DATA SHEET

1 PRODUCT NAME

Epilim 100 crushable tablet, 100 mg

Epilim EC modified release tablet, 200 mg

Epilim EC modified release tablet, 500 mg

Epilim Syrup, 200 mg/5 mL

Epilim Liquid oral solution (sugar free), 200mg/5mL

Epilim Intravenous solution for injection, 100 mg/mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Epilim 100 Crushable Tablets contain 100 mg sodium valproate.

Epilim EC Modified Release Tablets contain 200 mg sodium valproate.

Epilim EC Modified Release Tablets contain 500 mg sodium valproate.

Epilim Syrup, each 5 mL of syrup contains 200 mg sodium valproate.

Epilim Liquid Oral Solution, each 5mL of liquid contains 200 mg sodium valproate.

Epilim Intraveous (IV) Solution for Injection - each pack contains one glass vial of 400 mg sodium valproate freeze-dried powder and one glass ampoule containing 4 mL of solvent (Water for Injections).

For the full list of excipients, see Section 6.1, List of Excipients.

3 PHARMACEUTICAL FORM

Crushable tablet, 100 mg (white, scored).

Modified release tablet, 200 mg (lilac, enteric-coated).

Modified release tablet, 500 mg (lilac enteric-coated).

Syrup, 200 mg/5 mL (red, cherry flavoured).

Oral solution sugar free liquid, 200 mg/5 mL (red, cherry flavoured)

Powder 400 mg and solvent 4 mL for solution for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Epilepsy

Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsy and tonic-clonic grand mal seizures). Partial (focal) epilepsy either alone or as adjuvant therapy.

Bipolar Disorder

For the treatment of manic episodes, maintenance and prophylactic treatment of bipolar disease.

Epilim IV

The treatment of patients with epilepsy or bipolar disorder, who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

4.2 DOSE AND METHOD OF ADMINISTRATION

Epilim tablets may be given twice daily. Uncoated tablets may be crushed if necessary however, unlike other scored tablets, the 100 mg tablets are not designed to be given as half doses. Epilim Syrup and Sugar-Free Liquid should be given in divided doses.

Epilim should preferably be taken with or after food: the enteric-coated tablet (lilac) must be swallowed whole, if necessary with a little water: the plain tablet (white, 100 mg) may be taken whole or crushed and swallowed with water (not aerated).

Epilim 500 mg enteric-coated is recommended for patients requiring high doses. Where the possibility of dental caries represents a risk through long-term therapy with Epilim Syrup, it may be beneficial to consider Epilim Sugar-Free Liquid. Epilim may take several days to show an initial effect and in some cases may take from 2 to 6 weeks to exhibit its maximum effect.

Epilim oral - epilepsy

Monotherapy

Usual requirements are as follows:

Adults

Dosage should start with 600 mg daily increasing by 200 mg/day at three-day intervals until control is achieved. This is generally within the range 1,000 to 2,000 mg/day, (i.e. 20 to 30 mg/kg/day). Where adequate control is not achieved within this range the dose may be further increased to 2,500 mg/day.

Children > 20 kg

Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20 to 30 mg/kg/day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body weight per day.

Children < 20 kg

20 mg/kg/day: in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

General considerations

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

Epilim oral - bipolar disorder

Initially dosage should start with 600 mg daily in 2 to 3 divided doses. From day 2 the dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. Daily doses generally within the range 1,000 to 2,000 mg/day, (i.e. 20 to 30 mg/kg/day). Where adequate control is not achieved within this range the dose may be further increased to 2,500 mg/day.

The Bowden et al study (see Section 5.1) provided strong support for the greater efficacy of serum levels above 45 µg/mL (these levels achieved 20% or greater improvement on both subscales of the Mania Rating Scale). Bowden noted that > 125 µg/mL had greater drug-related adverse events. Between these extremes there does not appear to be a clear dose-response relationship.

Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

Epilim IV - epilepsy and bipolar disorder

Epilim IV may be given by direct slow intravenous injection or by slow intravenous infusion in 0.9% NaCL (normal saline), 5% glucose solution or glucose saline, using a separate intravenous line. The recommended concentration of the intravenous infusion solution is 4 mg/mL, with 8 mg/mL being the maximum concentration.

Epilim IV should not be administered at the same time as other intravenous additives via the same IV line. The intravenous solution is suitable for infusion by PVC, polyethylene or glass containers.

To reconstitute, inject the solvent provided (4mL) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95mg/mL. Epilim IV should be replaced by oral Epilim therapy as soon as practicable.

Each ampoule of Epilim IV is for single dose injection only. To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary hold at 2 to 8ºC for not more than 24 hours. Epilim IV is intended for use in one patient on one occasion only, any unused portion should be discarded. **NEVER ADMINISTER EPILIM IV OTHER THAN BY THE INTRAVENOUS ROUTE** (see Section 4.3).

Monotherapy

Daily dosage requirements vary according to age and body weight:

Adults

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous infusion. For example, a patient stabilised on 25 mg/kg administered daily should be continued with an infusion at the rate of 1 mg/kg/hr.

Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800 mg depending on body weight (up to 10 mg/kg) followed by continuous infusion of 1-2 mg/kg/hr up to a maximum of 2500 mg/day, according to the patient’s clinical response.

Children

The daily requirement for children is usually in the range 20-30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be

monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Special Populations

Female children, female adolescents, women of childbearing potential and pregnant women

Treatment 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 Section 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. The daily dose should be divided into at least two single doses during pregnancy.

Use in hepatic impairment

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate (see Section 4.4).

Use in renal impairment

Lower doses may be required since free drug levels may be high owing to lowered serum albumin and poor urinary excretion of free drug metabolites (see Section 4.4). Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading. (See Section 5.2).

