

Reproductive system and breast disorders
*Common:* dysmenorrhea
*Uncommon:* amenorrhea
*Rare:* male infertility (see section 4.6), polycystic ovaries
*Very rare:* gynaecomastia

Vascular disorders
*Common:* haemorrhage (see section 4.4. and 4.6)
*Uncommon:* vasculitis

Eye disorders
*Rare:* diplopia

Ear and labyrinth disorders
*Common:* deafness, a cause and effect relationship has not been established

Renal and urinary disorders
*Common:* urinary incontinence
*Uncommon:* renal failure

*Rare:* enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Episenta® therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions
*Uncommon:* hypothermia, non-severe oedema peripheral

Musculoskeletal and connective tissue disorders
*Uncommon:* bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Episenta®. The mechanism by which Episenta® affects bone metabolism has not been identified.
*Rare:* systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4)

Respiratory, thoracic and mediastinal disorders:
*Uncommon:* pleural effusion (eosinophilic)

Investigations:
*Rare:* coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

Paediatric population
The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (see details below).
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

## 4.9 Overdose

Symptoms
Cases of accidental and deliberate valproate overdose have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.
Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Management
Hospital management of overdose should be symptomatic, including cardio-respiratory-gastric monitoring. Gastric lavage may be useful up to 10–12 hours following ingestion.
In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Fatty acid derivatives, ATCcode: 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.

The increased expression of drug efflux transporters at the blood-brain barrier can result in lower concentrations of their respective substrate, i. e. the active substance, in the brain compared to its free concentration in plasma, and thereby reduce the concentration of antiepileptics at the site of action. This can lead to pharmacoresistance and thus to the development of a treatment-resistant status epilepticus or treatment-resistant epilepsy. However, in vitro data suggest that sodium valproate is not a substrate for transporters such as ATP-binding cassette (ABC) transporters (e. g. P-glycoprotein (Pgp)) or multidrug resistance-associated proteins (MRP1, MRP2 and MRP5). The development of pharmacoresistance against valproate by these transporters is therefore considered unlikely.

### 5.2 Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/L (278–694 μmol/L). This reported range may depend on time of sampling and presence of co-medication.

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 considerable lower. It is usually shorter in children.
Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults.
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 – 100 mg/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 CFS 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.

*Placental transfer (see section 4.6)*
Valproate crosses the placental barrier in animal species and in humans:
- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery.

Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

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

## 5.3 Preclinical safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in patients with

epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.
Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproductive and developmental toxicity
Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.
Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.
Behavioural abnormalities have been reported in the first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

Testicular toxicity
In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 465 mg/kg/day and 150 mg/kg/day, respectively. The safety margin based on plasma concentrations is unknown, however body-surface-area comparisons indicate that there may be no safety margin.
In juvenile (sexually immature) and young adult rats (pubertal), a significant dose-related reduction in testes weight was observed at 240 mg/kg/day following i.v. and i.p. administration with no apparent histopathological changes. However, testicular atrophy was observed in the young adult rat at an i.v. dose of 480 mg/kg/day. Despite the absence of apparent histopathology changes, the testicular weight reductions were considered part of a dose-related spectrum leading to testicular atrophy. There is no safety margin for the effect on testicular weight.
There is a limited number of published papers which report findings in juvenile animals consistent with those reported in the GLP adult and juvenile studies, with respect to testicular weights. Reductions in testicular weights are associated with adverse effects on the adult male reproductive tract in animal studies and impaired fertility in adult patients (see section 4.6.)
The toxicological significance of the testicular findings in juvenile animals has not been evaluated and hence the relevance to human testicular development, particularly in the paediatric population, is unknown.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Prolonged–release granule:

Calcium stearate

Colloidal anhydrous silicon dioxide, methylated Ammonium methacrylate copolymer (Type B) Sorbic acid

Sodium hydroxide

Granule coating:

Ethyl cellulose

Dibutyl sebacate

Oleic acid

Capsule shell:

Gelatin

Indigo carmine (E 132)

Sodium lauryl sulfate

## 6.2 Incompatibilities

None known.

## 6.3 Shelf life

18 months

## 6.4 Special precautions for storage

Do not store above 25ºC. Store in the original container. Keep the container tightly closed.

## 6.5 Nature and contents of container

Polyethylene container with polypropylene screw cap containing 30, 50, 100 or 200 prolonged-release capsules.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

DESITIN ARZNEIMITTEL GMBH
WEG BEIM JAEGER 214
HAMBURG
D-22335 GERMANY

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 14040/0024

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/11/2024

## 10 DATE OF REVISION OF THE TEXT

19/02/2025

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

# 1 NAME OF THE MEDICINAL PRODUCT

Episenta® 300 mg prolonged-release capsule

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release capsule contains 300 mg sodium valproate

Excipient(s) with known effect: 1.8 mmol (41.4 mg) sodium per capsule

For the full list of excipients see section 6.1

# 3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

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

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

Female patients:

- For all female patients aged under 55 years: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all female patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

Male patients:

- For all male patients aged under 55 years initiating treatment with valproate: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all male patients established on treatment with valproate or male patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

For the treatment of manic episode in bipolar disorder only when there is no other effective or tolerated treatment.
The continuation of treatment after manic episode could be considered in patients who have responded to sodium valproate for acute mania.

**4.2 Posology and method of administration**

Female children and women of childbearing potential aged under 55 years
No new female patients aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Valproate must be supervised by a specialist experienced in the management of epilepsy or bipolar disorder.
Valproate should not be prescribed in female children and women of childbearing potential aged under 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Where possible existing female children and women of childbearing potential aged under 55 years should be switched to another treatment unless two specialists independently consider and document there is no other effective or tolerated treatment. For those continuing to receive valproate, the benefits and risks of valproate should be carefully reconsidered at regular treatment reviews, at least annually (see section 4.4).
Valproate must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).
Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Male patients aged under 55 years
No new male children or men aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity are not applicable (see sections 4.4 and 4.6).
The specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the risk of infertility in males (see section 4.4, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

Posology

*Treatment in all forms of epilepsy:*
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.

Special populations
*Paediatric population*
*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. In children requiring doses higher than 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

*Children under 20kg*
20mg/kg body weight per day; in severe cases this may be increased up to 40mg/kg/day.

*Elderly*
Care should be taken when adjusting dosage in the elderly since the pharmacokinetics of 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.

*Renal impairment*
It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable (see section 4.9). Dosing should be modified according to clinical monitoring of the patient (see section 4.4).

*Hepatic impairment*
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see section 4.4 and 4.8).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see section 4.3 and 4.4).

Salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with sodium valproate, concomitant use in children under 3 years of age can increase the risk of liver toxicity (see section 4.4).

*Combined Therapy (see section 4.5)*
When starting Episenta® in patients already on other anticonvulsants, these should be tapered

slowly; initiation of Episenta® treatment should then be gradual, with target dose being reached after about 2 weeks. 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. 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.

N.B. In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2).

*Manic episodes in bipolar disorder*

*Adults*

The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg sodium valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1,000 and 2,000 mg sodium valproate. Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored. Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

*Paediatric population*

The efficacy of Episenta® in children below 18 years of age in the treatment of manic episodes in bipolar disorder has not been established. With respect to safety information in children see section 4.8.

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 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

Episenta® is contraindicated in the following situations:

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Patients with known urea cycle disorders (see section 4.4).
- Porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).

Treatment of epilepsy

- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

Treatment of bipolar disorder

- in pregnancy (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

## 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.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.

NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

The concomitant use of sodium valproate and carbapenem is not recommended (see section 4.5).

Aggravated convulsions:
As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

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 disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see section 4.3 and 4.4) 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 years of age due to the risk liver toxicity (see also section 4.5). 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 (see section 4.4 Severe liver damage and also section 4.5).

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 for patients at risk and those with a prior history of liver disease.

Upon changes in concomitant medicinal products (dose increase or additions) that are known to impact the liver, liver monitoring should be restarted as appropriate (see section 4.5).
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) requires cessation of valproate 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.

