IMPORTANT SAFETY WARNING FOR WOMEN AND GIRLS

Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.
Valproate is contraindicated in women of childbearing potential unless the conditions of "Prevent", the valproate pregnancy prevention programme are fulfilled.

HOW TO PRESCRIBE

O.D. or B.D.

Episenta®▼

Prolonged-release sodium valproate

To guarantee the correct Episenta® prescription:

℞ Episenta® prolonged-release capsules or granules*

Remember to prescribe by brand name to ensure ongoing supply of the correct medicine.

Episenta® is used for the treatment of all forms of epilepsy.

Information about the risks of valproate use in girls and women of childbearing potential can be found on the inside.

*Episenta® 150mg and 300mg presented in capsules.
Episenta® 500mg and 1000mg presented as granules in sachets.

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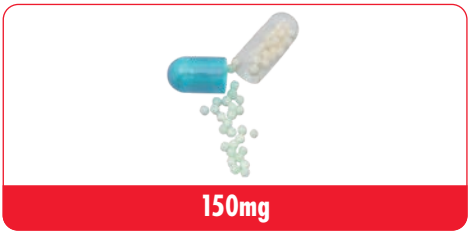
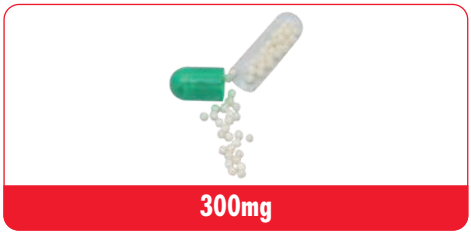
EPISENTA®: UNIFORM 2mm PROLONGED-RELEASE GRANULES IN CAPSULES OR SACHETS AT 4 STRENGTHS

A modified release oral formulation consistent with published EMA Guideline[1]



150mg



300mg

500mg

1000mg

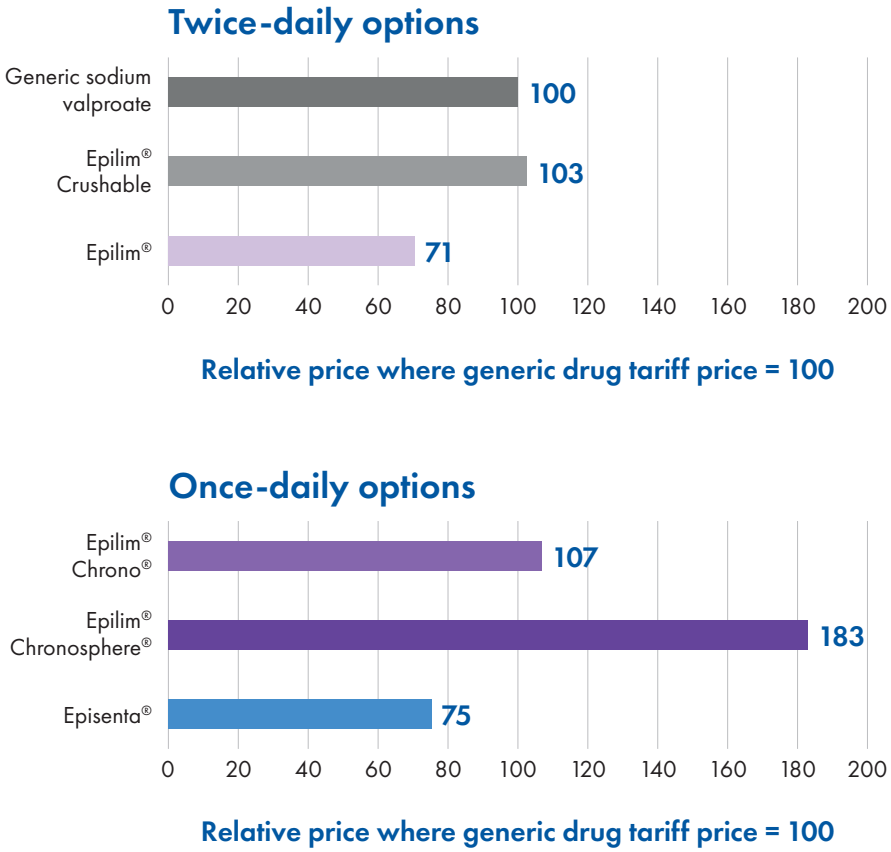
Also indicated for manic episode in adults with bipolar disorder when lithium is contraindicated or not tolerated. Please see Episenta® SmPC for specific dosing.[2]

