▼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 500mg prolonged-release granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of prolonged-release granules contains:

Sodium valproate	333.30mg
Valproic acid	145.14mg

Equivalent to 500mg sodium valproate.

Excipients with known effect:
Sodium 46.08 mg (see section 4.4).

For a full list of 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.

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).

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 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).

Males

It is recommended that Epilim is initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder (see sections 4.4 and 4.6).

In patients with renal insufficiency:

It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable (see section 4.9). Dosing should be modified according to clinical monitoring of the patient (see section 4.4).

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 section 4.5).

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 section 4.2).

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 section 4.4)

- 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 efficacy of Epilim Chronosphere in children below 18 years of age in the treatment of manic episodes of bipolar disorder has not been established. With respect to safety information in children see section 4.8.

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

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
- 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).
- Patients with known urea cycle disorders (see section 4.4)
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4 Patients at risk of hypocarnitinaemia)

4.4 Special Warnings and Special 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 section 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.3 and 4.6).

Treatment of bipolar disorder

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

<u>Female children</u>

- 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.

<u>Pregnancy test</u>

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.

Estrogen-containing products

Concomitant use with estrogen-containing products, including estrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

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.

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam. However, other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, available evidence is inconsistent and the causal role of valproate is uncertain (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

Withdrawal of treatment
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

Severe liver damage
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, mental retardation and (or) congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see sections 4.3 and 4.4) or degenerative disease.

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.

Severe Cutaneous Adverse Reactions and Angioedema
Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS),

Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

Sodium
This medicinal product contains 46.08 mg sodium per sachet, equivalent to 2.30% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Precautions

Severe liver damage
Liver function tests should be performed before therapy and then periodically during the first 6 months of therapy, especially in patients at risk. Upon changes in concomitant medicinal products (dose increase or additions) that are known to impact the liver, liver monitoring should be restarted as appropriate (see also section 4.5 on risk of liver damage with salicylates, other anticonvulsants including cannabidiol).

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 Severe liver damage and see also section 4.5).

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see also section 4.5).

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).

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 section 4.8).

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).

Urea cycle disorders and risk of 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 (see sections 4.3 and 4.4 Patients at risk of hypocarnitinaemia and Severe liver damage).

Patients at risk of hypocarnitinaemia
Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 Patients with known or suspected mitochondrial disease and Urea cycle disorders and risk of hyperammonaemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.

Patients should be warned to report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed.

Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative. In these patients, carnitine monitoring should be implemented.

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

See also sections 4.5, 4.8 and 4.9.

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 Interactions with Other Medicinal Products and Other Forms of Interaction

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.

Clozapine
Concomitant treatment of valproate and clozapine may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of valproate with clozapine is necessary, careful monitoring for both events is required.

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 plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem agents
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

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.

Metamizole
Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Methotrexate
Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Other Interactions

Risk of liver damage
The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section 4.4).
Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4).
Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be exercised when valproate is concomitantly used with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

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.
Concomitant food intake does not significantly influence the bioavailability of sodium valproate when administered as the Chronosphere formulation.

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.

Pivalate-conjugated medicines
Concomitant administration of valproate and pivalate-conjugated medicines (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4 Patients at risk of hypocarnitinaemia). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy and women of childbearing potential

Treatment of epilepsy
- Valproate is contraindicated during pregnancy, unless there is no suitable alternative treatment
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4)

Treatment of bipolar disorder
- Valproate is contraindicated during pregnancy
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4)

Teratogenicity and Developmental Effects from in utero exposure

Pregnancy Exposure Risk related to valproate

In females, both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. Valproate was shown to cross the placental barrier both in animal species and in humans (see section 5.2).

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3). In preclinical studies a dose-related foetal weight decrease was demonstrated in animals exposed to valproate *in utero* compared to unexposed animals (see section 5.3).

Congenital malformations from in utero exposure

A meta-analysis (including registries and cohort studies) showed that about 11% of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (about 2-3%).

