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. **Indications:** All female patients <55 yrs; male patients <55 yrs initiating treatment: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment. All female patients >55 yrs; male patients >55 yrs or <55 yrs if established on valproate: 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. Continuation of treatment after manic episode could be considered in patients who have responded to sodium valproate for acute mania. **Dose and Administration:** Female children and women of childbearing potential <55 yrs: Do not prescribe or initiate new patients unless 2 specialists independently consider and document no other effective or tolerated treatment. Benefit/risk should be carefully reconsidered at regular treatment intervals, at least annually. Where possible existing patients should be switched to another treatment. Must be supervised by a specialist in epilepsy or bipolar disorder. 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. Male patients <55 yrs: Do not initiate new patients unless 2 specialists independently consider and document no other effective or tolerated treatment, or that risks of infertility and potential risk of testicular toxicity are not applicable. Discuss and complete risk acknowledgement form at treatment initiation. *Epilepsy*: 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: It may be necessary to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable. Dosing should be modified according to clinical monitoring of the patient. 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. *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: 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. **Contraindications:** Hypersensitivity to valproate or excipients. Active liver disease; personal or family history of severe hepatic dysfunction, especially drug related; known urea cycle disorders; porphyria; known or suspected mitochondrial disease; uncorrected systemic primary carnitine deficiency; bipolar disorder in pregnancy. Epilepsy in pregnancy unless there is no suitable alternative. Epilepsy or bipolar disorder in women and girls of childbearing potential <55 yrs unless no suitable alternative and the conditions of the pregnancy prevention programme are met. **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 yrs most at risk especially with multiple anticonvulsants, severe seizure disorders, organic brain disease, congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations or diseases associated with mental retardation. Avoid concomitant salicylates in children <3 yrs. Monotherapy recommended in children <3 yrs. Measure liver function before treatment and during first 6 months; reinitiate monitoring following changes to concomitant liver-impacting drugs. Cease valproate in event of clinical symptoms of liver damage and/or abnormally low prothrombin rate detected. Transient increase in liver enzymes is common. 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; monitor for PCOS. Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases. Risk of occurrence or worsening of hypocartinaemia; warn patients to report signs of hyperammonaemia and consider carnitine supplementation if symptoms are observed. Patients with corrected systemic primary carnitine deficiency should only be treated if benefit outweighs risk and no therapeutic alternative; initiate carnitine monitoring. Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis. False positives for ketones may occur in urine testing for diabetes. Alcohol intake not recommended. Granule shells may be visible in stool; no clinical impact. Contains sodium. Male patients and/or carers should be made aware of risk of infertility and animal data available on testicular toxicity (see SmPC).

Pregnancy Prevention Programme

Valproate is highly teratogenic, and children exposed to valproate in utero have an increased risk for minor and major congenital malformations and neurodevelopmental disorders which may lead to permanent disability in mono or polytherapy compared to population not exposed to valproate. Women and girls of childbearing potential aged <55 yrs should only be treated with valproate when 2 specialists have independently considered and documented that there is no other effective or tolerated treatment. 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 including hormonal contraceptives, mefloquine, chloroquine, methotrexate and metamizole. Valproate levels may be increased with acetylsalicylic acid (and other highly protein bound agents), felbamate, and cimetidine or erythromycin (as a result of reduced hepatic metabolism). Other interactions: Risk of liver toxicity; avoid use with salicylates in children <3 yrs; caution with use of other anticonvulsants, including cannabidiol. Caution with newer antiepileptics; association with encephalopathy and/or hyperammonaemia. Avoid use of pivalate-conjugated drugs; risk of carnitine depletion. Increased risk of neutropenia/leucopenia with quetiapine. **Pregnancy/Lactation/Fertility:** 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. Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women. May impair fertility in men; may be reversible. **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 including neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects and multiple anomalies. Hearing impairment or deafness due to ear and/or nose malformations. Eye malformations that may impact vision. Developmental disorders which may lead to permanent disability including autism spectrum disorder, developmental delay, lower IQ, poor language skills or memory problems. 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. Uncommon: pancreatitis, sometimes lethal; renal failure: hypothermia: coma; encephalopathy, lethargy (occasionally progressing to stupor with hallucinations/convulsions), 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; obesity; bone marrow failure, including pure red cell aplasia; agranulocytosis; macrocytic anaemia; macrocytosis; toxic epidermal necrolysis, Stevens-Johnson syndrome; erythema multiforme; DRESS syndrome; male infertility (unknown reversibility); 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; hypocarnitinaemia. **Pack sizes and NHS price:** 150mg capsules: packs of 30, £2.76; packs of 100, £7.00 [PL14040/0024]; 300mg capsules: packs of 30, £4.56; packs of 100, £13.00 [PL14040/0025]; 500mg sachets: packs of 30, £6.30; packs of 100, £21.00 [PL14040/0026]; 1000mg sachets: packs of 30, £12.30; packs of 100, £41.00 [PL14040/0027]. **Legal category:** POM. **Marketing Authorisation Holder:** Desitin Arzneimittel GmbH Weg beim Jäger 214 D-22335 Hamburg Germany. **Prepared in:** Feb 2024. 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.