Patients with known or suspected mitochondrial disease
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase $\gamma$ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Urea cycle disorders and risk of hyperammonaemia
When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of risk of hyperammonaemia with sodium valproate (see sections 4.3 and 4.4).

Patients at risk of hypocarnitinaemia
Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 Patients with known or suspected mitochondrial disease and Urea cycle disorders and risk of hyperammonaemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.
Patients should be warned to report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when

symptoms of hypocarnitinaemia are observed. Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative. In these patients, carnitine monitoring should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Episenta®.
Carnitine supplementation should be considered in these patients. See also sections 4.5, 4.8 and 4.9.

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).

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 and 5.2).

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).

*Severe Cutaneous Adverse Reactions and Angioedema*

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

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).

Female children, women of childbearing potential aged under 55 years and pregnant women

**Pregnancy Prevention Programme**

Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk (11 %) for congenital malformations and neurodevelopmental disorders (30–40 %) which may lead to permanent disability (see section 4.6).
Valproate must only be initiated by two specialists who independently consider and document that there is no other effective or tolerated treatment.

Episenta® is contraindicated in the following situations:

Treatment of epilepsy

- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder

- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The specialist must ensure that

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion, to support her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability, including the magnitude of these risks for children exposed to valproate in utero.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorders.
- the patient understands the need to consult her general practitioner (GP) for referral to a specialist as soon as she is planning a pregnancy to ensure timely discussion and switching to another treatment prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her GP for urgent referral to a specialist in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also apply to women who are not currently sexually active unless the specialist considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children
The specialist must ensure that

- the parents/caregivers of female children understand the need to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist.
- the parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability including the magnitude of these risks for children exposed to valproate in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider other treatment options. If valproate is the only effective and tolerated treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to another treatment before they reach menarche.

Pregnancy test
Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception
Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to support her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

*Oestrogen-containing products*
Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing oestrogen-containing products.
On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist
The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss and complete the annual risk acknowledgement form with the patient and/or carer, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in

the management of epilepsy, must reassess valproate therapy and consider other treatment options. Every effort should be made to switch to an appropriate treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to another treatment prior to conception, and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must immediately contact her GP to be referred to a specialist to re-evaluate treatment with valproate and consider switching to other treatment options. The patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that
- the patient card is provided with every valproate pack dispensation and that the patients understand its content.
- the patients are advised not to stop valproate medication and to immediately contact their GP to be referred to a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.
An annual risk acknowledgement form needs to be discussed and completed with the patient and/or carer at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy or bipolar disorder.

Male children and men
All male patients and/or their carers should be made aware of the potential risk to children born to men treated with valproate in the 3 months before conception (see also section 4.6), of the risk of infertility in men (see section 4.2, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk (see section 4.6) and recommend the need for male patients and their female partner to use

effective contraception, while using valproate and for at least 3 months after treatment discontinuation.

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

For males aged under 55 years, at initiation of treatment, the specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

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

Alcohol
Alcohol intake is not recommended during treatment with valproate.

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.

Excipient with known effect
This medicinal product contains 41.4 mg sodium per dose, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of Episenta® on other drugs

*Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines*
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. In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

*Lithium*
Episenta® has no effect on serum lithium levels.

*Olanzapine*
Valproic acid may decrease the olanzapine plasma concentration.

*Phenobarbital*
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.

*Primidone*
Sodium valproate increases primidone plasma levels causing an exacerbation of side effects, e.g. sedation; these signs cease with long term treatment. Clinical monitoring is recommended especially when initiating combined therapy with dosage adjustment as necessary.

*Phenytoin*
Episenta® decreases phenytoin total plasma concentration and increases the free form of phenytoin leading to possible overdosage symptoms. Therefore, clinical monitoring is recommended with the free form of phenytoin being measured,when phenytoin plasma levels are determined

*Carbamazepine*
Clinical toxicity has been reported when Episenta® was administered with carbamazepine as Episenta® may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

*Lamotrigine*
Episenta® reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

*Felbamate*
Valproic acid may decrease the felbamate mean clearance by up to 16 %.

*Rufinamide*
Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

*Propofol*
Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

*Zidovudine*
Episenta® may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

*Nimodipine*
In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

*Vitamin K-dependent anticoagulants*
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproate. The prothrombin time should be closely monitored.

*Temozolomide*
Co-administration of temozolomide and Episenta® may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on Episenta®

*Antiepileptics*
Antiepileptics with enzyme inducing effects e.g. **phenytoin, phenobarbital, carbamazepine**, decrease valproate plasma levels. Plasma levels should be monitored and dosage adjusted accordingly.

Valproic acid metabolite levels may be increased in the case of concomitant use with **phenytoin** or **phenobarbital**. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of felbamate and Episenta® decreases valproic acid clearance by 22 %–50 % and consequently increase the valproic acid plasma concentrations. Episenta® dosage should be monitored.

*Anti-malaria agents*
**Mefloquine** and **chloroquine** increases valproate metabolism and therefore epileptic seizures may occur in combined therapy. The dosage of sodium valproate may need adjustment.

*Highly protein bound agents*
Free valproate levels may be increased in the case of concomitant use with highly protein bound agents e.g. **acetylsalicylic acid**.

*Cimetidine or erythromycin*
Valproate plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with **cimetidine** or **erythromycin**.

*Carbapenem antibiotics (such as imipenem, panipenem and meropenem)*
Decreases in blood levels of valproic acid have been reported when it is co-administered with **carbapenem agents** resulting in a 60 %–100 % decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

*Colestyramine*
**Colestyramine** may decrease the absorption of valproate.

*Rifampicin*

**Rifampicin** may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co- administered with rifampicin.

*Protease inhibitors*
Protease inhibitors such as **lopinavir** and **ritonavir** decrease valproate plasma level when co-administered.

*Oestrogen-containing products, including oestrogen-containing hormonal contraceptives*
**Oestrogens** are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.
On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

**Metamizole** may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

*Methotrexate*
Some case reports describe a significant decrease in valproate serum levels after **methotrexate** administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Other interaction
*Risk of liver damage*
The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section 4.4). Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4). Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be exercised when valproate is concomitantly used with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

*Newer anti-epileptics (including topiramate and acetazolamide)*
Caution is advised when using Episenta® in combination with newer **antiepileptics** whose pharmacodynamics may not be well established.

Concomitant administration of valproate and **topiramate** or **acetazolamide** has been associated with encephalopathy and/or hyperammonaemia. careful monitoring of signs and symptoms is advised in particularly at- risk patients such as those with pre-existing encephalopathy.

*Pivalate-conjugated medicines*
Concomitant administration of valproate and pivalate-conjugated medicines (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4 Patients at risk of hypocarnitinaemia). Patients in

whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

*Quetiapine*
Co-administration of Episenta® and **quetiapine** may increase the risk of neutropenia/leucopenia.

*Clozapine*
Concomitant treatment of valproate and clozapine may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of valproate with clozapine is necessary, careful monitoring for both events is required.

## 4.6 Fertility, pregnancy and lactation

- Episenta® is contraindicated as treatment for bipolar disorder in pregnancy.
- Episenta®is contraindicated as treatment for epilepsy in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see section 4.3 and 4.4).
- Episenta®is contraindicated for use in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and Developmental Effects
*Pregnancy Exposure Risk related to valproate*
In females, both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neuro-developmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate
Valproate was shown to cross the placental barrier in both animal species and humans (see section 5.2).

