This is a communication regarding the current stock situation with Sanofi’s valproate-based products (Epilim and Depakote).

Sanofi can confirm that supply of valproate (Epilim and Depakote) is available in the UK:
We have received reports from patients concerned about the current stock levels of certain presentations of valproate, or have received incorrect information from their pharmacist as to its availability. The stock levels for some presentations may be lower than usual. This was due to a temporary disruption in the production of valproate at a Sanofi manufacturing site outside of the UK.

To check the stock availability in your area, ordering codes or other elements related to the ordering process, please contact your Agent. Should you have additional enquiries regarding overall stock availability, please contact Sanofi Customer Services.

We are advising patients who have concerns to contact their pharmacist to ascertain information on the stock information on specific preparations.

Change from 100 tablet packs to 30 tablet packs – please check ordering codes with your Agent:
At the request of the Medicines and Healthcare products Regulatory Agency (MHRA) pack sizes of valproate have been changed from 100 to 30 tablets, to avoid splitting packs at dispensaries. Pharmacies may, therefore, see that the 100 tablet packs are “unavailable” and assume that valproate is out of stock. The codes for 30 tablet packs should be used. Contact your Agent for any queries regarding ordering codes.

This disruption is not due to Brexit:
The Department of Health & Social Care are aware of the situation of supply of valproate. This temporary disruption in some supply of some valproate-based treatments is not related to the United Kingdom’s exit from the European Union.

Important that patients continue taking their medication and any changes are discussed with their doctor:
We are advising publicly via our website and to patient groups that patients may find that their normal tablet or granule preparation is substituted by their doctor for a liquid or syrup preparation of valproate and vice versa. This may result in a change to the frequency of dosing, but it is important that patients continue taking their medication and any changes are discussed with their doctor.

To check the stock availability in your area, ordering codes or other elements related to the ordering process, please contact your Agent as follows:
AAH Customer Services: 0344 561 8899.
Phoenix Customer Services: 0844 736 2287.
Should you have additional enquiries regarding overall stock availability, please contact Sanofi Customer Services on 0800 854 430

Patients or carers with an enquiry about valproate medication should speak to their pharmacist or doctor in the first instance. If patients or carers need to speak directly to Medical Information at Sanofi, they should call 0845 372 7101.

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 Sanofi Tel: 0800 0902314. Alternatively, send via email to UK-drugsafety@sanofi.com.

SAGB.VPA.19.03.0466. March 2019
Prescribing Information: Epilim ▼® (sodium valproate)

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

Presentations: Epilim 200/500 Gastro-resistant tablets: containing 200mg and 500mg sodium valproate, respectively. Epilim Crushable tablets: containing 100 mg sodium valproate. Epilim Chrono 200/300/500 Controlled Release tablets: containing a mixture of sodium valproate and valproic acid equivalent to 200mg, 300mg and 500mg sodium valproate respectively. Epilim Chronosphere 50mg/100mg/250mg/500mg/750mg/1000mg modified release (MR) granules: sachets of microgranules containing a mixture of sodium valproate and valproic acid equivalent to 50mg, 100mg, 250mg, 500mg, 750mg and 1000mg of sodium valproate respectively. Epilim Syrup and Epilim Liquid (sugar free): both containing 200mg sodium valproate per 5ml. Epilim 400mg Powder and Solvent for solution for injection/infusion: freeze-dried powder containing 400mg of sodium valproate, with solvent for reconstitution.

Indications: All presentations: the treatment of generalised, partial and other epilepsy. Epilim Powder and Solvent for solution for injection/infusion: the treatment of epileptic patients who would normally be maintained on oral sodium valproate, when oral therapy is temporarily not possible.