- Episenta® granules have the potential to bring about lasting improvements in patient adherence, ***"...and to improve the efficacy of long term treatment in patients"*** [3]
- Specifically formulated for **children and adolescents**
- **Bioequivalent** to leading brand[4]
- Proven **effective and well-tolerated** treatment[3]
- Episenta® is an ability-appropriate granule formulation which can be prescribed to support the needs of **LD patients**[2]
- **Easy Read Booklets** available to support Episenta® prescribing[5]
- Formulation suitable for patients on **ketogenic diets**[2]

CURRENT PRESCRIBING OF SODIUM VALPROATE ORAL TABLETS

Episenta® is the least expensive once-daily sodium valproate tablet and is less expensive than the generic reimbursement price[6]

Sodium valproate relative tablet prices[6]



ONCE-DAILY vs. TWICE-DAILY ANTI-EPILEPTIC DRUG (AED) DOSING

Increasing the number of times per day AEDs are to be taken increases the risk of seizures[7]

- In a 2002 survey of 661 individuals with epilepsy, 45% of individuals reported having a seizure after having missed an AED dose
- Key predictors of seizures after having missed an AED dose were found to be:
  - *Frequency of taking seizure medication – there was a 36% increase in the odds of a seizure following a missed dose with each increase in the number of times a day seizure medication was taken*
  - *Number of seizure control tablets/capsules taken per day – there was a 43% increase in the odds of a seizure following a missed dose associated with each step on a scale from 1-3, 4-6, 7-10 or 11+ tablets/capsules per day*
- The authors concluded that:
  "...physicians should consider prescribing the simplest regimen with the fewest daily doses and tablets and the expectation of reducing the likelihood of breakthrough seizures."

O.D. or B.D.

Episenta®

Prolonged-release sodium valproate

THE RISK OF VALPROATE USE IN GIRLS (OF ANY AGE) AND WOMEN OF CHILDBEARING POTENTIAL

Valproate is highly teratogenic. Children born to women who take valproate during pregnancy are at significant risk of physical birth defects (approximately 10% of cases) and persistent developmental disorders (30 to 40% of cases). Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. Valproate is contraindicated in pregnancy unless there is no suitable alternative treatment. Valproate is contraindicated for girls and women of childbearing potential unless the conditions of the Pregnancy Prevention Programme ("Prevent") are met and only if other treatments are ineffective or not tolerated, as judged by a specialist.

How do I implement the prevent programme?

- Discuss the risks with the patient (or parent/caregiver/responsible person)
- Exclude pregnancy in women of childbearing potential (by serum pregnancy test) before the first prescription is issued
- Arrange for highly effective* contraception for women of childbearing potential before the first prescription is issued
- Complete the Annual Risk Acknowledgment Form with patient (or parent/caregiver/responsible person); give them a copy and send a copy to the GP
- See the patient urgently (within days) if referred back in case of unplanned pregnancy or if she wants to plan a pregnancy
- Provide the patient (or carer) with a copy of the patient guide which forms part of the Pregnancy Prevention Programme ("Prevent"). The materials forming the basis of the Pregnancy Prevention Programme can be accessed at: https://www.gov.uk/guidance/valproate-use-by-women-and-girls

*See 'Guide for Healthcare Professionals' at the above website for further details.

O.D. or B.D.

Episenta®▼

Prolonged-release sodium valproate

Episenta® ▼ (sodium valproate)