In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

*Congenital malformations from in utero exposure*
A meta-analysis (including registries and cohort studies) showed that approximately 11 % of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2–3 %).
The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.
The risk is dose dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

*In utero* exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.
*In utero* exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

*Neuro-developmental disorders from in utero exposure*
Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neuro-developmental disorders which may lead to permanent disability (including that of autism) seems to be dose-dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists cannot be established based on available data. When valproate is administered in polytherapy with other antiepileptic drugs during pregnancy, the risk of neuro-developmental disorders which may lead to permanent disability in the offspring were also significantly increased as compared with those in children from the general population or born to untreated women with epilepsy.
The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
When valproate is administered in monotherapy, studies in children exposed *in utero* to valproate show that up to 30-40 % experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics during pregnancy, although the role of confounding factors related to intellectual disability cannot be excluded. There is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data from a population-based study show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.
Available data from another population-based study show that children exposed to valproate *in utero* are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

*Female children and women of childbearing potential aged under 55 years (see above and section 4.4)*

*Oestrogen-containing products*
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

*If a woman plans a pregnancy*
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

*Pregnant women*
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).
If a woman using valproate becomes pregnant, she must be immediately referred by their GP to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

<u>Risk in the neonate</u>

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper- excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

<u>Breastfeeding</u>
Valproate is excreted in human milk with a concentration ranging from 1 % to 10 % of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Episenta® therapy taking into account the benefit of breast feeding for the child and the benefit of

therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8).
Valproate administration may also impair fertility in men (see sections 4.2, 4.4 and 4.8). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception.

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4).

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

## 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 Undesirable effects

Frequency categories are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Congenital, familial and genetic disorders
Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
*Rare:* myelodysplastic syndrome
*Not known:* acquired Pelger-Huet anomaly

Hepato-biliary disorders
*Common:* liver injury (see section 4.4); increased liver enzymes, particularly early in treatment, and may be transient (see section 4.4)
*Not known:* severe liver damage, including hepatic failure sometimes resulting in fatalities (see sections 4.2, 4.3 and 4.4)

Gastro-intestinal disorders
*Very common:* nausea
*Common:* vomiting, gingival disorder, (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea
The above three adverse events frequently occur at the start of the treatment, but usually disappearing after a few days without discontinuing treatment. These problems can usually be overcome by taking Episenta® with or after food.
*Uncommon:* pancreatitis, sometimes lethal (see section 4.4)

Psychiatric disorders
*Common:* confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
*Rare:* abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Nervous system disorders

| | |
|---|---|
| *Very common:* | tremor |
| *Common:* | extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus |
| *Uncommon:* | coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia, aggravated convulsions (see section 4.4) |
| *Rare:* | reversible dementia associated with reversible cerebral atrophy, cognitive disorder |

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 occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have uncommonly been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.
An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Endocrine disorders

| | |
|---|---|
| *Uncommon:* | Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased) |
| *Rare:* | hypothyroidism (see section 4.6) |

Metabolism and nutrition disorders

| | |
|---|---|
| *Common:* | hyponatraemia, weight increased* |

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

| | |
|---|---|
| *Rare:* | hyperammonaemia* (see section 4.4), obesity |

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, 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.
Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see sections 4.3 and 4.4).
*Not known:* hypocarnitinaemia (see section 4.3 and 4.4)

Blood and lymphatic system disorders

| | |
|---|---|
| *Common:* | anaemia, thrombocytopenia (see section 4.4) |
| *Uncommon:* | pancytopenia, leucopenia |
| *Rare:* | bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis. |

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Episenta® has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6).).

Skin and subcutaneous tissue disorders

| | |
|---|---|
| *Common:* | hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within 6 months, although the hair may become more curly than previously.<br>nail and nail bed disorders |
| *Uncommon:* | angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth) |
| *Rare:* | toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome |
| *Not known:* | hyperpigmentation |

Reproductive system and breast disorders

| | |
|---|---|
| *Common:* | dysmenorrhea |
| *Uncommon:* | amenorrhea |
| *Rare:* | male infertility (see section 4.6), polycystic ovaries |
| *Very rare:* | gynaecomastia |

Vascular disorders

| | |
|---|---|
| *Common:* | haemorrhage (see section 4.4. and 4.6) |
| *Uncommon:* | vasculitis |

Eye disorders

| | |
|---|---|
| Rare: | diplopia |

Ear and labyrinth disorders

| | |
|---|---|
| *Common:* | deafness, a cause and effect relationship has not been established |

Renal and urinary disorders

| | |
|---|---|
| *Common:* | urinary incontinence |
| *Uncommon:* | renal failure |
| *Rare:* | enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Episenta® therapy, but the mode of action is as yet unclear. |

General disorders and administration site conditions

| | |
|---|---|
| *Uncommon:* | hypothermia, non-severe oedema peripheral |

Musculoskeletal and connective tissue disorders

| | |
|---|---|
| *Uncommon:* | bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Episenta®. The mechanism by which Episenta® affects bone metabolism has not been identified. |
| *Rare:* | systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4) |

Respiratory, thoracic and mediastinal disorders

| | |
|---|---|
| *Uncommon:* | pleural effusion (eosinophilic) |

Investigations

| | |
|---|---|
| *Rare:* | coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged). |

Paediatric population
The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (see details below).
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

**4.9 Overdose**

Symptoms
Cases of accidental and deliberate valproate overdose have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.
Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Management
Hospital management of overdose should be symptomatic, including cardio-respiratory-gastric monitoring. Gastric lavage may be useful up to 10–12 hours following ingestion.
In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Fatty acid derivatives, ATCcode: 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.

The increased expression of drug efflux transporters at the blood-brain barrier can result in lower concentrations of their respective substrate, i. e. the active substance, in the brain compared to its free concentration in plasma, and thereby reduce the concentration of antiepileptics at the site of action. This can lead to pharmacoresistance and thus to the development of a treatment-resistant status epilepticus or treatment-resistant epilepsy. However, in vitro data suggest that sodium valproate is not a substrate for transporters such as ATP-binding cassette (ABC) transporters (e. g. P-glycoprotein (Pgp)) or multidrug resistance-associated proteins (MRP1, MRP2 and MRP5). The development of pharmacoresistance against valproate by these transporters is therefore considered unlikely.

### 5.2 Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/L (278–694 μmol/L). This reported range may depend on time of sampling and presence of co-medication.

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 considerable lower. It is usually shorter in children.
Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults.
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 – 100 mg/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 CFS 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.

*Placental transfer (see section 4.6)*
Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery.

Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

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

## 5.3 Preclinical safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.
Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

<u>Reproductive and developmental toxicity</u>
Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.
Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.
Behavioural abnormalities have been reported in the first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been observed in

the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

Testicular toxicity
In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 465 mg/kg/day and 150 mg/kg/day, respectively. The safety margin based on plasma concentrations is unknown, however body-surface-area comparisons indicate that there may be no safety margin.
In juvenile (sexually immature) and young adult rats (pubertal), a significant dose-related reduction in testes weight was observed at 240 mg/kg/day following i.v. and i.p. administration with no apparent histopathological changes. However, testicular atrophy was observed in the young adult rat at an i.v. dose of 480 mg/kg/day. Despite the absence of apparent histopathology changes, the testicular weight reductions were considered part of a dose-related spectrum leading to testicular atrophy. There is no safety margin for the effect on testicular weight.
There is a limited number of published papers which report findings in juvenile animals consistent with those reported in the GLP adult and juvenile studies, with respect to testicular weights. Reductions in testicular weights are associated with adverse effects on the adult male reproductive tract in animal studies and impaired fertility in adult patients (see section 4.6.)
The toxicological significance of the testicular findings in juvenile animals has not been evaluated and hence the relevance to human testicular development, particularly in the paediatric population, is unknown.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Prolonged–release granule:

Calcium stearate

Colloidal anhydrous silicon dioxide, methylated

Ammonium methacrylate copolymer (Type B)

Sorbic acid

Sodium hydroxide

Granule coating:

Ethyl cellulose

Dibutyl sebacate

Oleic acid

Capsule shell:
Gelatin
Indigo carmine (E 132)
Quinoline yellow (E104)
Sodium lauryl sulfate

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

18 months

### 6.4 Special precautions for storage

Do not store above 25ºC. Store in the original container. Keep the container tightly closed.