Use in elderly

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

Paediatric population

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

Combined Therapy

When starting Epilim in patients on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2

weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants, which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly, the dosage of barbiturate should be reduced if sedation is observed.

Estrogen-containing products

Valproate does not reduce the efficacy of hormonal contraceptives.

Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels (See Section 4.5).

4.3 CONTRAINDICATIONS

Known hypersensitivity to sodium valproate or any of the excipients listed in Section 6.1

Pregnancy (see Section 4.6).

Pre-existing, acute or chronic hepatic dysfunction or family history of severe hepatitis, particularly medicine related.

Known urea cycle disorders (see Section 4.4).

Known hepatic porphyria.

Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ (POLG eg Alpers-Huttenlocher Syndrome) and in children under two years of age who are suspected of having POLG-related disorder.

Epilim IV should not be injected intramuscularly as it may produce tissue necrosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatic Dysfunction

Conditions of occurrence

Severe liver damage and/or hepatic failure resulting in fatalities have occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are those on multiple anticonvulsant therapy and children, particularly those under the age of 3 years and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with brain damage and/or mental retardation.

The incidents usually occurred during the first six months of therapy, the period of maximum risk being 2 to 12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

After the age of 3 years, the risk is significantly reduced and it progressively decreases with age. In most cases, such liver damage occurred during the first 6 months of therapy.

Suggestive signs

Clinical symptoms are usually more helpful than laboratory investigations in the early stages of hepatic failure. Jaundice, serious or fatal hepatotoxicity may be preceded by nonspecific symptoms, usually of sudden onset, such as loss of seizure control, malaise, asthenia, weakness, lethargy, facial oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. In patients with epilepsy, recurrence of seizures can occur. These are an indication for immediate withdrawal of the medicine.

Patients should be monitored closely for the appearance of these symptoms. Patients (and their family) should be instructed to immediately report any such signs to the clinician for investigation should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.

Detection

Although published evidence does not establish which, if any investigation could predict this possible adverse effect, liver function tests should be performed prior to therapy and frequently thereafter until 6 months after the controlling dose is reached, when less frequent monitoring may be appropriate. It is also advisable to monitor tests that reflect protein synthesis, e.g. prothrombin time, serum fibrinogen and albumin levels, especially in those who seem most at risk and those with a prior history of hepatic disease.

As with most antiepileptic drugs, a slight increase in liver enzymes may be noted, particularly at the beginning of therapy. They are transient and isolated. More extensive biological investigations (including prothrombin rate) are recommended in those patients. An adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

Raised liver enzymes are not uncommon during treatment with Epilim, **particularly if used in conjunction with other anticonvulsants**, and are usually transient or respond to dosage reduction. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored more frequently. Among the usual investigations, tests which reflect protein synthesis particularly prothrombin rate, are most relevant. An abnormally low prothrombin rate, particularly in association with other relevant abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment and the substitution of alternative medicines to avoid precipitating convulsions. Uneventful recovery has been recorded in several cases where therapy with Epilim

has ceased, but death has occurred in some patients in spite of the medicine being withdrawn. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Pancreatitis

Severe pancreatitis, which may result in fatalities, has been very rarely reported. Some cases have occurred shortly after initial use while others have occurred after several years of use. There have also been cases in which pancreatitis recurred after rechallenge with sodium valproate. Some of the cases have been described as haemorrhagic with a rapid progression from initial symptoms to death. In clinical trials, there were two cases of pancreatitis without alternative aetiology in 2416 patients, representing 1044 patient-years experience.

Young children are at particular risk but this risk decreases with increasing age. Severe seizures, neurological impairment or anticonvulsant polytherapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.

Patients and guardians should be warned that acute abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical attention. If pancreatitis is diagnosed, sodium valproate should be discontinued and alternative treatment for the underlying medical condition initiated as clinically indicated.

Use in renal impairment

Lower doses may be required since free drug levels may be high owing to lowered serum albumin and poor urinary excretion of free drug metabolites. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Diabetes

Care should be taken when treating diabetic patients with Epilim syrup which contains sucrose 3.6 g/5 mL. In such patients, Epilim Sugar-Free Liquid would be a preferable medication. See also **Effects on Laboratory Tests.**

Dilutions

If it is necessary to dilute the syrup, the recommended diluent is Syrup BP. Syrup containing sulfur dioxide as a preservative should not be used. The diluted product will have a 14-day shelf-life. The Sugar-Free Liquid should not be diluted.

Lupus Erythematosus

Although immune disorders have been noted only exceptionally during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus.

Hyperammonaemia

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

Hyperammonaemia, which may be present in the absence of abnormal liver function tests, can occur in patients during treatment with sodium valproate. This may occasionally present clinically, with or without lethargy or coma, as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, hyperammonaemic encephalopathy should be considered (see **Urea Cycle Disorders**) and Epilim should be discontinued.

Urea Cycle Disorders (UCD)

Hyperammonaemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency.

Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients:

1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;

2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance;

3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males);

4) those with other signs or symptoms of UCD.

Patients who develop symptoms of unexplained hyperammonaemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders.

Ornithine Transcarbamylase (OTC) Deficiency

The females who are heterozygous for OTC deficiency have a spectrum of clinical and biochemical findings, depending on the extent of inactivation of the X-chromosome. Females may show a range of symptoms due to hyperammonaemia which, may be episodic, and therefore difficult to diagnose. The acute symptoms include headaches, vomiting, irritability, bizarre behaviour, lethargy, ataxia, tremors, seizures (generalised tonic-clonic or focal) and coma.