Abbreviated Prescribing Information

Prescribers should consult the SmPC before prescribing Episenta. Sodium valproate available as Episenta 150mg or 300mg prolonged-release capsules, Episenta sachets containing 500mg or 1000mg prolonged-release granules and Episenta 100mg/ml solution for injection (IV). **Indications:** Oral: All forms of epilepsy. Manic episode in bipolar disorder when lithium is contraindicated or not tolerated. Consider continuation of treatment after acute manic episode for those who have responded. IV: Epilepsy in patients normally maintained on oral sodium valproate but temporarily not possible. **Dose and Administration:** Female children and women of childbearing potential: Must be initiated and supervised by a specialist in epilepsy or bipolar disorder. Do not use unless other treatments are ineffective or not tolerated. Prescribe and dispense according to Valproate Pregnancy Prevention Programme. Preferably prescribe as monotherapy and at lowest effective dose; divide daily dose into at least two single doses. *Epilepsy*: Oral: Daily dosage given in 1-2 single doses. Monotherapy: Adults: 600mg daily increasing by 150-300mg at 3-day intervals until controlled; usual dose range 1000-2000mg/day. Max dose 2500mg/day. Children >20kg: 300mg/day increasing until controlled; usual dose range 20-30mg/kg/day. Max dose 35mg/kg/day. Children <20kg: 20mg/kg per day; in severe cases up to 40mg/kg/day. Doses >40mg/kg/day, monitor clinical chemistry and haematological parameters. Elderly: Care when adjusting dosage. Dosage should be determined by seizure control. Renal insufficiency: May be necessary to decrease dosage. Hepatic insufficiency: see Contraindications, Warnings and Undesirable effects. Salicylates should not be used concomitantly. Combined Therapy: Start Episenta in patients already on anticonvulsants gradually to reach target dose after about 2 weeks. In combination with barbiturates, reduce barbiturate dose, particularly if sedation observed. IV: Use current daily dosage for patients adequately controlled on oral therapy but divide into 3-4 single slow IV injections or give by continuous or repeated infusion. Adults: 400-800mg daily increasing by 150-300mg at 3-day intervals until controlled; usual dose range 1000-2000mg/day. Max dose 2500mg/day. Children: 300mg/day increasing until controlled; usual dose range 20-30mg/kg/day. Max dose 40mg/kg/day, only if plasma levels can be monitored. *Manic episodes*: Adults: initial daily dose 750mg or 20mg/kg, increase dose rapidly, mean daily dose 1000-2000mg. Monitor patients if dosage higher than 45mg/kg/day. Children/adolescents: Safety and efficacy not established in patients <18 years. Method of administration: Oral: Swallow capsules whole without chewing, with plenty of liquid. Contents of the capsule/sachet may be sprinkled or stirred into soft food or drinks (cold/room temperature) and swallowed immediately without chewing or crushing the granules. Changing from valproate enteric coated tablets to Episenta, keep the same daily dose. IV: Give by slow IV injection over 3-5 mins or by infusion in 0.9% saline or 5% dextrose. Do not administer via same line with other IV additives. Replace with oral therapy as soon as practicable. Monitor plasma levels during therapy and when changing to/back from parenteral therapy. **Contraindications:** Hypersensitivity to valproate or excipients. Active liver disease; Personal or family history of severe hepatic dysfunction, especially drug related; Porphyria; Known urea cycle disorders; Bipolar disorder in pregnancy. Epilepsy in pregnancy unless there is no suitable alternative. Epilepsy or bipolar disorder in women of childbearing potential unless the conditions of the pregnancy prevention programme are met. Known or suspected mitochondrial disease. **Warnings and Precautions:** Monitor for signs of suicidal ideation/behaviour. Discontinue gradually, under specialist supervision. Generic switching of valproate preparations not recommended. Use with carbapenem not recommended. Risk of aggravated convulsions. Monitor for early signs of liver damage. Risk of severe liver damage, including fatal hepatic failure; children <3 years most at risk especially with multiple anticonvulsants, severe seizure disorders, organic brain disease, diseases associated with mental retardation. Avoid concomitant salicylates in children <16 years. Measure liver function before treatment and during first 6 months. Risk of severe or fatal pancreatitis, particularly young children; risk decreases with increasing age. Blood cell count, platelet count, bleeding time and coagulation tests recommended prior to starting therapy or before surgery, or if spontaneous bruising/bleeding. Caution in patients with systemic lupus erythematosus. Risk of hyperammonaemia in patients with urea cycle enzymatic deficiency. Risk of marked weight gain. Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases. Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis. Alcohol intake not recommended. Contains sodium.

Pregnancy Prevention Programme
Valproate is highly teratogenic, and children exposed in utero to valproate have a high risk for congenital malformations neurodevelopmental disorders and hearing impairment or deafness due to ear and/or nose malformations. See Contraindications. See SmPC for full conditions of the Pregnancy Prevention Programme. The potential for pregnancy must be assessed for all female patients. Pregnancy must be excluded before start of treatment with valproate. Women of childbearing potential must use effective contraception without interruption and be provided with comprehensive information on pregnancy prevention. A specialist should review the patient at least annually and additionally if a woman is planning a pregnancy. If a woman using valproate becomes pregnant she must be immediately referred to a specialist to re-evaluate treatment. Women of childbearing potential must be provided with a patient guide and patient card. A risk acknowledgement form must be completed at treatment initiation and annual review.