### 6.5 Nature and contents of container

Polyethylene container with polypropylene screw cap containing 30, 50, 100 or 200 prolonged-release capsules.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

DESITIN ARZNEIMITTEL GMBH

WEG BEIM JAEGER 214
HAMBURG
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## 8 MARKETING AUTHORISATION NUMBER(S)

PL 14040/0025

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/11/2024

## 10 DATE OF REVISION OF THE TEXT

19/02/2025

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1 NAME OF THE MEDICINAL PRODUCT

Episenta® 500 mg prolonged-release granules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect: 3 mmol (69.0 mg) sodium per dose

For the full list of excipients see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged-release granules.

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Female patients:

- For all female patients aged under 55 years: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all female patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

Male patients:

- For all male patients aged under 55 years initiating treatment with valproate: For the treatment of generalised, partial or other epilepsy only when there is no other effective

or tolerated treatment.
- For all male patients established on treatment with valproate or male patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

For the treatment of manic episode in bipolar disorder only when there is no other effective or tolerated treatment.
The continuation of treatment after manic episode could be considered in patients who have responded to sodium valproate for acute mania.

## 4.2 Posology and method of administration

Female children and women of childbearing potential aged under 55 years
No new female patients aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Valproate must be supervised by a specialist experienced in the management of epilepsy or bipolar disorder.
Valproate should not be prescribed in female children and women of childbearing potential aged under 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Where possible existing female children and women of childbearing potential aged under 55 years should be switched to another treatment unless two specialists independently consider and document there is no other effective or tolerated treatment. For those continuing to receive valproate, the benefits and risks of valproate should be carefully reconsidered at regular treatment reviews, at least annually (see section 4.4).
Valproate must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).
Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Male patients aged under 55 years
No new male children or men aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity are not applicable (see sections 4.4 and 4.6).
The specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the risk of infertility in males (see section 4.4, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

Posology

*Treatment in all forms of epilepsy:*
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.

Special populations
*Paediatric population*
*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. In children requiring doses higher than 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

*Children under 20kg*
20mg/kg body weight per day; in severe cases this may be increased up to 40mg/kg/day.

*Elderly*
Care should be taken when adjusting dosage in the elderly since the pharmacokinetics of 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.

*Renal impairment*
It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable (see section 4.9). Dosing should be modified according to clinical monitoring of the patient (see section 4.4).

*Hepatic impairment*
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see section 4.4 and 4.8).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see section 4.3 and 4.4).

Salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with sodium valproate, concomitant use in children under 3 years of age can increase the risk of liver toxicity (see section 4.4).

*Combined Therapy (see section 4.5)*

When starting Episenta® in patients already on other anticonvulsants, these should be tapered slowly; initiation of Episenta® treatment should then be gradual, with target dose being reached after about 2 weeks. 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. 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.

N.B. In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2).

*Manic episodes in bipolar disorder*

*Adults*

The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg sodium valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1,000 and 2,000 mg sodium valproate. Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored. Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

*Paediatric population*

The efficacy of Episenta® in children below 18 years of age in the treatment of manic episodes in bipolar disorder has not been established. With respect to safety information in children see section 4.8.

Method of administration

For oral administration.

The contents of the sachet 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 the granules with liquid or soft food should not be stored for future use. If the contents of the sachet 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

**Episenta® is contraindicated in the following situations:**

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- **Active liver disease**
- Personal or family history of severe hepatic dysfunction, especially drug related
- Patients with known urea cycle disorders (see section 4.4).
- Porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).

Treatment of epilepsy

- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

Treatment of bipolar disorder

- in pregnancy (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

## 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.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.

NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

The concomitant use of sodium valproate and carbapenem is not recommended (see section 4.5).

Aggravated convulsions:
As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

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 disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see section 4.3 and 4.4) 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 years of age due to the risk liver toxicity(see also section 4.5). 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 (see section 4.4 Severe liver damage and also section 4.5).

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 for patients at risk and those with a prior history of liver disease. Upon changes in concomitant medicinal products (dose increase or additions) that are known to impact the liver, liver monitoring should be restarted as appropriate (see section 4.5). 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) requires cessation of

valproate 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.

Patients with known or suspected mitochondrial disease
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Urea cycle disorders and risk of hyperammonaemia
When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of risk of hyperammonaemia with sodium valproate (see sections 4.3 and 4.4).

Patients at risk of hypocarnitinaemia
Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 Patients with known or suspected mitochondrial disease and Urea cycle disorders and risk of hyperammonaemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.
Patients should be warned to report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed. Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative. In these patients, carnitine monitoring should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Episenta®.
Carnitine supplementation should be considered in these patients. See also sections 4.5, 4.8 and 4.9.

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).

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 and 5.2).

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).

*Severe Cutaneous Adverse Reactions and Angioedema*

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

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).

Female children, women of childbearing potential aged under 55 years and pregnant women

**Pregnancy Prevention Programme**

Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk (11 %) for congenital malformations and neurodevelopmental disorders (30–40 %) which may lead to permanent disability (see section 4.6).
Valproate must only be initiated by two specialists who independently consider and document that there is no other effective or tolerated treatment.

Episenta® is contraindicated in the following situations:

Treatment of epilepsy
- in pregnancy unless two specialists independently consider and document that there is no

other effective or tolerated treatment (see sections 4.3 and 4.6).

- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder

- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The specialist must ensure that

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion, to support her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability, including the magnitude of these risks for children exposed to valproate in utero.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorders.
- the patient understands the need to consult her general practitioner (GP) for referral to a specialist as soon as she is planning a pregnancy to ensure timely discussion and switching to another treatment prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her GP for urgent referral to a specialist in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also apply to women who are not currently sexually active unless the specialist considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The specialist must ensure that

- the parents/caregivers of female children understand the need to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist.
- the parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability including the magnitude of these risks for children exposed to valproate in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider other treatment options. If valproate is the only effective and tolerated

treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to another treatment before they reach menarche.

Pregnancy test
Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception
Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to support her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

*Oestrogen-containing products*
Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing oestrogen-containing products.
On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist
The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss and complete the annual risk acknowledgement form with the patient and/or carer, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider other treatment options. Every effort should be made to switch to an appropriate treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to another treatment prior to conception, and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must immediately contact her GP to be referred to a specialist to re-evaluate treatment with valproate and consider switching to other treatment options. The patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that
- the patient card is provided with every valproate pack dispensation and that the patients

understand its content.

- the patients are advised not to stop valproate medication and to immediately contact their GP to be referred to a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.
An annual risk acknowledgement form needs to be discussed and completed with the patient and/or carer at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy or bipolar disorder.

Male children and men
All male patients and/or their carers should be made aware of the potential risk to children born to men treated with valproate in the 3 months before conception (see also section 4.6), of the risk of infertility in men (see section 4.2, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk (see section 4.6) and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation.

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

For males aged under 55 years, at initiation of treatment, the specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

Diabetic patients
Sodium valproate is eliminated mainly through the kidneys, partly in the form of ketone

bodies: this may give false positive results in the urine testing of possible diabetics.

Alcohol
Alcohol intake is not recommended during treatment with valproate.

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.

Sodium content
This medicinal product contains 69.0 mg sodium per dose, equivalent to 3.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of Episenta® on other drugs

*Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines*
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. In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

*Lithium*
Episenta® has no effect on serum lithium levels.

*Olanzapine*
Valproic acid may decrease the olanzapine plasma concentration.

*Phenobarbital*
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.

*Primidone*
Sodium valproate increases **primidone** plasma levels causing an exacerbation of side effects, e.g. sedation; these signs cease with long term treatment. Clinical monitoring is recommended especially when initiating combined therapy with dosage adjustment as necessary.

*Phenytoin*
Episenta® decreases phenytoin total plasma concentration and increases the free form of phenytoin leading to possible overdosage symptoms. Therefore, clinical monitoring is recommended with the free form of phenytoin being measured,when phenytoin plasma levels are determined.

*Carbamazepine*

Clinical toxicity has been reported when Episenta® was administered with carbamazepine as Episenta® may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

*Lamotrigine*
Episenta® reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

*Felbamate*
Valproic acid may decrease the felbamate mean clearance by up to 16%.

