

DATA SHEET EPILIM[®]

NAME OF THE MEDICINE

Non-proprietary name

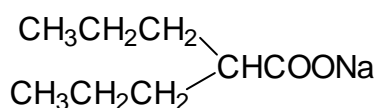
Sodium valproate, valproic acid (CR only)

Chemical name

Sodium Valproate

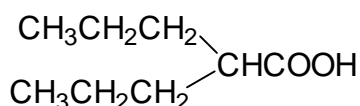
Sodium di-n-propylacetic acid

Chemical Structure:



Valproic acid

2-propylpentanoic acid



CAS Registry Number

Sodium valproate: 1069-66-5

Valproic acid: 99-66-1

DESCRIPTION

Active:

Sodium valproate. 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, hydantoin, succinamides, oxazolidinediones and acetylureas in that it has no nitrogen or aromatic moiety.

Valproic acid. Valproic acid is a colourless to pale yellow, viscous liquid. It is slightly soluble in water (1.2 mg/mL); fully soluble in acetone, chloroform, ether and methyl alcohol. Its molecular weight is 144.

Inactive:

Crushable: includes maize starch, kaolin, silicon dioxide and magnesium stearate.

Enteric-Coated: includes povidone, purified talc, magnesium stearate, calcium silicate, anhydrous citric acid, macrogol 6000, hypromellose, polyvinyl acetate phthalate, diethyl phthalate, stearic acid, amaranth aluminium lake, indigo carmine aluminium lake, titanium dioxide.

Sugar-Free Liquid: includes hydroxyethylcellulose, saccharin sodium, sorbitol solution (70%) (non-crystallising), anhydrous citric acid, brilliant scarlet 4R, purified water, flavour imitation cherry 17.40.0740, sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate.

Syrup: includes sucrose, sorbitol, saccharin sodium, brilliant scarlet 4R, purified water, flavour imitation cherry flavour 17.40.0740, sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate.

Modified release (CR): includes hypromellose, hydrated silica, ethyl cellulose, propylene glycol, titanium dioxide, erythrosine, indigo carmine, ferric oxide (black), water.

PHARMACOLOGY

Class: Anticonvulsant, antipsychotic.

Site and Mode 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/valproic acid.

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.

Pharmacodynamics

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/valproic acid varied considerably among the controlled studies, a fixed initial dose was used after which dosage was determined by serum levels.

Pharmacokinetics

Absorption: 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.

Distribution: Distribution of sodium valproate/valproic acid 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/valproic acid 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 phenobarbitone 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 ω -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 and valproic acid are 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/valproic acid may result in competitive metabolism or enzyme inhibition, thereby increasing valproate levels (see **Interactions with other medicines**).

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.

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.

CONTRAINDICATIONS

Pregnancy (see **PRECAUTIONS**). Pre-existing or acute hepatic dysfunction or family history of severe hepatitis, particularly medicine related. Known hypersensitivity to the medicine. Known urea cycle disorders (see **PRECAUTIONS**). Known hepatic porphyria.

PRECAUTIONS

1. Use with caution in the following circumstances:

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/valproic acid. 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/valproic acid should be discontinued and alternative treatment for the underlying medical condition initiated as clinically indicated.

Hepatic dysfunction: Hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate/valproic acid. Patients most at risk are 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 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. Clinical symptoms are usually more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, facial oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the medicine. Patients should be monitored closely for the appearance of these symptoms and should be instructed to report any such signs to the clinician for investigation should they occur.

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.

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. 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.

Impaired renal function: 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 **Interference with Clinical and Other 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/valproic acid. Hyperammonaemia, which may be present in the absence of abnormal liver function tests, can occur in patients during treatment with sodium valproate/valproic acid. 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, 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 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 behaviour.

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 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 antibiotics: The concomitant use of sodium valproate/valproic acid and carbapenem antibiotics is not recommended (see also Interactions with other medicines).

Pharmaceutical precautions: Epilim tablets are hygroscopic and must be kept in protective foil until taken. See also **PRESENTATION AND STORAGE CONDITIONS**.

2. Check the following before use:

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.