Valproate may precipitate hyperammonaemia symptoms in those who have pre-existing OTC deficiency. As the symptoms may include seizures, any female with valproate-associated symptomatic hyperammonaemia should be evaluated for OTC deficiency. Investigations should include measurement of plasma amino acids and the immediate cessation of valproate should result in clinical improvement.

Surgery

Prolongation of bleeding time, sometimes with thrombocytopenia, has occurred with Epilim therapy. Platelet function should be monitored before surgery is undertaken in patients receiving Epilim.

Other

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.

Suicidal Behaviour and Ideation

Antiepileptic drugs, including sodium valproate increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any anti-epileptic drug (AED) for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behavior, and appropriate treatment should be considered.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated.

There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed.

The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. The mechanism of this effect is unknown. The following Table shows absolute and relative risk by indication for all evaluated AEDs.

Indication	Placebo patients with events/1000 patients	Drug patients with events/1000 patients	Relative Risk: Incidence of events in Drug patients/Incidence in Placebo patients	Relative Difference: Additional Drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing sodium valproate or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour.

Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Abrupt Withdrawal

The possible risk of fits after sudden cessation of Epilim should be borne in mind. If it is the only anticonvulsant used and has to be withdrawn for more than 12 hours because of surgery, control of epilepsy may be lost.

Carbapenem Agents

The concomitant use of sodium valproate and carbapenem antibiotics is not recommended (see also Section 4.5).

Pharmaceutical Precautions

Epilim tablets are hygroscopic and must be kept in protective foil until taken (See Section 6.4).

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, acute liver failure and liver-related deaths have been associated with valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial enzyme polymerase γ (POLG eg 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 un-explained 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.

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).

Thrombocytopenia

Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. Evidence of haemorrhage, bruising or a disorder of haemostasis/coagulation is an indication for reduction of Epilim dosage or withdrawal of therapy.

Ornithine Transcarbamylase (OTC) Deficiency

A familial history of infant mortality or patient history of OTC deficiency, or of seizures or coma in the presence of mental retardation suggests the need to exclude OTC deficiency.

Weight Gain

Patients should be warned of the risk of weight gain at the initiation of therapy, and appropriate strategies should be adopted to minimise the risk.

Carnitine Palmitoyltransferase (CPT) Type II Deficiency

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

Female children, female adolescents, women of child bearing potential and pregnant women:

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

This assessment is to be made before sodium valproate is prescribed for the first time, or when a woman of child bearing potential treated with sodium valproate plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

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, 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. The daily dose should be divided into at least two single doses during pregnancy.

Women of child-bearing 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. 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 an appropriate alternate treatment prior to conception, if possible (see Section 4.6).

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

Estrogen-containing products

Valproate does not reduce the efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels (See Section 4.5).

Paediatric Use

The potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see Section 4.4). The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity and the concomitant use of barbiturates may require dosage adjustment (see Section 4.5). Monotherapy is recommended in children under 3 years of age, when prescribing Epilim. Young children are at particular risk for pancreatitis, however this risk decreases with increasing age.

The safety and efficacy of sodium valproate for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Effects on laboratory tests

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.

There have been reports of altered thyroid function test results associated with sodium valproate. The clinical significance of this is unknown.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Potential for valproate to effect other medicines

Sodium valproate is an inhibitor of a variety of hepatic enzymes, including cytochrome P450, glucuronyl transferase and epoxide hydrolase, and may displace various drugs from plasma protein binding sites. The following list provides information about potential effects of valproate co-administration on a range of commonly prescribed medications. The list is not exhaustive, as new interactions may be reported.

Alcohol

Valproic acid may potentiate the CNS depressant activity of alcohol. Alcohol intake is not recommended during treatment with valproate.

Antiepileptic drug

Several antiepileptic drugs often used in conjunction with valproate (eg phenytoin, carbamazepine, phenobarbital) have the ability to increase the intrinsic clearance of valproate, presumably by enzymatic induction of metabolism.

Carbamazepine

Valproate may displace carbamazepine from protein binding sites and may inhibit the metabolism of both carbamazepine and its metabolite carbamazepine 10, 11 epoxide and consequently potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy, with dosage adjustment when appropriate.

Lamotrigine

Sodium valproate reduces lamotrigine metabolism and increases mean half life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Clinical monitoring is recommended and lamotrigine dosage should be decreased as appropriate.

Phenobarbital

Sodium valproate blocks the metabolism of barbiturates causing an increase in phenobarbital plasma levels, which, particularly in children, may be associated with sedation. Combination of sodium valproate and phenobarbital can cause CNS depression without significant elevation of serum level of either drug. 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. A reduction in the dose of phenobarbital and/or valproate may be necessary and this should also be borne in mind if medicines that are metabolised to phenobarbital (e.g. primidone, methylphenobarbitone) are given with sodium valproate.

Phenytoin

There have been reports of breakthrough seizures occurring with the combination of sodium valproate and phenytoin. Valproate decreases total plasma phenytoin concentration, however increases in total phenytoin levels have been reported. An initial fall in total phenytoin levels with subsequent increase in phenytoin levels has also been reported. In addition, a decrease in total serum phenytoin with an increase in the free versus protein bound phenytoin levels has been reported with possible overdose 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. The dosage of phenytoin may require adjustment when given in conjunction with valproate as required by the clinical situation.

Medicines with extensive protein binding

The concomitant administration of sodium valproate with medicines that exhibit extensive protein binding (e.g. aspirin, carbamazepine, phenytoin, warfarin) may result in alteration of serum drug levels.

Anticoagulants

The effect of Epilim on anticoagulants which modify platelet function is unknown (see Section 4.8). Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and aspirin).

Ethosuximide

The interaction between ethosuximide and valproate is not normally of clinical significance. There is evidence that sodium valproate may inhibit ethosuximide metabolism, especially in the presence of other anticonvulsants. Patients receiving this combination should be monitored clinically.