*Rufinamide*
Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

*Propofol*
Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

*Zidovudine*
Episenta® may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

*Nimodipine*
In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

*Vitamin K-dependent anticoagulants*
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproate. The prothrombin time should be closely monitored.

*Temozolomide*
Co-administration of **temozolomide** and Episenta® may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on Episenta®

*Antiepileptics*
Antiepileptics with enzyme inducing effects e.g. **phenytoin, phenobarbital, carbamazepine,** decrease valproate plasma levels. Plasma levels should be monitored and dosage adjusted accordingly.

Valproic acid metabolite levels may be increased in the case of concomitant use with **phenytoin** or **phenobarbital**. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of felbamate and Episenta® decreases valproic acid clearance by 22 %–50 % and consequently increase the valproic acid plasma concentrations. Episenta® dosage should be monitored.

*Anti-malaria agents*
**Mefloquine** and **chloroquine** increases valproate metabolism and therefore epileptic seizures may occur in combined therapy. The dosage of sodium valproate may need adjustment.

*Highly protein bound agents*
Free valproate levels may be increased in the case of concomitant use with highly protein bound agents e.g. **acetylsalicylic acid**.

*Cimetidine or erythromycin*
Valproate plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with **cimetidine** or **erythromycin**.

*Carbapenem antibiotics (such as imipenem, panipenem and meropenem)*
Decreases in blood levels of valproic acid have been reported when it is co-administered with **carbapenem agents** resulting in a 60 %–100 % decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

*Colestyramine*
**Colestyramine** may decrease the absorption of valproate.

*Rifampicin*
**Rifampicin** may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co- administered with rifampicin.

*Protease inhibitors*
Protease inhibitors such as **lopinavir** and **ritonavir** decrease valproate plasma level when co-administered.

*Oestrogen-containing products, including oestrogen-containing hormonal contraceptives*
**Oestrogens** are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.
On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

**Metamizole** may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

*Methotrexate*
Some case reports describe a significant decrease in valproate serum levels after **methotrexate** administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

<u>Other interaction</u>
*Risk of liver damage*
The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section 4.4). Concomitant use of valproate and multiple

anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4). Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be exercised when valproate is concomitantly used with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

*Newer anti-epileptics (including topiramate and acetazolamide)*
Caution is advised when using Episenta® in combination with newer antiepileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. careful monitoring of signs and symptoms is advised in particularly at- risk patients such as those with pre-existing encephalopathy.

*Pivalate-conjugated medicines*
Concomitant administration of valproate and pivalate-conjugated medicines (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4 Patients at risk of hypocarnitinaemia). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

*Quetiapine*
Co-administration of Episenta® and quetiapine may increase the risk of neutropenia/leucopenia.

*Clozapine*
Concomitant treatment of valproate and clozapine may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of valproate with clozapine is necessary, careful monitoring for both events is required.

## 4.6 Fertility, pregnancy and lactation

- Episenta® is contraindicated as treatment for bipolar disorder in pregnancy.
- Episenta®is contraindicated as treatment for epilepsy in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see section 4.3 and 4.4).
- Episenta®is contraindicated for use in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and Developmental Effects
*Pregnancy Exposure Risk related to valproate*
In females, both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neuro-developmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate
Valproate was shown to cross the placental barrier in both animal species and humans (see section 5.2).

In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

*Congenital malformations from in utero exposure*
A meta-analysis (including registries and cohort studies) showed that approximately 11 % of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2–3 %).
The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.
The risk is dose dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.
*In utero* exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.
*In utero* exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

*Neuro-developmental disorders from in utero exposure*
Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neuro-developmental disorders which may lead to permanent disability (including that of autism) seems to be dose-dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists cannot be established based on available data. When valproate is administered in polytherapy with other antiepileptic drugs during pregnancy, the risk of neuro-developmental disorders which may lead to permanent disability in the offspring were also significantly increased as compared with those in children from the general population or born to untreated women with epilepsy.
The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
When valproate is administered in monotherapy, studies in children exposed *in utero* to valproate show that up to 30-40 % experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics during pregnancy, although the role of confounding factors related to intellectual disability cannot be excluded. There is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data from a population-based study show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.

Available data from another population-based study show that children exposed to valproate *in utero* are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

*Female children and women of childbearing potential aged under 55 years (see above and section 4.4)*

*Oestrogen-containing products*
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

*If a woman plans a pregnancy*
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

*Pregnant women*
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy.
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).
If a woman using valproate becomes pregnant, she must be immediately referred by their GP to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:
- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

<u>Risk in the neonate</u>
- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma

level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper- excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1 % to 10 % of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Episenta® therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8).
Valproate administration may also impair fertility in men (see sections 4.2, 4.4 and 4.8). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception.

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4).

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

## 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 Undesirable effects

Frequency categories are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Congenital, familial and genetic disorders
Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

| | |
|---|---|
| *Rare:* | myelodysplastic syndrome |
| *Not known:* | acquired Pelger-Huet anomaly |

Hepato-biliary disorders

| | |
|---|---|
| *Common:* | liver injury (see section 4.4); increased liver enzymes, particularly early in treatment, and may be transient (see section 4.4) |
| *Not known:* | severe liver damage, including hepatic failure sometimes resulting in fatalities (see sections 4.2, 4.3 and 4.4) |

Gastro-intestinal disorders

| | |
|---|---|
| *Very common:* | nausea |
| *Common:* | vomiting, gingival disorder, (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea<br>The above three adverse events frequently occur at the start of the treatment, but usually disappearing after a few days without discontinuing treatment. These problems can usually be overcome by taking Episenta® with or after food. |
| *Uncommon:* | pancreatitis, sometimes lethal (see section 4.4) |

Psychiatric disorders

| | |
|---|---|
| *Common:* | confusional state, hallucinations, aggression*, agitation*, disturbance in attention* |
| *Rare:* | abnormal behaviour*, psychomotor hyperactivity*, learning disorder* |

*These ADRs are principally observed in the paediatric population.

Nervous system disorders:

| | |
|---|---|
| *Very common:* | tremor |
| *Common:* | extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus |
| *Uncommon:* | coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia, aggravated convulsions (see section 4.4) |
| *Rare:* | reversible dementia associated with reversible cerebral atrophy, cognitive disorder |

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 occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have uncommonly been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.
An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Endocrine disorders

| | |
|---|---|
| *Uncommon:* | Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased) |
| *Rare:* | hypothyroidism (see section 4.6) |

*Metabolism and nutrition disorders*

| | |
|---|---|
| *Common:* | hyponatraemia, weight increased* |

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

| | |
|---|---|
| *Rare:* | hyperammonaemia* (see section 4.4), obesity |

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, 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.
Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see sections 4.3 and 4.4).
*Not known:* hypocarnitinaemia (see section 4.3 and 4.4)

Blood and lymphatic system disorders

| | |
|---|---|
| *Common:* | anaemia, thrombocytopenia (see section 4.4) |
| *Uncommon:* | pancytopenia, leucopenia |
| *Rare:* | bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis. |

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Episenta® has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6).).

