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 Chronosphere 750mg prolonged-release granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of prolonged-release granules contains:

Sodium valproate	500.06 mg
Valproic acid	217.75 mg

Equivalent to 750 mg sodium valproate.

For a full list excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release granules.

Sachets containing small, off-white to slightly yellow, waxy microgranules.

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 Chronosphere for acute mania.

4.2 Posology and method of administration

Epilim Chronosphere is a pharmaceutical form particularly suitable for children (when they are able to swallow soft food) and adults with swallowing difficulties.

Epilim Chronosphere is a controlled release formulation of Epilim, which reduces peak concentration and ensures more regular plasma concentration throughout the day.

Epilim Chronosphere may be given once or twice daily.

Female children, female adolescents, women of childbearing potential and pregnant women
Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.

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

Daily dosage should be established according to age and body weight and should be given to the nearest whole 50mg sachet. Partial sachets should not be used. However, the wide individual sensitivity to valproate should also be considered.

A good correlation has not been established between daily dose, serum concentration and therapeutic effect, and optimum dosage should be determined primarily according to the clinical response. The determination of valproic acid plasma levels should be considered in addition to clinical monitoring when adequate seizure control is not achieved, or when adverse effects are suspected. The reported effective range is usually between 40-100 mg/L (300-700 μmol/L).

Initiation of Epilim Chronosphere therapy (oral administration)

- In patients who are not currently using other antiepileptic drugs, the dosage should preferably be increased by successive dose levels at 2-3 day intervals in order to reach the optimum dosage in about one week.
- In patients who are already receiving antiepileptic agents, substitution with Epilim Chronosphere should be progressive, the optimum dosage being reached in about 2 weeks and other treatments being tapered off and then stopped.
- Other antiepileptic agent should be added progressively where necessary (see 4.5. "Drug interactions").

Oral administration of Epilim Chronosphere: practical considerations

Dosage in Epilepsy
Initial daily dosage is usually 10-15 mg/kg, then doses are titrated up to the optimum dosage (see 4.2 "Initiation of Epilim Chronosphere therapy").
This is generally within the range 20-30 mg/kg. Nevertheless, where seizure control is not achieved within this range, the dose may be further increased as required; patients should be carefully monitored when receiving daily doses higher than 50 mg/kg (see 4.4 "Precautions")

- In children, the usual dosage is about 30 mg/kg per day.
- In adults, the usual dosage is within the range 20-30 mg/kg per day.
- In elderly, although the pharmacokinetics of Epilim Chronosphere are modified, they have limited clinical significance and dosage should be determined by seizure control.

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).

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-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 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 Chronosphere for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Administration

Epilim Chronosphere prolonged-release granules should be sprinkled on a small amount of soft food or in drinks, which should be **cold or at room temperature,** for example yoghurt, mousse, jam, ice cream, milk shake, orange juice or something similar.

If the granules are taken in a drink, after the drink has been finished the glass should be rinsed with a small amount of water and this water should be taken as well, as some granules may stick to the glass.
The mixture of food or drink and granules should be swallowed immediately; the granules should not be crushed or chewed.
A mixture of the granules with liquid or soft food should not be stored for future use.
Epilim Chronosphere prolonged-release granules should **not be sprinkled on warm or hot foods and drinks,** for example soup, coffee, tea, or something similar.
If preferred the granules can be poured directly into the mouth and washed down with a cold drink.
Epilim Chronosphere prolonged-release granules should not be given in babies' bottles as they can block the nipple.
The chronosphere granules contain a non-absorbable matrix which is designed to slowly release the active substance. Occasionally the matrix may pass through the gastrointestinal tract without disintegrating and may be visible in the patient's stools but this does not indicate that the drug has a reduced effect.

4.3 Contraindications

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate or to any of the excipients
- 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).

4.4 Special warnings and precautions for use

Female children/Female adolescents/Women of childbearing potential/Pregnancy:

Epilim should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered atregular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Epilim plans a pregnancy or if she becomes pregnant.

Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Epilim during pregnancy (see section 4.6).

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6).

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy or bipolar disorder.

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)

4.4.1 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.

4.4.2 Precautions

Liver function tests should be carried out before therapy (see section 4.3 “Contraindications”), and periodically during the first 6 months, especially in patients at risk (see section 4.4.1 “Special warnings”).
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 4.4.1 “Special warnings”).

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 “Undesirable Effects”).

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 “Posology and Method of Administration” and 5.2 “Pharmacokinetic Properties”).

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 “Undesirable Effects”).

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 “Undesirable Effects”).

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).

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 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%.

- 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.

4.5.2 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.

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 to be adjusted 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 plasma 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 may decrease the absorption of Epilim.

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.

4.5.3 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*** 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.

Epilim usually has no enzyme-inducing effect; as a consequence, Epilim does not reduce the efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.
Concomitant food intake does not significantly influence the bioavailability of Epilim when administered as the Chronosphere formulation.

4.6 Fertility, pregnancy and lactation

Epilim should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

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).

Female children, female adolescents and woman of childbearing potential (see above and section 4.4)
If a Woman wants to plan a Pregnancy

- During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
- In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed
- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy or bipolar disorder. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:

- Use the lowest effective dose and divide the daily dose 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.

- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

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 Interactions with Other Medicinal Products and Other Forms of Interaction).

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. Special warnings and precautions for use)

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 Special Warnings and Special Precautions for Use).

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.

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.
Rare: hyperammonaemia* (see section 4.4.2 Precautions)

*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 4.4.2 Precautions). 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 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4.2 Precautions).
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 Fertility, pregnancy and lactation).

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.
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 4.4.2 Precautions), rhabdomyolysis (see section 4.4.2 Precautions)

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 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation).
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:
Common: Weight increased*
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.

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4.2 Precautions)

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 Pharmacokinetic Properties). 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

ATC Code: N03AG01 Antiepileptic
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 sodium valproate 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 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 Chronosphere may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Epilim Chronosphere is a prolonged (or modified) release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day compared with other established conventional and modified release Epilim formulations. Following twice daily administration of a same dose, the range of plasma fluctuations is approximately reduced by half.
Compared with immediate release forms of Epilim it is characterized at an equivalent dose by:
- a similar bioavailability,
- a lower Cmax (decrease of approximately 25%),
- a relatively stable plateau between 4 and 14 hours after administration.

Steady-state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of Epilim Chronosphere lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chronosphere make the measurement of plasma levels less dependent upon time of sampling.

The peak plasma level is achieved approximately 7 hours after administration, with an elimination half-life between 13 and 16 hours.
This pharmacokinetic profile is not affected by taking the drug with food.

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

Hard paraffin
Glycerol dibehenate
Colloidal hydrated silica

6.2 Incompatibilities

This medicinal product must not be administered with hot meals or drinks.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Epilim Chronosphere 750 mg prolonged-release granules are filled into sachets of:

- 3 layers complex, printed paper, aluminium, ionomer resin complex,

or

- 3 layers complex: printed paper with nitrocellulosic glaze, aluminium, ionomer resin complex.

Epilim Chronosphere sachets are available in pack sizes of 30 and 50 sachets.

Not all pack sizes may be marketed.

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 Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/150/008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 2nd March 2007

Date of Last Renewal: 2nd March 2012

10 DATE OF REVISION OF THE TEXT

April 2015