Oral contraceptives

The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Psychotropic agents

Epilim may potentiate the effects of other psychotropics such as MAOIs, neuroleptics, benzodiazepines and other antidepressants, therefore clinical monitoring is advised and the dose of these medicines should be reduced accordingly.

Clonazepam

The concomitant use of sodium valproate and clonazepam may produce absence status**.**

Clozapine

Caution is advised during concomitant administration as competitive protein binding may potentiate an increase in clozapine or valproate levels.

Diazepam

Sodium valproate displaces diazepam from its plasma binding sites and inhibits its metabolism. Monitoring of free diazepam levels may be necessary if the patient becomes sedated.

Lorazepam

A decrease in lorazepam plasma clearance may occur with concomitant administration of sodium valproate.

Midazolam

Free plasma midazolam may increase in patients receiving valproate. It appears likely that sodium valproate displaces midazolam from its plasma binding sites, potentially leading to an increase of the midazolam response.

Primidone

Valproate 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.

Zidovudine

Valproate may raise zidovudine plasma concentrations leading to increased zidovudine toxicity.

Tricyclic antidepressants

Sodium valproate may inhibit the metabolism of tricyclic antidepressants. Clinical monitoring of free antidepressant levels may be necessary.

Olanzapine

Valproic acid may decrease the olanzapine plasma concentration.

Felbamate

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

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

Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration.

Other medicines

There was no notable interaction between valproate and lithium.

Potential for other medicines to effect valproate

The dosage of Epilim may need to be increased by 5 to 10 mg/kg/day when used in combination with medicines which induce hepatic enzymes and thereby increase the clearance of valproate. In contrast, medicines that are inhibitors of cytochrome P450, may be expected to have only a minor effect on valproate clearance as cytochrome P450 mediated microsomal oxidation is a relatively minor secondary metabolic pathway to glucuronidation and ß-oxidation. The list is not exhaustive, as new interactions may be reported.

Aspirin

Concomitant administration of sodium valproate and aspirin may result in displacement of valproate from protein binding sites, resulting in a rise in free levels. In addition, aspirin appears to inhibit the metabolism of valproate. Thus caution is advisable when patients on sodium valproate are prescribed aspirin. Furthermore, patients requiring long-term aspirin therapy may require a reduction in dosage of sodium valproate.

Felbamate

Felbamate may decrease valproic acid clearance and consequently increase valproate serum concentrations. Valproate dosage should be monitored when given in combination with felbamate.

Phenobarbital, Phenytoin and Carbamazepine

These medicines can decrease steady-state valproate levels in patients by increasing the intrinsic clearance of valproate, presumably through enzymic induction of metabolism. The half-life is significantly reduced in patients on polytherapy with these medicines. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

Valproic acid metabolite levels may be increase in case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with either of these two drugs should be carefully monitored for signs and symptoms of hyperammonemia.

Antidepressants

Antidepressants (including MAOIs, tricyclic antidepressants and SSRIs) may have the potential to inhibit the metabolism of valproate via the cytochrome P450 system. However, there is not expected to be any significant interaction within normal therapeutic doses. Antidepressants can lower the seizure threshold of non-stabilised epileptic patients, and so careful and regular monitoring of their condition is indicated.

Clozapine

Caution is advised during concomitant administration as competitive protein binding may potentiate an increase in clozapine or valproate levels.

Chlorpromazine

Chlorpromazine may inhibit the metabolism of valproate.

Fluoxetine

Fluoxetine may inhibit the metabolism of valproate as it does with tricyclic antidepressants, carbamazepine and diazepam.

Mefloquine

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy.

Cimetidine or Erythromycin

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

Carbapenem antibiotics

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 in about two days. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided. If treatment with these antibiotics cannot be avoided close monitoring of valproate blood level should be performed.

Colestyramine

May decrease the absorption of valproate and may lead to a decrease in plasma level of valproate when co-administered.

Vitamin K dependent factor anticoagulant

Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent factor anticoagulant.

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 levels when co-administered.

Medicines with extensive protein binding

The concomitant administration of sodium valproate with medicines that exhibit extensive protein binding (e.g. aspirin, carbamazepine, phenytoin, warfarin) may result in alteration of serum drug levels.

Estrogen-containing products

Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of

valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

Valproate does not reduce the efficacy of oestroprogestative agents.

Other interactions

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Use in pregnancy

Category D

Before Epilim is prescribed for use in women with epilepsy of any form, who could become pregnant, they should receive specialist advice. Due to the potential risks to the foetus, the benefits of Epilim should be weighed against the risks. When treatment with Epilim is deemed necessary, precautions to minimise the potential teratogenic risk should be followed.

Overall, the risk of having a child with abnormalities as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, without reassessment of the risks and benefits, as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus. If after careful evaluation of the risks and benefits, sodium valproate treatment is to be continued during pregnancy, it is recommended to use sodium valproate in divided doses over the day at the lowest

effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.

In bipolar disorder, cessation of sodium valproate should be considered.

Risk associated with seizures

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.

Risk associated with sodium valproate

In animals, teratogenic effects have been demonstrated in mice, rats and rabbits.

Congenital malformations:

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in children born to mothers treated with valproate, when compared to the incidence for certain other antiepileptic drugs.

Data has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy. This is a greater risk of major malformations than for the general population. Women treated with Epilim IV have a potentially increased risk of giving birth to a baby with an abnormality due to the higher C_{max} of the intravenous formulation compared with the oral formulation. Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine.

Sodium valproate (valproic acid), if taken in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed foetus. This has been estimated to be in the region of 1-2%.

This risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Developmental disorders:

Data has 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 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 some children may experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Some data have suggested an association between in-utero valproate exposure and the risk of impaired cognitive function, including developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. IQ measured in school aged children with a history of valproate exposure in utero, was 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 is limited data on the long term outcomes.

Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.

Autism spectrum disorders have also been reported in children exposed to valproate in-utero.

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

Use in Pregnancy

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

In view of this data, the following recommendation should be taken into consideration:

This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary, that is, in situations where other treatments are ineffective or not tolerated. This assessment is to be made before sodium valproate is prescribed for the first time, or when a woman of child-bearing potential treated with sodium valproate plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Valproate does not reduce the efficacy of hormonal contraceptives.

However, estrogen containing products, including estrogen containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

Women of child-bearing potential should be informed of the risks and benefits of the use of valproate during pregnancy.

Treatment advice:

It is recommended that women of child-bearing potential taking sodium valproate should:

- receive counselling with regard to the risk of foetal abnormalities;
- have their drug treatment reviewed before conception. This may involve dose adjustments or alternative therapy options. If sodium valproate is to be continued, monotherapy should be used if possible at the lowest effective dose given in divided doses, as risk of abnormality is greater in women taking combined medication and in women taking a higher total daily dose;
- undergo routine ultrasound and amniocenteses for specialist prenatal diagnosis of such abnormalities;
- take folic acid supplementation (5mg daily) for at least 4 weeks prior to and 12 weeks after conception as folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy.

It is recommended that in bipolar disorders indication, cessation of valproate therapy should be considered.

Risk in neonate

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome is related to thrombocytopenia, hypofibrinaemia and/or to a decrease in other coagulation factors. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Phenobarbital and other enzyme inducers may also induce haemorrhagic syndrome as they decrease the vitamin-K factors. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

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

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

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

Use in lactation

Epilim is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentration. It is not known what effect this would have on a breast-fed infant. As a general rule, breastfeeding should not be undertaken whilst a patient is receiving Epilim.

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. However, patients should be warned of the risk of drowsiness, especially in cases of anticonvulsant polytherapy, too high a starting dose, too rapid a dose escalation or when used in association with benzodiazepines.

4.8 UNDESIRABLE EFFECTS

In Bipolar Disorder

No new or unexpected adverse events have been reported in clinical trials of Epilim in mania. The frequencies of adverse events (%) reported on valproate (as divalproex) in the largest controlled clinical trial described under Section 5.2 are summarised in Table 1.

Table 1 - Adverse events reported on divalproex in the Bowden et al. study (1994)

	Bowden *et al.* 1994		
Adverse event	VPA*	Lithium	Placebo
	n = 69	n = 36	n = 74
Body as a whole			
Pain	19	3	20
Asthenia	13	19	9
Fever	1	14	4
Gastrointestinal			
Nausea	23	31	15
Diarrhoea	12	14	18
Vomiting	14	25	4
Constipation	10	17	7
Nervous system			
Headache	22	39	32
Somnolence/Sedation/ Fatigue	19	19	15
Twitching	3	8	0

Adverse events reported at a frequency: >15% or significantly different between treatment groups, or > 5% or common events to other study (no events significantly more frequent in this study).

*VPA as divalproex

In this study, there were differences with placebo for vomiting only for divalproex (45% vs 14%), fever was more common for lithium (14%) than for divalproex (1%) and placebo (4%), pain was less common with lithium (3%) than with either divalproex (19%) or placebo (20%).

List of adverse effects by system organ class

The following CIOMS frequency rating is used:

very common	≥ 1/10 (≥ 10%)
common	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
uncommon	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1.0%)
rare	≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
very rare	< 1/10,000 (< 0.01%)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Myelodysplastic syndrome is rare.

Blood and lymphatic system disorders

Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time, as well as thrombocytopenia, have been reported but have usually been associated with doses above those recommended (see Section 4.4).

Common cases of thrombocytopaenia and anaemia have been reported.

Uncommon cases of leucopenia and pancytopaenia with or without bone marrow depression have been reported.

Bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic and macrocytosis have rarely been reported.

Isolated cases of decreased blood fibrinogen and prolonged prothrombin time have been reported.

Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigation (see Section 4.4).

Red cell hypoplasia, neutropenia and leucopenia have also been reported. In most cases the blood picture returned to normal when the medicine was discontinued.

Immune system disorders

Angioedema, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome and allergic reactions have been observed.

Endocrine disorders

Hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased) and Syndrome of Inappropriate Secretion of ADH (SIADH) is uncommon.

Hypothyroidism is rare.

Metabolism and nutrition disorders

Common cases of hyponatremia have been reported.

Increased weight is common and since this is a risk factor for polycystic ovary syndrome, it should be carefully monitored.

Obesity has been reported rarely. Hyperammonaemia is rare. This has been reported in association with valproate therapy and may be present despite normal liver function tests. Isolated and moderate hyperammonaemia may occur frequently and should not cause treatment discontinuation.

Hyperammonaemia associated with neurological symptoms has been reported, In patients who develop unexplained lethargy and vomiting or changes in mental status, further investigations and hyperammonaemic encephalopathy should be considered. In these patients, EEG and ammonia level should be checked and, if ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonaemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see Section 4.4).

Asymptomatic elevations of ammonia are more common and, when present, require close monitoring of plasma ammonia levels. If the elevation is significant (above 3N) and persists, discontinuation of valproate therapy should be considered.

Psychiatric disorders

Confusional state, hallucinations, aggression, agitation and disturbance in attention are common.

Abnormal behaviour, psychomotor hyperactivity and learning disorder are rare.