Skin and subcutaneous tissue disorders

| | |
|---|---|
| *Common:* | hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within 6 months, although the hair may become more curly than previously.<br>nail and nail bed disorders |
| *Uncommon:* | angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth) |
| *Rare:* | toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome. |
| *Not known:* | hyperpigmentation |

Reproductive system and breast disorders

| | |
|---|---|
| *Common:* | dysmenorrhea |
| *Uncommon:* | amenorrhea |
| *Rare:* | male infertility (see section 4.6), polycystic ovaries |
| *Very rare:* | gynaecomastia |

Vascular disorders

| | |
|---|---|
| *Common:* | haemorrhage (see section 4.4. and 4.6) |
| *Uncommon:* | vasculitis |

Eye disorders

| | |
|---|---|
| *Rare:* | diplopia |

Ear and labyrinth disorders

| | |
|---|---|
| *Common:* | deafness, a cause and effect relationship has not been established |

Renal and urinary disorders

| | |
|---|---|
| *Common:* | urinary incontinence |
| *Uncommon:* | renal failure |
| *Rare:* | enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Episenta® therapy, but the mode of action is as yet unclear. |

General disorders and administration site conditions

| | |
|---|---|
| *Uncommon:* | hypothermia, non-severe oedema peripheral |

Musculoskeletal and connective tissue disorders

| | |
|---|---|
| *Uncommon:* | bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Episenta®. The mechanism by which Episenta® affects bone metabolism has not been identified. |
| *Rare:* | systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4) |

Respiratory, thoracic and mediastinal disorders

| | |
|---|---|
| *Uncommon:* | pleural effusion (eosinophilic) |

Investigations:

*Rare:* coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

Paediatric population

The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (see details below).
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

## 4.9 Overdose

Symptoms

Cases of accidental and deliberate valproate overdose have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.
Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Management

Hospital management of overdose should be symptomatic, including cardio-respiratory-gastric monitoring. Gastric lavage may be useful up to 10–12 hours following ingestion.
In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Fatty acid derivatives, ATCcode: 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.

The increased expression of drug efflux transporters at the blood-brain barrier can result in lower concentrations of their respective substrate, i. e. the active substance, in the brain compared to its free concentration in plasma, and thereby reduce the concentration of antiepileptics at the site of action. This can lead to pharmacoresistance and thus to the development of a treatment-resistant status epilepticus or treatment-resistant epilepsy. However, in vitro data suggest that sodium valproate is not a substrate for transporters such as ATP-binding cassette (ABC) transporters (e. g. P-glycoprotein (Pgp)) or multidrug resistance-associated proteins (MRP1, MRP2 and MRP5). The development of pharmacoresistance against valproate by these transporters is therefore considered unlikely.

### 5.2 Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/L (278–694 μmol/L). This reported range may depend on time of sampling and presence of co-medication.

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 considerable lower. It is usually shorter in children.
Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults.
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 – 100 mg/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 CFS 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.

*Placental transfer (see section 4.6)*
Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery.

Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

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

## 5.3 Preclinical safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.
Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

<u>Reproductive and developmental toxicity</u>
Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.
Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.
Behavioural abnormalities have been reported in the first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

<u>Testicular toxicity</u>

In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 465 mg/kg/day and 150 mg/kg/day, respectively. The safety margin based on plasma concentrations is unknown, however body-surface-area comparisons indicate that there may be no safety margin.
In juvenile (sexually immature) and young adult rats (pubertal), a significant dose-related reduction in testes weight was observed at 240 mg/kg/day following i.v. and i.p. administration with no apparent histopathological changes. However, testicular atrophy was observed in the young adult rat at an i.v. dose of 480 mg/kg/day. Despite the absence of apparent histopathology changes, the testicular weight reductions were considered part of a dose-related spectrum leading to testicular atrophy. There is no safety margin for the effect on testicular weight.
There is a limited number of published papers which report findings in juvenile animals consistent with those reported in the GLP adult and juvenile studies, with respect to testicular weights. Reductions in testicular weights are associated with adverse effects on the adult male reproductive tract in animal studies and impaired fertility in adult patients (see section 4.6).
The toxicological significance of the testicular findings in juvenile animals has not been evaluated and hence the relevance to human testicular development, particularly in the paediatric population, is unknown.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Prolonged–release granule:

Calcium stearate

Colloidal anhydrous silicon dioxide, methylated

Ammonium methacrylate copolymer (Type B)

Sorbic acid

Sodium hydroxide

Granule coating:

Ethyl cellulose

Dibutyl sebacate

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.

### 6.5 Nature and contents of container

30, 50, 100 or 200 Clay coated kraftpaper/Aluminium/PE sachets.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

DESITIN ARZNEIMITTEL GMBH
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## 8 MARKETING AUTHORISATION NUMBER(S)

PL 14040/0026

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/11/2024

## 10 DATE OF REVISION OF THE TEXT

19/02/2025

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

# 1 NAME OF THE MEDICINAL PRODUCT

Episenta® 1000 mg prolonged-release granules

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect: 6 mmol (137.9 mg) sodium per dose

For the full list of excipients see section 6.1

# 3 PHARMACEUTICAL FORM

Prolonged-release granules.

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

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

Female patients:

- For all female patients aged under 55 years: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all female patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

Male patients:

- For all male patients aged under 55 years initiating treatment with valproate: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.

- For all male patients established on treatment with valproate or male patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

For the treatment of manic episode in bipolar disorder only when there is no other effective or tolerated treatment.
The continuation of treatment after manic episode could be considered in patients who have responded to sodium valproate for acute mania.

**4.2 Posology and method of administration**

Female children and women of childbearing potential aged under 55 years
No new female patients aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Valproate must be supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Valproate should not be prescribed in female children and women of childbearing potential aged under 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).
Where possible existing female children and women of childbearing potential aged under 55 years should be switched to another treatment unless two specialists independently consider and document there is no other effective or tolerated treatment. For those continuing to receive valproate, the benefits and risks of valproate should be carefully reconsidered at regular treatment reviews, at least annually (see section 4.4).
Valproate must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).
Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Male patients aged under 55 years
No new male children or men aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity are not applicable (see sections 4.4 and 4.6).
The specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the risk of infertility in males (see section 4.4, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

Posology
*Treatment in all forms of epilepsy:*
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.

Special populations
*Paediatric population*
*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. In children requiring doses higher than 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

*Children under 20kg*
20mg/kg body weight per day; in severe cases this may be increased up to 40mg/kg/day.

*Elderly*
Care should be taken when adjusting dosage in the elderly since the pharmacokinetics of 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.

*Renal impairment*
It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable (see section 4.9). Dosing should be modified according to clinical monitoring of the patient (see section 4.4).

*Hepatic impairment*
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see section 4.4 and 4.8).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see section 4.3 and 4.4).

Salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with sodium valproate, concomitant use in children under 3 years of age can increase the risk of liver toxicity (see section 4.4).

*Combined Therapy (see section 4.5)*
When starting Episenta® in patients already on other anticonvulsants, these should be tapered slowly; initiation of Episenta® treatment should then be gradual, with target dose being reached after about 2 weeks. 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. 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.

N.B. In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2).

*Manic episodes in bipolar disorder*
*Adults*
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg sodium valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1,000 and 2,000 mg sodium valproate. Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored.
Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

*Paediatric population*
The efficacy of Episenta® in children below 18 years of age in the treatment of manic episodes in bipolar disorder has not been established. With respect to safety information in children see section 4.8.

Method of administration
For oral administration.
The contents of the sachet 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 the granules with liquid or soft food should not be stored for future use. If the contents of the sachet 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**

**Episenta® is contraindicated in the following situations:**

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- **Active liver disease**
- Personal or family history of severe hepatic dysfunction, especially drug related
- Patients with known urea cycle disorders (see section 4.4).
- Porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).

Treatment of epilepsy
- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

Treatment of bipolar disorder
- in pregnancy (see sections 4.4 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

## 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.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.

NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

The concomitant use of sodium valproate and carbapenem is not recommended (see section 4.5).

Aggravated convulsions:
As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or

the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

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 disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see section 4.3 and 4.4) 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 years of age due to the risk liver toxicity (see also section 4.5). 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 (see section 4.4 Severe liver damage and also section 4.5).

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 for patients at risk and those with a prior history of liver disease. Upon changes in concomitant medicinal products (dose increase or additions) that are known to impact the liver, liver monitoring should be restarted as appropriate (see section 4.5).
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) requires cessation of valproate 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.

Patients with known or suspected mitochondrial disease
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase $\gamma$ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Urea cycle disorders and risk of hyperammonaemia
When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of risk of hyperammonaemia with sodium valproate (see sections 4.3 and 4.4).