Women of child bearing potential:

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

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/valproic acid treatment is to be continued during pregnancy, it is recommended to use sodium valproate/valproic acid in divided doses over the day at the lowest effective dose. The prolonged release formulation may be preferable to any other treatment.

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

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

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 and multiple anomalies involving various body systems has been reported in children born to mothers with epilepsy treated with valproate/valproic acid. 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%.

Some data have suggested an association between in-utero valproate/valproic acid exposure and the risk of impaired cognitive function, including developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. 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/valproic acid in-utero.

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/valproic acid is prescribed for the first time, or when a woman of child-bearing potential treated with sodium valproate/valproic acid plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

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/valproic acid 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/valproic acid 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.

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate/valproic acid during pregnancy. This syndrome is related to hypofibrinaemia. 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. 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.

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.

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 PRECAUTIONS). 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 'Interactions with other medicines'). 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/valproic acid for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Carcinogenicity/Mutagenicity

Carcinogenesis: Sodium valproate/valproic acid 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.

Interactions with other medicines

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

a. Effects of valproate/valproic acid on other medicines: sodium valproate/valproic acid 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.

Antiepileptic drugs: Several antiepileptic drugs often used in conjunction with valproate (eg phenytoin, carbamazepine, phenobarbitone) 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/valproic acid 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.

Phenobarbitone: Sodium valproate/valproic acid may block the metabolism of barbiturates causing an increase in phenobarbitone plasma levels, which, particularly in children, may be associated with sedation. Combination of sodium valproate/valproic acid and phenobarbitone 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. A reduction in the dose of phenobarbitone and/or valproate may be necessary and this should also be borne in mind if medicines that are metabolised to phenobarbitone (e.g. primidone, methylphenobarbitone) are given with sodium valproate/valproic acid. Clinical monitoring is recommended throughout the first two weeks of combined treatment.

Phenytoin: There have been reports of breakthrough seizures occurring with the combination of sodium valproate/valproic acid and phenytoin. Most reports have noted a decrease in 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. 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/valproic acid 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 **ADVERSE EFFECTS**). 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/valproic acid 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/valproic acid 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 MAOIs, neuroleptics, benzodiazepines and other antidepressants, and the dose of these medicines should be reduced accordingly.

Clonazepam: The concomitant use of sodium valproate/valproic acid 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/valproic acid 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/valproic acid.

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

Primidone: Valproate/valproic acid 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/valproic acid may raise zidovudine plasma concentrations leading to increased zidovudine toxicity.

Tricyclic antidepressants: Sodium valproate/valproic acid may inhibit the metabolism of tricyclic antidepressants. Clinical monitoring of free antidepressant levels may be necessary.

Other medicines: There was no notable interaction between valproate/valproic acid and lithium.

b. Effects of other medicines on 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 β -oxidation. The list is not exhaustive, as new interactions may be reported.

Aspirin: Concomitant administration of sodium valproate/valproic acid 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/valproic acid are prescribed aspirin. Furthermore, patients requiring long-term aspirin therapy may require a reduction in dosage of sodium valproate/valproic acid.

Felbamate: Felbamate may increase valproate serum concentrations. Valproate dosage should be monitored when given in combination with felbamate. Valproic acid may decrease the felbamate mean clearance by up to 16%.

Phenobarbitone, 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.

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.

Cholestyramine: May decrease the absorption of valproate.

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.

c. Other interactions:

Topiramate: Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.

Interference with Clinical Laboratory and Other 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/valproic acid. The clinical significance of this is unknown.

Effect on Ability to Drive or Operate Machinery

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 transient drowsiness, especially in cases of anticonvulsant polytherapy, too high a starting dose, too rapid a dose escalation or association with benzodiazepines.

ADVERSE EFFECTS

Skin and subcutaneous tissue disorders: Transient and/or dose related alopecia has often been observed. Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and rash have been reported very rarely. Caution should be observed when using the medicine in patients with systemic lupus erythematosus.

Reproductive system and breast disorders: There have been reports of irregular menses and secondary amenorrhoea and rare cases of breast enlargement and galactorrhoea. There have been reports of male infertility.