Nervous system disorders

The true incidence of drowsiness and sedation with Epilim is difficult to assess, as mostly it was administered in combination with other medicines. Epilim, however, may have an intrinsic sedative action in addition to potentiating sedative effects of other anticonvulsants (e.g. barbiturates, clonazepam) and CNS depressants, including alcohol. In monotherapy, sedation occurred early in treatment on rare occasions and is usually transient.

Very common cases of tremor have been reported.

Common cases of stupor, somnolence, convulsion, memory impairment, headache, nystagmus and dizziness have been reported.

When using Epilim intravenously, dizziness may occur within a few minutes after injection; it disappears spontaneously within a few minutes.

Common cases of extrapyramidal disorder which may not be reversible, including reversible parkinsonism has been reported.

Uncommon cases of ataxia, coma, encephalopathy, aggravated convulsions (see Section 4.4), lethargy and paresthesia have been reported.

Diplopia and depression have occurred rarely and usually in association with other

anticonvulsants. Excitement, alertness, hyperactivity and behavioural disorders have been rarely reported, usually in children at the start of treatment.

Rare cases of reversible dementia associated with reversible cerebral atrophy and cognitive disorder have been reported.

A few cases of stupor and lethargy sometimes leading to transient coma (encephalopathy) have been reported. They were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage. These cases mostly occurred during combined therapy (in particular with phenobarbital or topiramate) or after a sudden increase in valproate doses.

Ear and labyrinth disorders

Deafness, either reversible or irreversible, has been reported commonly.

Vascular disorders

Haemorrhage is common and the occurrence of vasculitis is uncommon.

Respiratory, thoracic and mediastinal disorders

Pleural effusion has uncommonly been reported.

Gastrointestinal disorders

Nausea is very common.

Upper abdominal pain, vomiting, diarrhoea, gingival disorder (mainly gingival hyperplasia) and stomatitis are common and frequently occur at the start of treatment and usually disappear after a few days without discontinuing treatment.

Vomiting, abdominal cramp, upper abdominal pain, anorexia, increased appetite and diarrhoea are usually transient and rarely require discontinuation of therapy or limitation of dose.

The overall incidence of adverse GI effects are reported to be 9 to 16% in adults and over 22% in children when plain tablets are prescribed. GI side effects may be minimised by taking the tablets with or after food or by substituting the enteric-coated tablets. As some of these symptoms may also indicate early stage hepatic dysfunction, patients should be monitored closely for the appearance of these symptoms. Patients should be instructed to report such signs to the clinician for investigation should they occur (see Section 4.4).

There have been uncommon reports of pancreatitis, sometimes lethal, occurring in patients receiving valproic acid or sodium valproate, usually within the first 6 months of therapy. Patients

experiencing acute abdominal pain should have their serum amylase estimated promptly; if these levels are elevated the medicine should be withdrawn (see Section 4.4).

Hepatobiliary disorders

Liver injury is common.

Hepatic dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate (see Section 4.4).

Skin and subcutaneous tissue disorders

Hypersensitivity and transient and/or dose related alopecia has been observed commonly. Nail and nail bed disorders have been commonly reported.

Angiodema, rash and hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal) are uncommon.

Toxic epidermal necrolysis, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome and erythema multiforme have been reported rarely.

Caution should be observed when using the medicine in patients with systemic lupus erythematosus.

Musculoskeletal and connective tissue disorders

Decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with valproate have been uncommon. The mechanism by which valproate affects bone metabolism has not been identified.

Systemic lupus erythematosus and rhabdomyolysis are rare.

Renal and urinary disorders

Urinary incontinence is common.

Renal failure is uncommon.

Rare cases of enuresis and tubulointerstitial nephritis have been reported.

Rare cases of reversible Fanconi’s syndrome associated with valproate therapy have been reported but the mode of action is as yet unclear.

Reproductive system and breast disorders

Dysmenorrhoea is common and amenorrhoea is uncommon.

There have been rare reports of male infertility and polycystic ovaries.

There have been reports of irregular menses and secondary amenorrhoea and rare cases of breast enlargement and galactorrhoea.

General disorders and administration site conditions

Non-severe peripheral oedema and hypothermia are uncommon.

Oedema has been reported. Increase in appetite may occur.

Investigations

Coagulation factors decreased, abnormal coagulation tests (such as prolonged prothrombin time, activated partial thromboplastin time, thrombin time and INR) and biotin deficiency/biotinidase deficiency have rarely been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Cases of accidental and suicidal overdosage have been reported. Fatalities are rare.

Symptoms

At plasma concentrations of up to 5 or 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Symptoms of overdosage may include serious CNS depression and impairment of respiration. In cases of overdose, long half-lives up to 30 hours have been reported. Signs of an acute massive overdose usually include coma, with muscular hypotonia, hyporeflexia and miosis, impaired respiratory functions and metabolic acidosis, hypotension and circulatory collapse/shock. Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported. Deaths have occurred following massive overdose. Hospital management of overdose including

assisted ventilation and other supportive measures are recommended. The presence of sodium content in the valproate formulations may lead to hypernatraemia when taken in overdose.

Treatment

Establish airway and breathing and evaluate circulatory status. Assisted mechanical ventilation may be required in cases of respiratory depression. For ingested medicine, activated charcoal may reduce the absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube, once the airway is protected. Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

Provided that adequate supportive treatment is given, full recovery usually occurs. Particular attention should be given to the maintenance of an adequate urinary output. Hepatic and pancreatic function should be monitored.

Contact the Poisons Information Centre on 0800 POISON or 0800 764 766 for advice on management of overdosage.

