1 NAME OF THE MEDICINE
Sodium valproate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each enteric-coated tablet contains either 200 mg or 500 mg of Sodium valproate as the active ingredient.

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

3 PHARMACEUTICAL FORM
VALPRO 200 is presented as 10 mm enteric-coated tablets which are normal convex and violet in colour.

VALPRO 500 is presented as 13 mm enteric-coated tablets which are normal convex and violet in colour.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Epilepsy
Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsies and tonic-clonic grand mal seizures). Partial (focal) epilepsies, either alone or as adjuvant therapy.

Mania
For the treatment of mania where other therapy has proved inadequate or is inappropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION
VALPRO tablets may be given twice daily. VALPRO should preferably be taken with or after food. The tablet must be swallowed whole, if necessary with a little water, but not aerated water.

It is recommended that the 200 mg tablet be used until the patient is stabilised. The 500 mg enteric coated tablet is recommended for patients requiring high dosages, once the optimum dosage has been established.

VALPRO 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 (including children over 15 years)
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). If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,500 mg/day.
Children over 20 kg

Initial dosage should be 400 mg/day (irrespective of weight) in divided doses, with spaced increases until control is achieved; this is usually within the range 20 to 30 mg/kg bodyweight/day.

Children under 20 kg

20 mg/kg bodyweight/day; in severe cases this may be increased but should be undertaken 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, measurement of plasma levels may be helpful where there is poor control or side effects are suspected.

Combined therapy

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 VALPRO. When barbiturates are being administered concomitantly, the dosage of barbiturate should be reduced if sedation is observed.

Mania

Initially 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.

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

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, Special Warnings and Precautions for Use).

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, Special Warnings and Precaution for Use).

Use in the Elderly

Although the pharmacokinetics of sodium valproate 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.

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

See section 4.4, Special Warning and Precautions for Use
VALPRO 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 VALPRO 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.

**Estrogen containing products**

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.

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, Interactions with Other Medicines and Other Forms of Interactions).

### 4.3 CONTRAINDICATIONS

- Pregnancy (see Section 4.4, Special Warnings and Precautions for Use).
- Pre-existing acute or chronic hepatic dysfunction or family history of severe hepatitis, particularly medicine related.
- Known hypersensitivity to sodium valproate or to any other component of the tablet (see Section 6.1 List of Excipients).
- Known urea cycle disorders (see Section 4.4, Special Warnings and Precautions for Use).
- 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.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Use with caution in the following circumstances**

**Hepatic dysfunction**

**Conditions of occurrence**

Severe liver damage and/or hepatic failure resulting in fatalities has 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.

**Suggestive signs**
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, 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 and carers) should be instructed to 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 (especially in patients at risk) 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 which 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 sodium valproate, 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 level, 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 sodium valproate 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

Cases of life-threatening pancreatitis have been reported in both children and adults receiving sodium valproate. 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 therapy 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.
**Lupus erythematosus**

Although immune disorders have been noted only exceptionally during the use of sodium valproate, the potential benefit of sodium valproate 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 sodium valproate 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 of UCD should be considered in the following patients:

1. those with 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 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 headache, vomiting, irritability, bizarre behaviour, lethargy, ataxia, tremors, seizures (generalised tonic-clonic or focal) and coma.

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

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

**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 (AEDs), 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, 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. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

**Table 1** Risk by indication for antiepileptic drugs in the pooled analysis

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

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 VALPRO should be borne in mind. If it is the only anticonvulsant used and must be withdrawn for more than 12 hours because of surgery, control of epilepsy may be lost.

**Carbapenem antibiotics**

The concomitant use of sodium valproate and carbapenem antibiotics is not recommended (see Section 4.5, Interactions with Other Medicines and Other Forms of Interactions).

**Pharmaceutical precautions**

VALPRO tablets are hygroscopic and must be kept in protective foil until taken (see Section 6.4, Special Precautions for Storage).

**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 e.g Alpers-Huttenlocher Syndrome).

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, 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, Adverse Effects (Undesirable Effects)).

**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 VALPRO 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 minimize the risk.

Carnitine Palmitoyltransferase (CPT) Type II Deficiency

Patients with an underlying carnitine palmitoyltransferase (CPT) 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 sodium valproate 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.

VALPRO 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 VALPRO 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 sodium valproate during pregnancy. 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, Fertility, Pregnancy and Lactation).

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

Estrogen containing products

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.
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, Interactions with Other Medicines and Other Forms of Interactions).

*Use in the Elderly*

Although the pharmacokinetics of VALPRO 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.

*Paediatric Use*

The potential benefit of sodium valproate should be weighed against the risk of pancreatitis or liver damage in such patients prior to initiation of therapy (see Section 4.4, Special Warnings and Precautions for Use). 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, Interactions with Other Medicines and Other Forms of Interactions). Monotherapy is recommended in children under 3 years of age, when prescribing sodium valproate. Young children are at particular risk for pancreatitis; however, this risk decreases with increasing age.

*Effects on Laboratory tests*

Sodium valproate 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 these is unknown.