Interactions (see SmPC): Effects of Episenta on other drugs: Episenta may potentiate the effect of other psychotropics, such as antipsychotics, MAOIs, antidepressants, benzodiazepines. Episenta may increase plasma levels/toxicity of other drugs: phenobarbital, primidone, lamotrigine, carbamazepine, felbamate, rufinamide, propofol, zidovudine, nimodipine warfarin and other coumarin anticoagulants. Episenta may decrease plasma levels of other drugs: olanzapine and phenytoin. Effects of other drugs on Episenta: Valproate plasma levels may be decreased with phenytoin, phenobarbital, carbamazepine, carbapenem agents, cholestyramine, rifampicin, lopinavir, ritonavir, protease inhibitors, oestrogen containing products, mefloquine, chloroquine and metamizole. Valproate levels may be increased with acetylsalicylic acid (and other highly protein bound agents) and cimetidine or erythromycin (as a result of reduced hepatic metabolism). Other interactions: Caution with newer antiepileptics; increased risk of neutropenia/leucopenia with quetiapine. **Pregnancy/Lactation:** See Contraindications and Warnings and Precautions. Refer patients with a valproate-exposed pregnancy to a specialist in prenatal medicine for evaluation and counselling. Neonate risks: haemorrhagic syndrome, hypoglycaemia, hypothyroidism, withdrawal syndrome. Valproate is excreted in human milk. Haematological disorders have been shown in breastfed infants of treated women. Consider benefit:risk. **Effects on ability to drive and use machines:** Reaction time may be altered; risk of transient drowsiness. **Undesirable effects (See SmPC for full details):** Congenital malformations, developmental disorders and hearing impairment or deafness due to ear and/or nose malformations. Risk of developing attention deficit/hyperactivity disorder. Very common: nausea; tremor. Common: liver injury; increased liver enzymes; vomiting; gingival disorder; stomatitis; gastralgia; diarrhoea; urinary incontinence; confusional state; hallucinations; aggression; agitation; disturbance in attention; extrapyramidal disorder; stupor; somnolence (sedation occasionally reported, usually in combination with other anticonvulsants); convulsion; memory impairment; headache; nystagmus; hyponatraemia; weight increased: anaemia; thrombocytopenia; hypersensitivity; transient/or dose related hair loss; nail and nail bed disorders; dysmenorrhea; haemorrhage; deafness; weight increased (monitor since a factor for polycystic ovary syndrome). Uncommon: pancreatitis, sometimes lethal; renal failure: hypothermia: coma; encephalopathy, lethargy, reversible parkinsonism, ataxia, paresthesia; aggravated convulsions SIADH; hyperandrogenism; pancytopenia; leucopenia; angioedema; hair disorder rash; amenorrhea; non-severe peripheral oedema; vasculitis; bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy; pleural effusion. Rare: myelodysplastic syndrome; abnormal behaviour; diplopia psychomotor hyperactivity; learning disorder; reversible dementia with reversible cerebral atrophy; cognitive disorder; hypothyroidism; hyperammonaemia; bone marrow failure, including pure red cell aplasia; agranulocytosis; macrocytic anaemia; macrocytosis; toxic epidermal necrolysis, Stevens-Johnson syndrome; erythema multiforme; DRESS syndrome; male infertility; polycystic ovaries; enuresis; tubulointerstitial nephritis; reversible Fanconi syndrome; systemic lupus erythematosus; rhabdomyolysis; coagulation factors decreased; abnormal coagulation tests. Very rare: gynaecomastia. Not known: Severe liver damage, including hepatic failure, sometimes fatal. **Pack sizes and NHS price:** Packs of 100, 150mg capsules £7.00 [PL14040/0024]; Packs of 100 300mg capsules £13.00 [PL14040/0025]; Packs of 100, 500mg sachets £21.00 [PL14040/0026]; Packs of 100, 1000mg sachets £41.00 [PL14040/0027]. Packs of 5, 3ml ampoules 100mg/ml solution for injection £35.00 [PL14040/0028]. **Legal category:** POM. **Marketing Authorisation Holder:** Desitin Arzneimittel GmbH Weg beim Jäger 214 D-22335 Hamburg Germany. **Prepared in:** Aug 2021. For further information on Episenta 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 www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Desitin Pharma Limited on MedInfo@desitin.co.uk.

References

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4. Data on file 001.
5. Department of Health and Social Care. Making written information easier to understand for people with learning disabilities. Guidance for people who commission or produce Easy Read information – Revised Edition 2010. Dept Health & Social Care 2010. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/215923/dh_121927.pdf (last accessed August 2021).
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UK/EP/0087 Date of preparation: September 2021.

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