Summary of Product Characteristics

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Epilim Chrono 300mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Epilim Chrono 300mg Prolonged Release Tablet contains 199.8mg Sodium Valproate and 87.0 mg Valproic Acid. Equivalent to 300mg sodium valproate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.
Violet, oblong, biconvex film-coated prolonged release tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of generalised, partial or other epilepsy.
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 Epilim Chrono for acute mania.

4.2 Posology and method of administration

Epilim Chrono Prolonged Release Tablets are for oral administration.

Epilim Chrono is a prolonged release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Epilim Chrono may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.

Daily dosage requirements vary according to age and body weight.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or prolonged release formulations on an equivalent daily dosage basis.

Female children and women of childbearing potential
Epilim must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Valproate should not be used in female children and women of childbearing potential unless if other treatments are ineffective or not tolerated (see section 4.4 and 4.6).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see section 4.3 and 4.4). Epilim 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 (see section 4.6).
Manic Episodes in bipolar disorder:

In adults:
The daily dosage should be established and controlled individually by the treating physician.

The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-releaseformulations 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 daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient.

The mean daily dose usually ranges between 1000 and 2000 mg 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.

In children and adolescents:
The safety and efficacy of Epilim for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Dosage in Epilepsy
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, i.e. 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children
Among the oral pharmaceutical forms, the following formulations are more appropriate for administration to children less than 11 years (syrup, oral solution and granules).

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is 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.

Children under 20kg
An alternative formulation of Epilim should be used in this group of patients, due to the tablet size and need for dose titration. Epilim Liquid (sugar-free) or Epilim Syrup are alternatives.

Elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2).

Combined 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. In certain cases it may be necessary to raise the dose by 5 to 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 seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Epilim is contraindicated in the following situations:

Treatment of epilepsy
- in pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.4 and 4.6).

Treatment of bipolar disorder
- in pregnancy (see section 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.4 and 4.6).

All indications
- Hypersensitivity to sodium valproate
- Active liver disease (acute or chronic hepatitis)
- Personal or family history of severe hepatic dysfunction, especially drug related
- Porphyria

Valproate is contraindicated in patients known to have 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 (see section 4.4).

Patients with known urea cycle disorders (see section 4.4)

4.4 Special warnings and precautions for use

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6)

Epilim is contraindicated in the following situations:

Treatment of epilepsy

in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder

in pregnancy (see sections 4.3 and 4.6).
in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The prescriber must ensure that

Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.

the potential for pregnancy is assessed for all female patients.

the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.

the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.

the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders.

the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.

the patient understands the need to urgently consult her physician in case of pregnancy.

the patient has received the patient guide.

the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

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.

Female children

The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.

The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.

In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist

The specialist should at least annually review 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
For the indication epilepsy, 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 (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the indication bipolar disorder 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 options. The patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in obstetrics for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that

the patient card is provided with every valproate dispensing and that the patients understand its content.

the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

An annual risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Stopping treatment may lead to an immediate relapse of the underlying symptoms; care should therefore be taken when consideration is being given to the withdrawal of treatment.

Carbapenems agents
The concomitant use of valproic acid/sodium valproate and carbapenem agents is not recommended (see section 4.5)

Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been exceptionally reported.
Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.
In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before 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.
Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.
Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.
As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Pancreatitis: Severe pancreatitis, which may result in fatalities, has been very rarely reported. Patients experiencing acute abdominal pain should have a prompt medical evaluation. Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Precautions
Liver function tests should be carried out before therapy (see section 4.3), and periodically during the first 6 months, especially in patients at risk (see section 4.4).
As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.
Alcohol intake is not recommended during treatment with valproate.

Children: Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see section 4.4).

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity.

Haematological: 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 (see section 4.8).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 and 5.2).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its risk in patients with systemic lupus erythematosus (see also section 4.8).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see 4.8)

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate.

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.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Aggravated convulsions
As with other antiepileptic drugs, some patients may experience, instead of an improvement, 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, the patients should be advised to consult their physician immediately. (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interactions

Effects of Epilim on Other Drugs
- ***Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines***
Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate therapy may significantly increase the risk of certain adverse events associated with olanzapine.

- ***Lithium***
Epilim has no effect on serum lithium levels.

- ***Phenobarbital***
Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Epilim reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Zidovudine***
Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Felbamate***
Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Olanzapine***
Valproic acid may decrease the olanzapine plasma concentration.

