Prescribing Information: Syonell®▼ (*valproate semisodium*)

Consult the Summary of Product Characteristics (SmPC) before prescribing.

Presentations: Syonell 250mg gastro-resistant tablet contains 269.06mg valproate semisodium per tablet (equivalent to 250mg valproic acid). Syonell 500mg gastro-resistant tablet contains 538.12mg valproate semisodium per tablet (equivalent to 500mg valproic acid). Valproate semisodium is a compound comprising sodium valproate and valproic acid in a 1:1 molar relationship. **Indication:** Treatment of manic episode in bipolar disorder only when there is no other effective or tolerated treatment. The continuation of treatment after a manic episode could be considered in patients who have responded to valproate semisodium for acute mania. **Dosage and Administration:** Must be supervised by a specialist experienced in management of bipolar disorder. Tablet(s) should be swallowed whole with water, not crushed or chewed. The daily dosage should be established according to age, body weight and individual sensitivity to Syonell. **Manic episodes in bipolar disorder**: Daily dosage should be established and controlled by the treating physician. Initial recommended daily dose is 750 mg in 2-3 divided doses. Also, a starting dose of 20 mg valproate/kg has been shown to have an acceptable safety profile. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The mean daily dose usually ranges between 1000-2000mg valproate. Patients receiving daily doses higher than 45mg/kg/day should be carefully monitored. Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose. **Combined Therapy:** When starting Syonell in patients taking anticonvulsants, taper slowly if clinically possible; initiation of Syonell should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitored. Dose may need to increase by 5-10mg/kg/day when taken with anticonvulsants which induce liver enzyme activity e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn, it may be possible to maintain control on a reduced dose of Syonell. When barbiturates are administered concomitantly, particularly if sedation is observed, the dosage of barbiturate should be reduced. When using Syonell with other psychotropics, a reduced dose may be required. See SmPC for more details. **Special Populations: Elderly patients:** Dosage should be determined based on clinical response. **Children/adolescents**: Efficacy not established in patients <18 years. **Women of childbearing potential, females and males under 55 years:** No new women of childbearing potential, females or males under 55 years to be initiated on valproate unless two independent specialists consider and document no other treatment effective or tolerated, or male infertility risk or potential testicular toxicity risk are not applicable. Where possible, existing female children, or women of childbearing potential aged under 55 yrs. should be switched to another treatment unless two specialists independently consider and document that there is no other effective or tolerated treatment. Those continuing should have benefits and risks reconsidered at regular treatment reviews, at least annually. Valproate must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (PPP). Specialist to discuss infertility risk and animal testicular toxicity data with all men under 55 years, including children and/or carer, and complete the risk acknowledgement form at initiation. Valproate should preferably be prescribed as monotherapy at the lowest effective dose, if possible as a prolonged release formulation. Daily dose should be divided into at least two single doses. **Renal impairment:** Dosage should be adjusted according to clinical monitoring. **Hepatic impairment:** Salicylates should not be used concomitantly with Syonell and avoided in children under 3 years. Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients taking valproic acid. **Contraindications:** Pregnancy, and in women of childbearing potential aged under 55 years, unless two independent specialists consider and document no other treatment effective or tolerated and conditions of the PPP are fulfilled. Active liver disease, personal or family history of severe hepatic dysfunction, especially drug related. Known urea cycle disorder(s), hypersensitivity to valproate semisodium (or any other excipients), porphyria or uncorrected systemic primary carnitine deficiency. Patients with mitochondrial disorders caused by mutations in the 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. **Precautions and Warnings:** To ensure the correct medication is prescribed, care must be taken not to confuse Syonell with Epilim or sodium valproate. Discontinuation should be done gradually under specialist supervision due to the possibility of sudden alterations in plasma concentrations giving rise to symptom recurrence. **Liver dysfunction:** Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Liver function should be measured before therapy, then periodically monitored during the first 6 months of therapy, especially in patients most at risk, and those with a 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 soon as appropriate. **Known or suspected mitochondrial disease:** Valproate may cause or worsen signs of mitochondrial diseases, including syndromes caused by mutations in POLG. Valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes from gene mutations for mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome. **Urea cycle disorders and those at risk of hyperammonaemia:** Perform metabolic investigations prior to treatment due to risk of hyperammonaemia with valproate. **Hypocarnitinaemia:** Valproate may cause or worsen hypocarnitinaemia (may lead to encephalopathy). Patients at risk include those with metabolic disorders related to carnitine, impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or other antiepileptics. Only treat patients with systemic primary carnitine deficiency corrected for hypocarnitinaemia with valproate if benefits outweigh risks and there is no alternative. **Pancreatitis:** Very rarely reported but may be severe and fatal; in such cases, Syonell should be discontinued. **Aggravated convulsions:** Some epileptic patients may experience a reversible worsening of convulsion frequency and severity (including status epilepticus), or onset of new types of convulsions with valproate. In such cases, patients should consult their physician immediately. **Suicidal ideation and behaviour**: Reported in patients treated with anti-epileptic agents in several indications. Patients (and caregivers) should be advised to seek medical advice should such signs or behaviours emerge. **Carbapenem agents:** Concomitant use with valproate is not recommended. **Haematological tests:** Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to starting therapy, before surgery and with spontaneous bruising or bleeding. **Systemic lupus erythematosus (SLE):** The potential benefit of Syonell should be weighed against its potential risk in patients with SLE. **Weight gain:** can be marked and progressive. **Diabetic patients:** Syonell may give false positives in urine tests for possible diabetics. **Alcohol:** not recommended during valproate treatment. **Breastfeeding:** Valproate is excreted in human milk. Haematological disorders have been shown in breastfed newborns/infants of treated women: consider benefit:risk. **Fertility:** Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate and may also impair fertility in men. Reversibility of male infertility unknown. **Male children and men:** All male patients and/or carers should be made aware of infertility risk and data showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance. For males under 55 years, the specialist should discuss and complete the risk acknowledgement form at initiation to ensure risks are known.

