Prescribing Information: Syonell ▼ (valproate semisodium)

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentations: Syonell 500mg gastro-resistant tablet contains 538.12mg of valproate semisodium per tablet (equivalent to 500mg of valproic acid). Syonell 250mg gastro-resistant tablet contains 269.06mg of valproate semisodium per tablet (equivalent to 250mg of valproic acid). Valproate semisodium is a compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. **Indication** Syonell is indicated for the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate semisodium for acute mania. **Dosage and Administration:** Valproate must be initiated and supervised by a specialist experienced in the management of bipolar disorder. Tablet(s) should be swallowed whole with a drink of water, not crushed or chewed. The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Syonell should also be considered. **Manic episodes in bipolar disorder**: The daily dosage should be established and controlled by the treating physician. Initial recommended daily dose is 750 mg. A starting dose of 20 mg valproate/kg body weight has shown, in clinical trials, to have 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 mean daily dose usually ranges between 1000 and 2000mg valproate. Patients receiving daily doses higher than 45mg/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. **Combined Therapy in Adults:** When starting Syonell in patients already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Syonell therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 510mg/kg/day when used in combination 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 being administered concomitantly and particularly if sedation is observed, the dosage of barbiturate should be reduced. When using Syonell with other psychotropics, a reduced dose may be required. Please refer to the SmPC for more details. **Special Populations: Elderly patients:** dosage should be determined on the basis of clinical response. **Female children and women of childbearing potential:** Valproate should not be used in female children or women of childbearing potential unless other treatments are ineffective or not tolerated. Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (PPP) and the benefit and risk should be carefully reconsidered at regular treatment reviews. 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. **Renal insufficiency:** Dosage should be adjusted according to clinical monitoring, since monitoring of plasma concentrations may be misleading. **Hepatic insufficiency:** Salicylates should not be used concomitantly with Syonell. Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid. **Contraindications:** Pregnancy, and in women of childbearing potential unless the conditions of the pregnancy prevention programme (PPP) are fulfilled. In patients with active liver disease, personal or family history of severe hepatic dysfunction, drug related, a known urea cycle disorder(s), hypersensitivity to valproate semisodium (or any other ingredient of the preparation) or porphyria. Valproate is contraindicated in patients known to have any mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. AlpersHuttenlocher 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 for the patient's condition, care must be taken not to confuse Syonell with Epilim or sodium valproate. Discontinuation should normally only be done under the supervision of a specialist in a gradual manner, due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. **Liver dysfunction:** Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. **Pancreatitis:** may be severe and result in fatalities, has been very rarely reported. In case of pancreatitis, Syonell should be discontinued. **Aggravated convulsions:** Patients may experience 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, patients should be advised to consult their physician immediately. Suicidal ideation and behaviour: **Suicidal ideation and behaviour**: have been reported in patients treated with anti-epileptic agents in several indications. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. **Carbapenem agents:** The concomitant use of valproate and carbapenem agents is not recommended. **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. AlpersHuttenlocher Syndrome. **Haematological tests:** 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. **Systemic lupus**

erythematosus (SLE): Although immune disorders have only rarely been noted during the use of Syonell, the potential benefit of Syonell should be weighed against its potential risk in patients with SLE. **Urea cycle disorders**: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment. **Weight gain:** can be marked and progressive. **Diabetic patients:** Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomylosis when taking sodium valproate. **Carnitine palmitoyltransferase (CPT) type II deficiency:** Patients with this deficiency should be warned of the greater risk of rhabdomylosis when taking sodium valproate. **Alcohol:** not recommended during treatment with valproate. **Breastfeeding:** Valproate is excreted in human milk. Haematological disorders have been shown in breastfed newborns/infants of treated women. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Syonell 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. Valproate administration may also impair fertility in men although; case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