- Rufinamide
Valproic acid may lead to an increase in plasma level of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

- Propofol
Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- Nimodipine
In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

Effects of Other Drugs on Epilim
Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid serum concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.
On the other hand, combination of ***felbamate*** and Epilim decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Epilim dosage should be monitored.
Valproic acid serum levels may be increased in case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia.
Mefloquine and ***chloroquine*** increase valproic acid metabolism and have a convulsing effect. They may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. The dosage of Epilim may need adjustment accordingly.
In case of concomitant use of Epilim and ***highly protein bound agents (e.g. aspirin)***, valproic acid free serum levels may be increased.
Valproic acid serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.
Decreases in blood levels of valproic acid have been reported when it is co-administered with ***carbapenem agents*** resulting in a 60-100% decrease in valproic acid levels within two days. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid is not considered to be manageable and therefore should be avoided (see section 4.4).). If treatment with these antibiotics cannot be avoided, close monitoring of valproate blood level should be performed.

Colestyramine
Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

Protease inhibitors
Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma level when co-administered.

Other Interactions
Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.
Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.

Quetiapine
Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.
Estrogen-containing products, including estrogen-containing hormonal contraceptives
Estrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.

On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate
does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

4.6 Fertility, pregnancy and lactation

Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.3 and 4.4).

Pregnancy Exposure Risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors

cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

If a Woman plans a pregnancy
For the indication epilepsy, 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 (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the indication bipolar disorder 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.

Pregnant women
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

> Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in obstetrics for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate
- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of pregnancy.

- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim 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 (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepatobiliary disorders:
Common: liver injury (see section 4.4)

Gastrointestinal disorders :
Very common: nausea,
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis. abdominal pain upper, diarrhoea

The above three adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Uncommon: pancreatitis, sometimes lethal (see section 4.4).

Nervous system disorders:

Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus,
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia.
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder, diplopia.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy and confusion, occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Cognitive disorders:

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural disorders have been reported.

Metabolic disorders:
Common: hyponatraemia, weight increased*.

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (See Section 4.4).
Rare: hyperammonaemia* (see section 4.4), obesity.

*Cases of isolated and moderate hyperammonaemia without change in liver function may occur frequently and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased)
Rare: hypothyroidism (see section 4.6)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4).
Uncommon: pancytopenia, leucopenia.

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.

Isolated finding of a reduction in blood fibrinogen and/or increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6).

Deficiency in Factor VIII / Von Willebrand.

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and/or dose related alopecia. Regrowth normally begins within six months, although the hair may become more curly than previously. Nail and nail bed disorders.
Uncommon: angioedema, rash, hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal)

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim. The mechanism by which Epilim affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4)

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4 and 4.6).

Uncommon: vasculitis

Ear and labyrinth disorders:
Common: Deafness

Renal and urinary disorders:
Uncommon: renal failure
Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.
Psychiatric disorders:
Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

General disorders and administration site conditions:
Uncommon: hypothermia, non-severe oedema peripheral

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged), biotin deficiency/biotinidase deficiency.

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Cases of accidental and deliberate Epilim overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock.

Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the valproate formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic: gastric lavage, cardio-respiratory monitoring. Haemodialysis and haemoperfusion have been used successfully.
Naloxone has also been used in a few isolated cases. In cases of massive overdose, hemodialysis and hemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Valproic acid and sodium valproate are anticonvulsants.
The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.
In certain in vitro studies, it has been reported that Epilim can stimulate HIV. However this effect is modest, variable, unrelated to the dose and not documented in man.

5.2 Pharmacokinetic properties

The half-life of Epilim is usually reported to be within the range of 8-20 hours. It is usually shorter in children.
The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.
The pharmacological (or therapeutic) effects of Epilim Chrono may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Metabolism
The major pathway of valproate biotransformation is glucuronidation (~40%), mainly via UGT1A6, UGT1A9, and UGT2B7.
Epilim Chrono formulations are prolonged release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and prolonged release Epilim formulations.
In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chrono make the measurement of plasma levels less dependent upon time of sampling.
The Epilim Chrono formulations are bioequivalent to Epilim Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of Epilim Chrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Ethylcellulose
Silica colloidal hydrated.

Film-coat
Violet coat containing:
Titanium dioxide (E171)
Erythrosine BS (E127)
Indigo carmine (E132)
Iron oxide black (E172)
Hypromellose (E464)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in original package. Epilim Chrono tablets should be stored in a dry place. Epilim Chrono tablets are hygroscopic and must be kept in their protective foil until taken.

6.5 Nature and contents of container

Epilim Chrono 300mg Prolonged Release Tablets are supplied in PVC/aluminium laminate blister packs further packed into a cardboard carton. Pack size 30 or 100 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/150/011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First date of authorisation: 24 August 1992

Date of last renewal: 24 August 2007

10 DATE OF REVISION OF THE TEXT

April 2019