Dosage and administration: Dose Frequency: Epilim Chrono and Chronosphere may be given once or twice daily. All other formulations should be given twice daily. Adults: Dosage should start at 600mg/day increasing by 200mg/day at three-day intervals until seizure control is achieved, usually within the range 1000mg-2000mg, to a maximum dose of 2500mg/day. Children over 20kg: Dosage should start at 400mg/day (irrespective of weight) with spaced increases until control is achieved, 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 35mg/kg body weight per day. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored. Children under 20kg: Dosage 20mg/kg of body weight per day (to the nearest 50mg sachet); in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored. Epilim Chrono should not be used in this group of patients due to the tablet size and need for dose titration. Epilim Chronosphere MR Granules should be sprinkled on a small amount of soft food or into a drink, which should be cold or at room temperature. Food/drink containing granules should be swallowed immediately; the granules should not be crushed or chewed; the mixture should not be stored for future use. Granules should not be given in babies’ bottles as they can block the nipple. Epilim Solution for Injection/Infusion: Patients already treated with Epilim may continue at their current daily dose using continuous or repeated infusion in normal saline, 5% dextrose or dextrose saline. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800mg (up to 10mg/kg) followed by continuous or repeated infusion up to a maximum of 2500mg/day. Using the solvent provided, the concentration of reconstituted sodium valproate solution is 95mg/ml. Each vial is for single use only, should be reconstituted immediately prior to use and infusion solutions used within 24 hours. Any unused portion should be discarded. Injection or infusion should not be through the same IV line as other IV additives. The solution is suitable for infusion by PVC, polyethylene or glass containers. Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable. Female children and women of childbearing potential Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme. The benefits and risks 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. Combination therapy: When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. It may be necessary to increase the dose by 5-10mg/kg/day when used with hepatic enzyme-inducing anticonvulsants; the dose may be reduced when these are withdrawn. Elderly: Dosage should be determined by seizure control. Renal impairment: clinical monitoring required. Decrease in dosage may be necessary. Hepatic impairment: Salicylates should not be used concomitantly with Epilim.

Contraindications: In pregnancy unless there is no suitable alternative treatment; in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled. Hypersensitivity to sodium valproate, valproic acid or to any of the excipients listed. Active liver disease; personal, or family history of severe liver dysfunction, hepatic dysfunction, or hepatitis; especially drug related. Patients with urea cycle disorders or porphyria. Patients with known mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), or children under age 2 suspected of having a POLG-related disorder.

Precautions and Warnings: Liver dysfunction: Severe liver damage, including hepatic failure, sometimes fatal, has been very rarely reported. Most at risk, young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and/or congenital metabolic or degenerative disease associated with mental retardation. Monotherapy is recommended in children under the age of 3 years; potential benefit should be weighed against the risk of liver damage or pancreatitis. Liver function should be measured before therapy and then periodically monitored during
the first 6 months of treatment, especially in those who seem most at risk and those with a prior history of liver disease. Epilim should be withdrawn immediately if early symptoms of liver dysfunction develop. In cases of elevated hepatic enzymes (common, particularly at the beginning of therapy), a reduction in dosage may be considered and appropriate tests should be repeated as necessary. **Pancreatitis:** which may be severe and sometimes fatal, has been very rarely reported. If pancreatitis is confirmed Epilim should be discontinued. **Aggravated convulsions:** Some patients may experience a reversible worsening of convulsion frequency and severity, or the onset of new types of convulsions when treated with Epilim. Patients should be advised to consult their physician immediately should this occur. **Suicidal ideation and behaviour:** has been reported in patients treated with anti-epileptic agents in several indications. Patients should be monitored and advised to watch for signs of suicidal ideation and behaviours, in which case medical care should be sought immediately and appropriate treatment should be considered. **Carbapenem agents (e.g. panipenem, imipenem and meropenem):** The concomitant use of Epilim and carbapenem agents is not recommended. **Patients with known or suspected mitochondrial disease:** Valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neutrometabolic syndromes caused by mutations in the mitochondrial enzyme polymerase γ (POLG) gene. In patients with a family history or suggestive symptoms, POLG mutation testing should be performed. **Haematological tests:** Blood cell count, bleeding time and coagulation tests are recommended prior to initiation of therapy or before surgery, and in the case of spontaneous bruising or bleeding. **Renal impairment:** See “Dosing and Administration” above. **Systemic lupus erythematosus (SLE):** The potential benefit should be weighed against 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 because of the risk of hyperammonaemia. **Diabetic patients:** Epilim treatment may lead to false positives in urinary ketone testing. **Carnitine palmitoyltransferase (CPT) type II deficiency:** Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Epilim. **Alcohol:** Intake is not recommended during treatment with Epilim. **Weight gain:** Epilim very commonly causes weight gain which may be marked and progressive. **Lactation:** Valproate is excreted in human milk and haematological disorders have occurred in breastfed infants of treated women. The decision to abstain from Epilim or stop breastfeeding must balance the benefits of treatment for the mother and breastfeeding for the child.