5 PHARMACOLOGICAL PROPERTIES

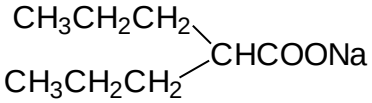
5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01

Chemical Name

Sodium di-n-propylacetic acid

Chemical structure



CAS Registry Number

1069-66-5

Description

Sodium valproate is a white, odourless, crystalline powder with a saline taste. It is highly soluble in water and alcohol. Its molecular weight is 166. It is quite dissimilar to other established anticonvulsants such as barbiturates, hydantoins, succinamides, oxazolidinediones and acetylureas in that it has no nitrogen or aromatic moiety.

Mechanism of Action

The mode of action of Epilim has not been fully established. Its anticonvulsant effect is attributed to the blockade of voltage dependent Na+ channels and increased brain levels of γ-aminobutyric acid (GABA). The GABA-ergic effect is also believed to possibly contribute towards the antimanic properties of sodium valproate.

In animals, Epilim raises cerebral and cerebellar levels of the inhibitory synaptic transmitter, GABA, possibly by inhibiting GABA degradative enzymes, such as GABA transaminase and/or succinic semialdehyde dehydrogenase and/or by inhibiting the reuptake of GABA by neuronal cells.

Epilim exhibits marked anticonvulsant activity in animals, demonstrated by the various tests used to detect antiepileptic activity.

Epilim appears to have no significant hypnotic effect (an incidence of about 0.2% was noted for drowsiness in a survey of unwanted effects), nor does it have any significant action on the autonomic nervous system, respiration, blood pressure, renal function or body temperature. It does have a spasmolytic action on the isolated ileum preparation but no effect on the nictitating membrane.

Pharmacodynamic effects

In epilepsy

Epilim has been shown to be effective in the treatment of absence seizures (petit mal), tonic-clonic seizures (grand mal) and myoclonic seizures. It has also been shown to be effective in patients with partial (focal) seizures. Epilim appears to have less sedative effect than conventional antiepileptic drugs and this, together with the reduction in fit frequency in children, has often led to improvements in alertness and performance in school.

In bipolar disorder

In one study valproate has been shown to be significantly more effective than placebo in the treatment of acute mania and has been reported to be comparable to lithium. Potential medicine interactions likely to be relevant to valproate in the management of patients with mania are outlined under Interactions with other medicines. Although the dosage of sodium valproate varied considerably among the controlled studies, a fixed initial dose was used after which dosage was determined by serum levels.

Clinical Trials

In epilepsy

Epilim’s efficacy in this therapeutic indication is widely known and recognised.

In bipolar disorder

There have been at least five double-blind trials comparing sodium valproate or the bioequivalent active, divalproex sodium with either placebo and/or lithium in the treatment of mania. Only one of these trials was of adequate size. Bowden et al (1994) demonstrated most convincingly the superior effectiveness of valproate as compared to placebo in the treatment of acute mania. Marked improvement, defined as at least 50% improvement on the Manic Syndrome Subscale of the Mania Rating Scale occurred in 48% of valproate-treated patients and 25% of placebo-treated patients respectively (p=0.0040). Comparable efficacy to lithium in this study was reported. Marked improvement, defined as at least 50% improvement on the Manic Syndrome Subscale of the Mania Rating Scale, occurred in a similar number of patients receiving sodium valproate and lithium, 48% and 49% respectively.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Oral

Valproic acid is rapidly and almost completely absorbed in fasting patients following oral dosing with Epilim plain tablets, syrup and sugar-free liquid, with peak blood levels occurring within 1 to 4 hours. Absorption of valproic acid from the enteric-coated tablets given to fasting subjects is delayed with peak blood levels occurring within 3 to 7 hours. Overall absorption is not significantly altered by co-administration with milk products, but is delayed if the medicine is taken with food. However, the extent of absorption is not affected. Local gastric irritation may occur with the plain tablets, sugar-free liquid or syrup when administered on an empty stomach, due to transformation of sodium valproate into valproic acid. Gastric irritation is less likely to occur with the enteric-coated tablets.

In most adult patients, daily doses of 1,200 to 1,500 mg result in therapeutic plasma levels of 50 to 100 microgram/mL (0.35 to 0.69 mmol/L). However, correlation between the daily dose per bodyweight and plasma levels of drug has been poor as this reported range might 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.

IV

The pharmacokinetic profile of Epilim Powder for IV Injection differs from that of oral Epilim preparations. As expected, after intravenous and oral dosage (enteric-coated tablets) of Epilim (400 mg), Tmax is reached sooner following intravenous administration (7.3 ± 2.6 min) than after oral administration (227.7 ± 59.2 min) and Cmax is higher after intravenous dosage (55.4 ± 9.38 microgram/mL) than after oral administration (39.1 ± 3.51 microgram/mL). The bioavailability of Epilim enteric-coated (EC) tablets is only slightly less than that of intravenous Epilim with a mean AUC ratio of 100:87 for intravenous to oral forms respectively. The distribution, metabolism, excretion and elimination of intravenous Epilim are not different to orally administered Epilim.

In most adult patients, daily doses of 1,200 to 1,500 mg result in therapeutic plasma levels of 50 to 100 microgram/mL (0.35 to 0.69 mmol/L). However, correlation between the daily dose per bodyweight and plasma levels of drug has been poor.

Distribution

Distribution of sodium valproate is rapid and most likely restricted to the circulation and rapidly exchangeable extracellular water. CSF and breast milk levels were found to be 5 to 15% and about 1 to 10% of plasma levels, respectively.

Valproic acid shows non-linear kinetics, due to concentration-dependent plasma protein binding as well as a relatively short half-life. The half-life of sodium valproate is usually reported to be within the range 8-20 hours. It is usually shorter in children.