The risk of major congenital malformations in children after in utero exposure to antiepileptic drug polytherapy including valproate is higher than that of anti-epileptic drugs polytherapy not including valproate.
This risk is dose-dependent in valproate monotherapy, and available data suggest it is dose-dependent in valproate polytherapy. However, 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.

In utero exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Neurodevelopmental disorders from in utero exposure

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when valproate is used in monotherapy but a threshold dose below which no risk exists cannot be established based on available data. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated epileptic mothers.
The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

When valproate is administered in monotherapy, 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 from a population-based study show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.

Available data from another population-based study show that children exposed to valproate in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

Small for gestational age from in utero exposure
Some epidemiological studies have suggested a higher risk of being born small for gestational age (SGA defined as birth weight below the 10th percentile corrected for their gestational age, stratified by gender) for children exposed to valproate *in utero* in comparison to unexposed or lamotrigine-exposed children. SGA was observed in approximately 11-15% of children exposed to valproate *in utero*, 8-9% of lamotrigine-exposed children, and 5-10% of unexposed children.
Available data in human do not allow to conclude on a potential dose-related effect.

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.

Women of childbearing potential
Estrogen-containing products

Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (sections 4.4 and 4.5).

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.

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group.

Other observational population-based studies did not show an increased risk of NDDs in children born to men treated with valproate as monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam as monotherapy.

Differences in study design, including control for confounding and population selection, may contribute to differences in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, the evidence regarding an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is inconsistent, and the causal role of valproate is uncertain.

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.

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). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some other cases, the reversibility of male infertility was unknown.

4.7 Effects on Ability to Drive and to 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 (see sections 4.3 and 4.4 Urea cycle disorders and risk of hyperammonaemia and Patients at risk of hypocarnitinaemia).
Not known: hypocarnitinaemia (see sections 4.3 and 4.4).

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.
Not known: Hyperpigmentation.

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 (see section 4.6), 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:
Common: urinary incontinence
Uncommon: renal failure
Rare: enuresis, tubulointerstitial nephritis, 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 (eosinophilic).

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.
Not known: acquired Pelger-Huet anomaly*
*Acquired Pelger-Huet anomaly has been reported in cases with and without myelodysplastic syndrome.

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

Paediatric population
The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population.

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. Website: www.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.

Management

In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalize ammonia levels.

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

Pharmacotherapeutic group: Anti-epileptics, fatty acid derivatives, ATC Code: N03A G01

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

Placental transfer (see section 4.6)

Valproate crosses the placental barrier in animal species and in humans.

- In animal species, valproate crosses the placenta, to a similar extent as in humans.

- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the foetuses, was similar to or slightly higher than that in the mothers.

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 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 Chronosphere 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 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.

Paediatric patients
Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults.

5.3 Preclinical Safety Data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay in vitro and did not induce DNA repair in primary rat hepatocyte cultures. In vivo, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in epileptic patients exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in epileptic patients treated with valproate with those in untreated epileptic patients. The clinical relevance of these DNA/chromosome findings is unknown.
Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproductive toxicity
Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.
In mice, rats, and rabbits, in utero exposure to valproate induced a dose-related decrease in foetal weight, intra-uterine growth restriction and reduction in crown rump length compared to unexposed animals.

Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.
Behavioural abnormalities have been reported in first generation offspring of mice and rats after in utero exposure. Some behavioural changes have been also observed in the 2nd generation and those were less pronounced in the 3rd generation of mice following acute in utero exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

In repeat-dose toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs.
The safety margin comparisons based on extrapolated AUC in rats and dogs indicate that there may be no safety margin.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Based on these data, juvenile animals were not considered more susceptible to testicular findings than adults. Relevance of the testicular findings to paediatric population is unknown.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance. However, male infertility has been identified as an undesirable effect in humans (see sections 4.6 and 4.8).

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 25ºC.

6.5 Nature and contents of container

Epilim Chronosphere 500 mg prolonged-release granules are filled into sachets of 3 layers complex: printed paper, aluminium, ionomer resin complex.

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

Not all packs sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PA 540/150/7

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Date of First Authorisation: 02March 2007

10. DATE OF (PARTIAL) REVISION OF THE TEXT

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