Gastrointestinal disorders: Nausea, 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 (refer **PRECAUTIONS** section).

There have been very rare 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 **PRECAUTIONS**).

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 **Check the Following Before Use**). Frequent occurrence of thrombocytopaenia, rare cases of pancytopenia with or without bone marrow depression. 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 **PRECAUTIONS**).

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

Bone marrow failure, including pure red cell aplasia, and agranulocytosis have also been reported.

Hepatobiliary disorders: Hepatic dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate/valproic acid (see **PRECAUTIONS**).

Metabolism and nutrition disorders: Hyperammonaemia has been reported in association with valproate therapy and may be present despite normal liver function tests. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation.

In patients who develop unexplained lethargy and vomiting or changes in mental status, 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 **PRECAUTIONS**).

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.

Very rare cases of hyponatremia have been reported. Syndrome of Inappropriate Secretion of ADH (SIADH) has been reported.

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.

Uncommon cases of ataxia have been reported. Headache, nystagmus, diplopia, tremor, dizziness, depression, hallucinations, encephalopathy and coma have occurred rarely and usually in association with other anticonvulsants. Excitement, alertness, hyperactivity, aggression and behavioural disorders have been rarely reported, usually in children at the start of treatment.

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.

Rare cases of lethargy and confusion.

Very rare cases of reversible dementia associated with reversible cerebral atrophy have been reported.

Extrapyramidal disorder which may not be reversible, including reversible parkinsonism has been reported.

Ear and labyrinth disorders: Deafness, either reversible or irreversible, has been reported rarely.

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

Renal and urinary disorders: Very rare cases of enuresis have been reported.

There have been isolated reports of a reversible Fanconi's syndrome associated with valproate therapy but the mode of action is as yet unclear.

Vascular disorders: The occurrence of vasculitis has been reported.

General disorders and administration site conditions: Oedema has been reported. Increase in appetite and weight may occur. Since it is a risk factor for polycystic ovary syndrome, it should be carefully monitored.

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 **PHARMACOLOGY (Clinical Trials)** are summarised in Table 2.

Table 2. Adverse events reported on divalproex in the Bowden *et al.* study (1994)

Adverse event	Bowden <i>et al.</i> 1994		
	VPA* n = 69	Lithium n = 36	Placebo 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%).

DOSAGE AND ADMINISTRATION

Epilim tablets may be given twice daily. Uncoated tablets may be crushed if necessary. 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.

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.

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, phenobarbitone 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.

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 **PHARMACOLOGY, Clinical Trials**) 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.

Hepatic Impairment: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate (see **PRECAUTIONS**).

Impaired renal function: 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

PRECAUTIONS). Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading. (See **Pharmacokinetic Properties**).

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

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

OVERDOSAGE

Cases of accidental and suicidal overdose 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 overdose 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, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels, usually include coma, with muscular hypotonia, hyporeflexia and miosis, impaired respiratory functions and metabolic acidosis. 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.

Treatment

Establish airway and breathing and evaluate circulatory status. Assisted mechanical ventilation may be required in cases of respiratory depression. 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 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

1. Crushable Tablets, 100 mg (white, scored): Blister packs of 100 tablets. Store below 30°C. Store in a dry place.
2. Tablets, 200 mg (lilac, enteric-coated): Blister packs of 10, 20 and 100 tablets. Store below 30°C. Store in a dry place.
3. Tablets, 500 mg (lilac enteric-coated): Blister packs of 10 and 100 tablets. Store below 30°C. Store in a dry place.

4. Syrup, 200 mg/5 mL (red, cherry flavoured): 300 mL amber glass bottle. Store below 25°C. Store away from direct sunlight.
5. Sugar free liquid, 200 mg/5 mL (red, cherry flavoured): 300 mL amber glass bottle. below 25°C. Store away from direct sunlight.
6. Modified release tablets, 300 mg (oblong violet film-coated): Blister packs of 100 tablets. Store below 30°C. Store in a dry place. Epilim Tablets are hygroscopic and must be kept in protective foil until taken

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

MEDICINE CLASSIFICATION

Prescription Only Medicine

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