**Female children, women of childbearing potential and pregnant women:** 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. The prescriber must ensure that conditions of PPP are followed before prescribing. An Annual Risk Acknowledgement Form needs to be completed at the time of treatment initiation and during each annual review of valproate treatment by the specialist. Please see the SmPC for more details. 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 (seizure control) 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. 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 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. If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding planning a pregnancy. **In case of pregnancy:** The patient 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. Maternal tonic clonic seizures and status epilepticus carry a particular risk of death for the mother and unborn child; if valproate is used as treatment in pregnancy in the absence of other effective therapies and in acceptance of the known risks, it should be at the lowest effective dose, divided into small doses throughout the day. Use of a prolonged release formulation to avoid high peak plasma concentrations may be preferable. **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 all 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.
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. **Epilim may potentiate the effect of:** antipsychotics, MAO inhibitors, antidepressants, benzodiazepines and anti-epileptics with enzyme inducing effect; for example phenytoin, phenobarbital, carbamazepine, primidone, lamotrigine, felbamate, rufinamide, zidovudine, temozolomide, nimodipine, propofol and olanzapine. **Valproic acid plasma levels may be increased** in 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: anti-malarial agents (mefloquine and chloroquine), rifampicin, cholestyramine, carbapenem antibiotics (such as panipenem, imipenem and meropenem), protease inhibitors (such as lopinavir, ritonavir), anti-epileptics (such as phenytoin, phenobarbital or carbamazepine and oestrogen-containing products, including oestrogen-containing hormonal contraceptives. **Topiramate or acetazolamide:** Concomitant administration of either, with valproate, has been associated with encephalopathy and/or hyperammonaemia. Co-administration of Epilim and **Quetiapine** may increase the risk of neutropenia or leucopenia. Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established. **Storage:** Epilim is hygroscopic - keep tablets in blister pack until use and avoid cutting blister strips. Epilim Liquid should not be diluted.

**Adverse Reactions: Teratogenicity and developmental effects:** 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniosenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. Data have also shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. Studies in preschool children exposed to valproate in utero show 30-40% experience delays in early development and later, lower intellectual ability and memory problems. Intelligence quotient measured in school aged children exposed in utero was on average 7-10 points lower than children exposed to other anti-epileptics. Long term data on outcomes are limited. Children exposed in utero are at increased risk of autistic spectrum disorder (approx. three-fold) and childhood autism (approx. five-fold). Limited data suggest that children exposed in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder. **Very common (**≥ 1/10:**); nausea, tremor. **Common (**≥ 1/100 to ≤ 1/10:**); liver injury, severe liver damage, including hepatic failure. Increased liver enzymes (particularly early in treatment, and may be transient). Vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea (frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment). Extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness (for intravenous injection, dizziness may occur within a few minutes and usually resolves spontaneously within a few minutes), confusional state, hallucinations, aggression, agitation, disturbance in attention, hyponatraemia, weight increase, anaemia, thrombocytopenia, cutaneous 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. Please refer to the SmPC for full information on adverse reactions.