Female children and women of childbearing potential: Pregnancy Prevention Programme (PPP): Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders. 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 bipolar disorder. Syonell is contraindicated in women of childbearing potential unless the conditions of the PPP are fulfilled. These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. Pregnancy test: Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy. Contraception: Women of childbearing potential (even if she has amenorrhea) who are prescribed valproate must use effective contraception (one user independent method, or two user dependent methods in combination) without interruption during the entire duration of treatment with valproate. Oestrogen-containing products Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy. Prescribers should monitor clinical response (mood control) when initiating, or discontinuing oestrogen-containing products. On the opposite, 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. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content. Pregnancy planning: 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. In case of pregnancy: If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Female children: Parents/caregivers of female children who have experienced menarche must be provided with comprehensive information about the risks for children exposed to valproate in utero; otherwise, they must understand the need to contact the specialist once the female child using valproate experiences menarche. In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the PPP should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood. Pharmacists must ensure that: The Patient Card is provided with every valproate dispensation and that patients understand its content and advise patients not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy. Educational materials: The Marketing Authorisation Holder has provided educational materials to reinforce the warnings provide guidance regarding use of valproate in women of childbearing potential and provide details of the PPP. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

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 decrease the effect of:** olanzapine. **Syonell may potentiate the effect of:** antipsychotics, MAO inhibitors, antidepressants, benzodiazepines; for example carbamazepine, phenobarbital, primidone, phenytoin free form, lamotrigine, felbamate, propofol, rufinamide, 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 (such as panipenem, imipenem and meropenem), cholestyramine, rifampicin and protease inhibitors (e.g. lopinavir and ritonavir). 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. **Topiramate or acetazolamide** : Concomitant administration of either, with valproate, has been associated with encephalopathy and/or hyperammonaemia. Co-administration of with **Quetiapine** may

increase the risk of neutropenia or leucopenia. Caution is advised when using Syonell in combination with newer anti-epileptics whose pharmacodynamics may not be well established. **Adverse Reactions:** Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. 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 (mainly gingival hyperplasia), stomatitis, liver injury, gastralgia, diarrhoea, extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness, confusional state, hallucinations, aggression, agitation, disturbance in attention, hyponatremia, weight increase, anaemia, thrombocytopenia, hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders dysmenorrhea, haemorrhage, deafness (a cause and effect relationship has not been established), urinary incontinence and weight gain. Please refer to the SmPC for full information on adverse reactions. **UK price:** List price £4.55 for 30 tablets of 250mg Syonell; £9.10 for 30 tablets of 500mg Syonell **Marketing Authorization Holder** Lupin Healthcare (UK) Limited, The Urban Building, 2nd floor, 3-9 Albert Street, Slough, Berkshire, SL1 2BE, United Kingdom. **Marketing Authorization Number** PL 35507/0192 **Legal Category** POM **Date of Preparation or Last Review** 7th December 2020

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Lupin Europe GmbH by email at EU-PV@lupin.com

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WARNING FOR WOMEN AND GIRLS

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

Syonell is contraindicated in pregnancy unless there is no suitable alternative treatment.

Syonell is contraindicated in women of childbearing potential unless the conditions of "Prevent", the valproate pregnancy prevention programme are fulfilled.

Risks: Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders. Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children.

Prevent Toolkit: Valproate must not be used in any woman or girl able to have children unless there is a pregnancy prevention programme (PPP) in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant. Healthcare professionals who seek to prescribe valproate to their female patients must make sure they are enrolled in the PPP. This includes the completion of a signed risk acknowledgement form when their treatment is reviewed by a specialist, at least annually.

The Medicines and Healthcare products Regulatory Agency (MHRA), developed in consultation with stakeholders including healthcare professional and patient groups has launched a toolkit to ensure female patients are better informed about the risks of taking valproate medicines during pregnancy.

Valproate educational materials have been developed specifically for girls (of any age) and women of childbearing potential treated with valproate It is comprised of: the Patient Guide, the Annual Risk Acknowledgment Form and the Patient Card. For more information and access to the Toolkit, please visit

https://www.gov.uk/guidance/valproate-use-by-women-and-girls