Epilim is approximately 90% bound to plasma proteins but only 60% to albumin. However, if the plasma level of valproic acid rises above 120 microgram/mL or if the serum albumin concentration is lowered, the binding sites may become saturated, causing the amount of free drug to rise rapidly, out of proportion to any increase in dosage. Epilim may displace phenobarbital or phenytoin from plasma protein binding sites.

Saliva levels of Epilim are poorly correlated with those in plasma in contrast to the good correlation found for other antiepileptics.

In animals, the drug crosses the placenta.

Metabolism

Its metabolism is complex; the major elimination pathway is via glucuronidation (40-60%). The remainder is largely metabolised via oxidation pathways, β-oxidation accounting for 30-40% and w-oxidation (cytochrome P450 dependent), the remaining fraction. Only 1 to 3% of the ingested dose is found to be excreted unchanged in the urine.

Excretion

Sodium valproate is almost completely metabolised prior to excretion. Plasma half-life is variable but generally appears to be 8 to 12 hours (range 3.84 to 15.77 hours). It may be shorter in patients receiving other anticonvulsants or in children and patients receiving the medicine for long periods. In cases of overdose, long half-lives up to 30 hours have been reported. Antipsychotic agents or antidepressants including MAOIs, tricyclics and SSRIs co-administered with sodium valproate may result in competitive metabolism or enzyme inhibition, thereby increasing valproate levels (see Section 4.5).

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

Sodium valproate was administered in the diet to Sprague-Dawley rats and ICR (HA/ICR) mice at approximate dosage levels of 0, 80 and 160 mg/kg/day for up to 2 years. There was equivocal evidence of an increased incidence of subcutaneous fibrosarcomas in male rats and of bronchoalveolar adenomas in male mice. The presence of these tumours was not considered to be biologically significant because of the published variable incidence of spontaneously occurring fibrosarcomas and pulmonary adenomas in rats and mice respectively and the fact that statistical

significance of tumour incidence was only attained in males. The significance of these findings for humans is unknown at present.

Toxicology

No significant toxic effects were seen in rats receiving 270 mg/kg/day for 3 months or in dogs receiving 90 mg/kg/day for 12 months. At higher doses sedation, ataxia and various histopathological effects (testicular atrophy and reduction in lymphoid tissue) were observed at levels of 256 to 568 microgram/mL (1.78 to 3.94 mmol/L).

Testicular Function

Epilim has been shown to cause atrophy of the seminiferous epithelium with impairment of spermatogenesis, and to cause a decrease of the testicular weight of adult rats and of offspring of female rats, when administered in high doses. On the other hand, a reproductive study carried out in rats with similarly high doses in both sexes has not shown any evidence of impaired fertility. The relevance of these findings to humans is not clear.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Crushable tablets

maize starch, light kaolin, hydrated silica, purified water and magnesium stearate.

Enteric-Coated tablets

povidone, purified talc, magnesium stearate, calcium silicate, violet enteric coat excipient blend, violet sub-coat excipient blend.

Syrup

sucrose, sorbitol, saccharin sodium, ponceau 4R, purified water, cherry flavour 17.40.0740, sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate.

Sugar-Free Liquid

hyetellose, saccharin sodium, sorbitol, citric acid, ponceau 4R, purified water, cherry flavour 17.40.0740, sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate.

Intravenous

Dilutent: water for injection.

6.2 INCOMPATIBILITIES

Epilim IV should not be administered via the same line as other IV additives.

6.3 SHELF LIFE

Crushable: 36 months

Enteric-Coated (EC): 36 months

Syrup: 36 months

Sugar Free Liquid: 24 months

Intravenous: 5 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Epilim tablets are hygroscopic and must be kept in protective foil until taken.

Crushable tablets

Store below 30°C. Store in a dry place.

Enteric-Coated tablets

Store below 30°C. Store in a dry place.

Sugar free liquid

Store below 25°C. Store away from direct sunlight.

Syrup

Store below 25°C. Store away from direct sunlight.

Intravenous

Store in a dry place below 25°C.

For intravenous use, the reconstituted solution should be used as soon as practicable after reconstitution, to reduce microbiological hazard. If storage is necessary hold at 2 to 8ºC for not more than 24 hours and discard any remaining solution.

6.5 NATURE AND CONTENTS OF CONTAINER

Crushable Tablets, 100 mg

Blister packs of 100 tablets.

Tablets, 200 mg

Blister packs of 100 tablets.

Tablets, 500 mg

Blister packs of 100 tablets.

Syrup, 200 mg/5 mL

300mL amber glass bottle.

Sugar Free Liquid, 200 mg/5 mL

300mL amber glass bottle.

Intravenous Solution for Injection

Epilim IV powder for injection is presented in single packs. Each pack contains one glass vial of 400 mg sodium valproate freeze-dried powder and one glass ampoule containing 4 mL of solvent (water for injections).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie
Auckland
New Zealand

Toll Free Number (medical information): 0800 283 684

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

11 October 1977

10 DATE OF REVISION OF THE TEXT

28 March 2018

SUMMARY TABLE OF CHANGES

Below highlights the main differences between the current and the new formatted Datasheet document:

Section	Change
All	Format changes to align with new data sheet format, editorial changes and changes in headings Sections 1, 2, 3, 5, 6 and 9 updated as per data sheet guidelines
4.2	Updated information on female patients, and on use of estrogen containing products
4.4	Updated information on hepatic dysfunction, suicidal behavior and ideation, female patients, use of estrogen products, effects on laboratory tests
4.5	Updated information on potential interactions with medicines
4.6	Updated information on fertility, developmental disorders and use in pregnancy
4.7	Updated information on effects on ability to drive and use machines
4.8	Updated information on metabolism and nutrition disorders, gastrointestinal disorders, skin and subcutaneous disorders, renal and urinary disorders