**UK List prices and Marketing Authorisation Numbers:** **Epilim 200 Gastro-resistant** 04425/0302: (100 tablets) £7.70, (30 pack) £2.31; **Epilim 500 Gastro-resistant** 04425/0303: (100 tablets) £19.25, (30 tablets) £5.78; **Epilim 100mg Crushable Tablets** 04425/0317: (100 tablets) £5.60, (30 tablets) £1.68; **Epilim Syrup 200mg/5ml** 04425/0301: (300ml) £9.33; **Epilim Liquid 200mg/5ml** 11723/0024: (300ml) £7.78; **Epilim Chrono CR 200mg** 04425/0307: (100 tablets) £11.65, (30 tablets) £3.50; **Epilim Chrono CR 300mg** 04425/0308: (100 tablets) £17.47, (30 tablets) £5.24; **Epilim Chrono CR 500mg** 04425/0309: (100 tablets) £29.10, (30 tablets) £8.73; **Epilim Chronosphere MR 50mg** 04425/0310: (30 sachets) £30.00; **Epilim Chronosphere MR 100mg** 04425/0312: (30 sachets) £30.00; **Epilim Chronosphere MR 250mg** 04425/0313: (30 sachets) £30.00; **Epilim Chronosphere MR 500mg** 04425/0314: (30 sachets) £30.00; **Epilim Chronosphere MR 750mg** 04425/0315: (30 sachets) £30.00; **Epilim Chronosphere MR 1000mg** 04425/0316: (30 sachets) £30.00; **Epilim Powder and Solvent for solution for injection/infusion 400mg** 11723/0022: (1 vial) £13.32.

**Legal Category:** POM. **Marketing Authorisation Holder:** Sanofi, One Onslow Street, Guildford, Surrey, GU1 4SY, UK. **Further information is available from:** Sanofi, One Onslow Street, Guildford, Surrey, GU1 4SY, UK. **Date of Preparation:** December 2018

**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 Sanofi Tel: 0800 0902314. Alternatively, send via email to UK-drugsafety@sanofi.com.
Prescribing Information: Depakote ▼ (valproate semisodium)

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

Presentations: Depakote 250mg tablets, containing 269.10mg of valproate semisodium per tablet (equivalent to 250mg of valproic acid) and Depakote 500mg tablets containing 538.20mg of valproate semisodium per tablet (equivalent to 500mg of valproic acid).

Indications: 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 Depakote 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 Depakote 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 Depakote in patients already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote 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 5-10mg/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 Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed, the dosage of barbiturate should be reduced. When using Depakote 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 Depakote. 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. 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 for the patient's condition, care must be taken not to confuse Depakote 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. Generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations. 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, Depakote should be discontinued. Aggravated convulsions: Patients may experience a reversible worsening of convolution frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravation 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. Alpers-Huttenlocher 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 Depakote, the potential benefit of Depakote 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 undertaken 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 rhabdomyolysis when taking sodium valproate. **Carnitine palmitoyltransferase (CPT) type II deficiency:** Patients with this deficiency should be warned of the greater risk of rhabdomyolysis 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 Depakote 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. Depakote 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. **Depakote may decrease the effect of:** olanzapine. **Depakote may potentiate the effect of:** antipsychotics, MAO inhibitors, antidepressants, benzodiazepines; for example carbamazepine, phenobarbital, primidone, phentoyin 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 Depakote 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 Depakote 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 List Prices:** Depakote 250mg tablets x 90: £17.08, x30: £5.69; Depakote 500mg tablets x 90: £34.11, x30: £11.37. **Legal Category:** POM. **Marketing Authorisation Numbers:** 250mg: 04425/0199, 500mg: 04425/0200. **Marketing Authorisation Holder:** Aventis Pharma Limited, One Onslow Street, Guildford, Surrey, GU1 4YS, UK. **Further information is available from:** 1 Onslow Street, Guildford, Surrey, GU1 4YS, UK, +44 (0)845 372 7101. **Date of Preparation:** December 2018

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Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Sanofi Tel: 0800 0902314. Alternatively, send via email to [UK-drugsafety@sanofi.com](mailto:UK-drugsafety@sanofi.com)