Women of childbearing potential under 55 years and pregnant women: Pregnancy Prevention Programme (PPP) (see SmPC): Valproate has high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders which may lead to permanent disability. Valproate must only be initiated by two specialists who independently consider and document that there is no other effective or tolerated treatment. Syonell is contraindicated in pregnancy and in women of childbearing potential under the age of 55 years unless two independent specialists consider no other treatment effective or tolerated and the conditions of the PPP are fulfilled. Pregnancy test: Valproate must not be initiated in women of childbearing potential without a negative pregnancy test confirmed by a healthcare provider. Contraception: Women of childbearing potential must use effective contraception without interruption during the entire duration of treatment with valproate. Oestrogen-containing products: Concomitant use may potentially result in decreased valproate efficacy. Monitor clinical response when initiating or discontinuing oestrogen-containing products. Valproate does not reduce efficacy of hormonal contraceptives. Annual treatment reviews: The specialist should review at least annually whether valproate is the most suitable treatment for the patient, discuss and complete the Annual Risk Acknowledgement Form at initiation and during each annual review and ensure the patient understands the content. Pregnancy planning: A specialist experienced in the management of bipolar disorder must be consulted and the treatment discontinued. Switch to an alternative treatment, prior to conception and before contraception is stopped. In case of pregnancy: Refer immediately to a specialist to re-evaluate treatment with valproate and consider switching to other treatments. Female children: Parents/caregivers of female children must be given comprehensive information on the risks and understand the need for specialist reassessment at menarche. Pharmacists must ensure: The Patient Card is provided with every valproate pack dispensation, patients understand the contents, advise patients not to stop valproate and immediately contact their GP to be referred to a specialist in case of planned or suspected pregnancy. Educational materials: Must be provided to reinforce the warnings and provide guidance regarding the use of valproate in women of childbearing potential and provide details of the PPP.