Patients at risk of hypocarnitinaemia
Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 Patients with known or suspected mitochondrial disease and Urea cycle disorders and risk of hyperammonaemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.
Patients should be warned to report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed. Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative. In these patients, carnitine monitoring should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Episenta®.
Carnitine supplementation should be considered in these patients. See also sections 4.5, 4.8 and 4.9.

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).

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 and 5.2).

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).

*Severe Cutaneous Adverse Reactions and Angioedema*

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

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).

Female children, women of childbearing potential aged under 55 years and pregnant women

**Pregnancy Prevention Programme**

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk (11 %) for congenital malformations and neurodevelopmental disorders (30–40 %) which may lead to permanent disability (see section 4.6).
Valproate must only be initiated by two specialists who independently consider and document that there is no other effective or tolerated treatment.

Episenta® is contraindicated in the following situations:

Treatment of epilepsy
- in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder

- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The specialist must ensure that

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion, to support her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability, including the magnitude of these risks for children exposed to valproate in utero.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorders.
- the patient understands the need to consult her general practitioner (GP) for referral to a specialist as soon as she is planning a pregnancy to ensure timely discussion and switching to another treatment prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her GP for urgent referral to a specialist in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also apply to women who are not currently sexually active unless the specialist considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children
The specialist must ensure that

- the parents/caregivers of female children understand the need to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist.
- the parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders which may lead to permanent disability including the magnitude of these risks for children exposed to valproate in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider other treatment options. If valproate is the only effective and tolerated treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to another treatment before they reach menarche.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception
Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to support her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

*Oestrogen-containing products*
Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing oestrogen-containing products.
On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist
The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss and complete the annual risk acknowledgement form with the patient and/or carer, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider other treatment options. Every effort should be made to switch to an appropriate treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to another treatment prior to conception, and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must immediately contact her GP to be referred to a specialist to re-evaluate treatment with valproate and consider switching to other treatment options. The patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that
- the patient card is provided with every valproate pack dispensation and that the patients understand its content.
- the patients are advised not to stop valproate medication and to immediately contact their GP to be referred to a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.
An annual risk acknowledgement form needs to be discussed and completed with the patient and/or carer at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy or bipolar disorder.

Male children and men
All male patients and/or their carers should be made aware of the potential risk to children born to men treated with valproate in the 3 months before conception (see also section 4.6), of the risk of infertility in men (see section 4.2, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk (see section 4.6) and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation.

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

For males aged under 55 years, at initiation of treatment, the specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

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

Alcohol
Alcohol intake is not recommended during treatment with valproate.

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.

Excipient with known effect
This medicinal product contains 137.9 mg sodium per dose, equivalent to 7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of Episenta® on other drugs

*Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines*
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. In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

*Lithium*
Episenta® has no effect on serum lithium levels.

*Olanzapine*
Valproic acid may decrease the olanzapine plasma concentration.

*Phenobarbital*
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.

*Primidone*
Sodium valproate increases **primidone** plasma levels causing an exacerbation of side effects, e.g. sedation; these signs cease with long term treatment. Clinical monitoring is recommended especially when initiating combined therapy with dosage adjustment as necessary.

*Phenytoin*
Episenta® decreases **phenytoin** total plasma concentration and increases the free form of phenytoin leading to possible overdosage symptoms. Therefore, clinical monitoring is recommended with the free form of phenytoin being measured, when phenytoin plasma levels are determined.

*Carbamazepine*
Clinical toxicity has been reported when Episenta® was administered with **carbamazepine** as Episenta® may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

*Lamotrigine*

Episenta® reduces the metabolism of **lamotrigine** and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

*Felbamate*
Valproic acid may decrease the **felbamate** mean clearance by up to 16%.

*Rufinamide*
Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

*Propofol*
Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

*Zidovudine*
Episenta® may raise **zidovudine** plasma concentration leading to increased zidovudine toxicity.

*Nimodipine*
In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

*Vitamin K-dependent anticoagulants*
The anticoagulant effect of **warfarin** and other **coumarin anticoagulants** may be increased following displacement from plasma protein binding sites by valproate The prothrombin time should be closely monitored.

*Temozolomide*
Co-administration of **temozolomide** and Episenta® may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

<u>Effects of other drugs on Episenta®</u>

*Antiepileptics*
Antiepileptics with enzyme inducing effects e.g. **phenytoin, phenobarbital, carbamazepine,** decrease valproate plasma levels. Plasma levels should be monitored and dosage adjusted accordingly.

Valproic acid metabolite levels may be increased in the case of concomitant use with **phenytoin** or **phenobarbital**. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of **felbamate** and Episenta® decreases valproic acid clearance by 22 %–50 % and consequently increase the valproic acid plasma concentrations. Episenta® dosage should be monitored.

*Anti-malaria agents*
**Mefloquine** and **chloroquine** increases valproate metabolism and therefore epileptic seizures may occur in combined therapy. The dosage of sodium valproate may need adjustment.

*Highly protein bound agents*

Free valproate levels may be increased in the case of concomitant use with highly protein bound agents e.g. **acetylsalicylic acid**.

*Cimetidine or erythromycin*
Valproate plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

*Carbapenem antibiotics (such as imipenem, panipenem and meropenem)*
Decreases in blood levels of valproic acid have been reported when it is co-administered with **carbapenem agents** resulting in a 60 %–100 % decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

*Colestyramine*
**Colestyramine** may decrease the absorption of valproate.

*Rifampicin*
**Rifampicin** may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co- administered with rifampicin.

*Protease inhibitors*
Protease inhibitors such as **lopinavir** and **ritonavir** decrease valproate plasma level when co-administered.

*Oestrogen-containing products, including oestrogen-containing hormonal contraceptives*
**Oestrogens** are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.
On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

**Metamizole** may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

*Methotrexate*
Some case reports describe a significant decrease in valproate serum levels after **methotrexate** administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

<u>Other interaction</u>
*Risk of liver damage*
The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section 4.4). Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4). Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be

exercised when valproate is concomitantly used with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

*Newer anti-epileptics (including topiramate and acetazolamide)*
Caution is advised when using Episenta® in combination with newer **antiepileptics** whose pharmacodynamics may not be well established.

Concomitant administration of valproate and **topiramate** or **acetazolamide** has been associated with encephalopathy and/or hyperammonaemia. careful monitoring of signs and symptoms is advised in particularly at- risk patients such as those with pre-existing encephalopathy.

*Pivalate-conjugated medicines*
Concomitant administration of valproate and pivalate-conjugated medicines (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4 Patients at risk of hypocarnitinaemia). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

*Quetiapine*
Co-administration of Episenta® and **quetiapine** may increase the risk of neutropenia/leucopenia.

*Clozapine*
Concomitant treatment of valproate and clozapine may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of valproate with clozapine is necessary, careful monitoring for both events is required.

## 4.6 Fertility, pregnancy and lactation

- Episenta® is contraindicated as treatment for bipolar disorder in pregnancy.
- Episenta®is contraindicated as treatment for epilepsy in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see section 4.3 and 4.4).
- Episenta®is contraindicated for use in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and Developmental Effects
*Pregnancy Exposure Risk related to valproate*
In females, both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neuro-developmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate
Valproate was shown to cross the placental barrier in both animal species and humans (see section 5.2).

In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

*Congenital malformations from in utero exposure*
A meta-analysis (including registries and cohort studies) showed that approximately 11 % of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2–3 %).
The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.
The risk is dose dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.
*In utero* exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.
*In utero* exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

*Neuro-developmental disorders from in utero exposure*
Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neuro-developmental disorders which may lead to permanent disability (including that of autism) seems to be dose-dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists cannot be established based on available data. When valproate is administered in polytherapy with other antiepileptic drugs during pregnancy, the risk of neuro-developmental disorders which may lead to permanent disability in the offspring were also significantly increased as compared with those in children from the general population or born to untreated women with epilepsy.
The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
When valproate is administered in monotherapy, studies in children exposed *in utero* to valproate show that up to 30-40 % experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics during pregnancy, although the role of confounding factors related to intellectual disability cannot be excluded. There is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data from a population-based study show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.
Available data from another population-based study show that children exposed to valproate *in utero* are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

*Female children and women of childbearing potential aged under 55 years (see above and section 4.4)*

*Oestrogen-containing products*
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

*If a woman plans a pregnancy*
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

*Pregnant women*
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy.
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).
If a woman using valproate becomes pregnant, she must be immediately referred by their GP to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:
- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

<u>Risk in the neonate</u>
- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper- excitability,

jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1 % to 10 % of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Episenta® therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8).
Valproate administration may also impair fertility in men (see sections 4.2, 4.4 and 4.8). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception.

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4).

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

## 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 Undesirable effects

Frequency categories are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Congenital, familial and genetic disorders
Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

| | |
|---|---|
| *Rare:* | myelodysplastic syndrome |
| *Not known:* | acquired Pelger-Huet anomaly |

Hepato-biliary disorders

| | |
|---|---|
| *Common:* | liver injury (see section 4.4); increased liver enzymes, particularly early in treatment, and may be transient (see section 4.4) |
| *Not known:* | severe liver damage, including hepatic failure sometimes resulting in fatalities (see sections 4.2, 4.3 and 4.4) |

Gastro-intestinal disorders

| | |
|---|---|
| *Very common:* | nausea |
| *Common:* | vomiting, gingival disorder, (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea<br>The above three adverse events frequently occur at the start of the treatment, but usually disappearing after a few days without discontinuing treatment. These problems can usually be overcome by taking Episenta® with or after food. |
| *Uncommon:* | pancreatitis, sometimes lethal (see section 4.4) |

Psychiatric disorders

| | |
|---|---|
| *Common:* | confusional state, hallucinations, aggression*, agitation*, disturbance in attention* |
| *Rare:* | abnormal behaviour*, psychomotor hyperactivity*, learning disorder* |

*These ADRs are principally observed in the paediatric population.

Nervous system disorders:

| | |
|---|---|
| *Very common:* | tremor |
| *Common:* | extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus |
| *Uncommon:* | coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia, aggravated convulsions (see section 4.4) |
| *Rare:* | reversible dementia associated with reversible cerebral atrophy, cognitive disorder |

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 occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have uncommonly been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.
An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Endocrine disorders

| | |
|---|---|
| *Uncommon:* | Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased) |
| *Rare:* | hypothyroidism (see section 4.6) |

Metabolism and nutrition disorders

| | |
|---|---|
| *Common:* | hyponatraemia, weight increased* |

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

| | |
|---|---|
| *Rare:* | hyperammonaemia* (see section 4.4), obesity |

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, 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.
Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see sections 4.3 and 4.4).
*Not known:* hypocarnitinaemia (see section 4.3 and 4.4)

Blood and lymphatic system disorders

| | |
|---|---|
| *Common:* | anaemia, thrombocytopenia (see section 4.4) |
| *Uncommon:* | pancytopenia, leucopenia |
| *Rare:* | bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis. |

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Episenta® has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see

also section 4.6).).

Skin and subcutaneous tissue disorders

| | |
|---|---|
| *Common:* | hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within 6 months, although the hair may become more curly than previously.<br>nail and nail bed disorders |
| *Uncommon:* | angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth) |
| *Rare:* | toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome. |
| *Not known:* | hyperpigmentation |

Reproductive system and breast disorders

| | |
|---|---|
| *Common:* | dysmenorrhea |
| *Uncommon:* | amenorrhea |
| *Rare:* | male infertility (see section 4.6), polycystic ovaries |
| *Very rare:* | gynaecomastia |

Vascular disorders

| | |
|---|---|
| *Common:* | haemorrhage (see section 4.4. and 4.6) |
| *Uncommon:* | vasculitis |

Eye disorders:

| | |
|---|---|
| *Rare*: | diplopia |

Ear and labyrinth disorders

| | |
|---|---|
| *Common:* | deafness, a cause and effect relationship has not been established |

Renal and urinary disorders

| | |
|---|---|
| *Common:* | urinary incontinence |
| *Uncommon:* | renal failure |
| *Rare:* | enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Episenta® therapy, but the mode of action is as yet unclear. |

General disorders and administration site conditions

| | |
|---|---|
| *Uncommon:* | hypothermia, non-severe oedema peripheral |

Musculoskeletal and connective tissue disorders

| | |
|---|---|
| *Uncommon:* | bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Episenta®. The mechanism by which Episenta® affects bone metabolism has not been identified. |
| *Rare:* | systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4) |

Respiratory, thoracic and mediastinal disorders

| | |
|---|---|
| *Uncommon:* | pleural effusion (eosinophilic) |

Investigations

| | |
|---|---|
| *Rare:* | coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged). |

Paediatric population
The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (see details below).
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

## 4.9 Overdose

Symptoms
Cases of accidental and deliberate valproate overdose have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.
Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Management
Hospital management of overdose should be symptomatic, including cardio-respiratory-gastric monitoring. Gastric lavage may be useful up to 10–12 hours following ingestion.
In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Fatty acid derivatives, ATCcode: 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.

The increased expression of drug efflux transporters at the blood-brain barrier can result in lower concentrations of their respective substrate, i. e. the active substance, in the brain compared to its free concentration in plasma, and thereby reduce the concentration of antiepileptics at the site of action. This can lead to pharmacoresistance and thus to the development of a treatment-resistant status epilepticus or treatment-resistant epilepsy. However, in vitro data suggest that sodium valproate is not a substrate for transporters such as ATP-binding cassette (ABC) transporters (e. g. P-glycoprotein (Pgp)) or multidrug resistance-associated proteins (MRP1, MRP2 and MRP5). The development of pharmacoresistance against valproate by these transporters is therefore considered unlikely.

### 5.2 Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/L (278–694 μmol/L). This reported range may depend on time of sampling and presence of co-medication.

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 considerable lower. It is usually shorter in children.
Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults.
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 – 100 mg/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 CFS 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.

*Placental transfer (see section 4.6)*
Valproate crosses the placental barrier in animal species and in humans:
- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery.

Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

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

## 5.3 Preclinical safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. I*n vivo,* however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.
Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproductive and developmental toxicity
Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.
Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.
Behavioural abnormalities have been reported in the first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

Testicular toxicity
In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 465 mg/kg/day and

150 mg/kg/day, respectively. The safety margin based on plasma concentrations is unknown, however body-surface-area comparisons indicate that there may be no safety margin.
In juvenile (sexually immature) and young adult rats (pubertal), a significant dose-related reduction in testes weight was observed at 240 mg/kg/day following i.v. and i.p. administration with no apparent histopathological changes. However, testicular atrophy was observed in the young adult rat at an i.v. dose of 480 mg/kg/day. Despite the absence of apparent histopathology changes, the testicular weight reductions were considered part of a dose-related spectrum leading to testicular atrophy. There is no safety margin for the effect on testicular weight.
There is a limited number of published papers which report findings in juvenile animals consistent with those reported in the GLP adult and juvenile studies, with respect to testicular weights. Reductions in testicular weights are associated with adverse effects on the adult male reproductive tract in animal studies and impaired fertility in adult patients (see section 4.6.)
The toxicological significance of the testicular findings in juvenile animals has not been evaluated and hence the relevance to human testicular development, particularly in the paediatric population, is unknown.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Prolonged–release granule:

Calcium stearate

Colloidal anhydrous silicon dioxide, methylated

Ammonium methacrylate copolymer (Type B)

Sorbic acid

Sodium hydroxide

Granule coating:

Ethyl cellulose

Dibutyl sebacate

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 package.

### 6.5 Nature and contents of container

30, 50, 100 or 200 Clay coated kraftpaper/Aluminium/PE sachets.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

## 7 MARKETING AUTHORISATION HOLDER

DESITIN ARZNEIMITTEL GMBH
WEG BEIM JAEGER 214
HAMBURG
D-22335 GERMANY

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 14040/0027

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10 DATE OF REVISION OF THE TEXT

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