Interactions: All combined therapies should be closely monitored, especially at the start of treatment. When appropriate, dosages should be adjusted according to clinical response and blood levels. Syonell may significantly increase risks of certain adverse events associated with olanzapine and decrease olanzapine plasma concentrations. Syonell may potentiate the effect of antipsychotics, MAO inhibitors, antidepressants, benzodiazepines; e.g. carbamazepine, phenobarbital, primidone, phenytoin, lamotrigine, felbamate, propofol, rufinamide, also zidovudine, temozolomide, nimodipine and vitamin K-dependent anticoagulants. Valproic acid plasma levels may be increased in the case of concomitant use with: felbamate, cimetidine, erythromycin or highly protein bound agents (e.g. aspirin). Valproic acid plasma levels may be decreased in concomitant use with: antiepileptics with enzyme inducing effects (including phenytoin, phenobarbital and carbamazepine), anti-malarial agents (mefloquine and chloroquine), carbapenem antibiotics (e.g. panipenem, imipenem and meropenem), oestrogen-containing products, metamizole, cholestyramine, rifampicin, methotrexate and protease inhibitors (e.g. lopinavir and ritonavir). Valproic acid metabolite levels may be increased with concomitant use of phenytoin or phenobarbital, hence such patients should be carefully monitored for signs and symptoms of hyperammonaemia. Caution advised when using with newer anti-epileptics (including topiramate and acetazolamide) whose pharmacodynamics may not be well-established. Concomitant administration of valproate with topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. Co-administration with quetiapine may increase the risk of neutropenia or leukopenia. Concomitant use with cannabidiol elevates enzyme transaminases. Avoid concomitant use with pivalent-conjugated medicines. Where concomitant use cannot be avoided, monitor signs and symptoms of hypocarnitinaemia. **Adverse Reactions:** Valproate monotherapy and polytherapy are associated with abnormal pregnancy outcomes, see Precautions and Warnings. The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Syonell in the treatment of manic episodes have been identified. **Very common (≥1/10):** Nausea, tremor. **Common (≥1/100 to < 1/10):** Vomiting, gingival disorder (gingival hyperplasia), stomatitis, liver injury, transient raised liver enzymes, gastralgia, diarrhoea, extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, confusional state, hallucinations, aggression, agitation, disturbance in attention, hyponatraemia, weight increase, anaemia, thrombocytopenia, hypersensitivity, transient and/or dose-related alopecia, nail and nail bed disorders, dysmenorrhea, haemorrhage, deafness (a cause and effect relationship has not been established) and urinary incontinence. **Unknown:** Hypocarnitinaemia. Safety of Syonell in children: Some ADRs more severe or mainly observed in children. Please refer to the SmPC for full information on adverse reactions. **UK Price & Quantity:** Syonell 250mg: Pack of 30 tablets, £4.55. Syonell 500mg: Pack of 30 tablets, £9.10. **Marketing Authorisation (MA) Holder:** Lupin Healthcare (UK) Limited, The Urban Building, 2nd floor, 3-9 Albert Street, Slough, Berkshire, SL1 2BE, United Kingdom. **MA No:** Syonell 250mg: PL 35507/0191; 500mg: PL 35507/0192 **Legal Category:** POM **PI Last Revised:** February 2024 For further information please contact Lupin Healthcare (UK) Ltd. Tel: 01565 751378. E-mail: information@lupin.com

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App store. Adverse events should also be reported to Lupin Healthcare UK Limited on +44 (0)1565 751 378 or EU-PV@lupin.com

Syonell® ▼ (valproate semi-sodium) is contraindicated in pregnancy

Syonell® ▼ (valproate semi-sodium) is contraindicated 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 valproate pregnancy prevention programme (PPP) are fulfilled.

Syonell® ▼ (valproate semi-sodium) should not be used in female children, unless two specialists independently consider and document that there is no other effective or tolerated treatment.

Syonell® ▼ (valproate semi-sodium) should not be initiated in male children or men aged under 55 years 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.