**4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

**Effects of valproate on 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 sodium valproate co-administration on a range of commonly prescribed medications; however, this 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 drugs:** Several antiepileptic drugs often used in conjunction with valproate (e.g. phenytoin, carbamazepine, phenobarbitone) have the ability to increase the intrinsic clearance of valproate, presumably by enzymatic induction of metabolism.

**Carbamazepine:** Sodium 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 its mean half life. 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 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 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 which are metabolised to phenobarbitone (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. Most reports have noted a decrease in total plasma phenytoin concentration, however increases in total phenytoin serum concentration 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 sodium valproate on anticoagulants which modify platelet function is not known (see Section 4.8, Adverse Effects (Undesirable Effects)). Caution is advised when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and aspirin).

**E 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:** Sodium valproate may potentiate the effects of other psychotropics such as monoamine oxidase inhibitors (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 sodium valproate levels.

**Diazepam:** Sodium valproate displaces diazepam from its plasma protein binding sites and inhibits its metabolism. Monitoring of free diazepam levels is 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 sodium 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.

Rufinamide: Valproic acid may lead to an increase ion 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.

**Effects of other medicines on valproate**

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

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.

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. Caution is therefore advised 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 sodium valproate serum concentrations, therefore dosage should be monitored when given in combination with felbamate. Valproic acid may decrease the felbamate mean clearance.

Phenobarbitone, Phenytoin and Carbamazepine: These medicines can decrease the steady state levels in patients by increasing the intrinsic clearance of sodium valproate, presumably through enzymic induction of
metabolism. The half-life is significantly reduced in patients on polytherapy of 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 selective serotonin reuptake inhibitors (SSRIs)] may have the potential to inhibit the metabolism of sodium valproate via the cytochrome P450 system. However, there is not expected to be any significant interaction with 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 sodium valproate.

**Fluoxetine:** Fluoxetine may inhibit the metabolism of sodium 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 case 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 valproate blood levels sometimes associated with convulsions has been observed when valproate and carbapenem antibiotics (panipenem, meropenem, imipenem, ertapenem, biapenem) were combined. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem antibiotics in patients stabilised on valproic acid should be avoided (see Section 4.4, Special Warnings and Precautions for Use). If treatment with these antibiotics cannot be avoided, close monitoring of valproate blood level should be performed.

**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.

**Cholestyramine:** Cholestyramine may lead to a decrease in plasma levels of valproate 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 valproic acid free serum 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.
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.

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, Adverse Effects (Undesirable Effects)). Valproate administration may also impair fertility in men (see Section 4.8, Adverse Effects (Undesirable Effects)).

Use in Pregnancy

Category D

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. 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 to 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 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).

Valproate Therapy 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.

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.

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 (foetal birth defects and adverse cognitive effects) and benefits of the use of valproate during pregnancy.

Women taking sodium valproate (valproic acid) who become pregnant or wish to become pregnant should be encouraged to consider routine ultrasound and amniocenteses for prenatal diagnosis of such abnormalities. As folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy, such women are recommended to take folic acid supplementation (5 mg daily) four weeks prior to and 12 weeks after conception.

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.

It is recommended that:

- in bipolar disorders indication, cessation of valproate therapy should be considered;
- women on AEDs receive pre-pregnancy counselling with regard to the risk of foetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- if appropriate, folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception as it may minimize the risk of neural tube defects;
- specialist prenatal diagnosis, including detailed mid-trimester ultrasound, should be offered in order to detect the possible occurrence of neural tube defects or other malformations.

Before VALPRO 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 its use should be weighed against the risks. When treatment with VALPRO is deemed necessary, precautions to minimise the potential teratogenic risk should be followed (see above recommendations).

Risk in the 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, hypofibrininaemia 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. Haemorrhagic syndrome must also be distinguished from the decreased of the vitamin-K factors induced by phenobarbitone and other enzyme inducers. Platelet count, fibrinogen plasma levels 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, jitteriness, 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

Sodium valproate 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, breast-feeding should not be undertaken whilst a patient is receiving VALPRO.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Use of sodium valproate 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 the cases of anticonvulsant polytherapy, too high a starting dose, too rapid a dose escalation or association with benzodiazepines.
4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In Epilepsy

The incidence of adverse reactions to marketed medicines such as sodium valproate is difficult to reliably assess due to the nature of spontaneous reporting systems and the problems associated with estimating the total exposure to the drug. With these limitations in mind, adverse events received by the Australian Drug Reactions Committee (ADRAC) on sodium valproate products for the twenty-year period 1977-1997 are presented, summarised in Table 2. The data are presented in accordance with system organ class and include all adverse events reported, independent of drug causality i.e. adverse events classified as certain, probable or possible.

Table 2. Distribution of adverse events for sodium valproate products reported to ADRAC in the period 1977-1997 according to organ system or symptomatology.

<table>
<thead>
<tr>
<th>Organ system/symptom</th>
<th>Sodium Valproate 1977 - 1997</th>
<th>Frequency (%)</th>
<th>Frequency (CIOMS format)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformations</td>
<td>6.0</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Fatigue and sleeping disorders</td>
<td>4.0</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Pyrexia or flu-like symptoms</td>
<td>2.0</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Psychiatric/affective reactions/disorders</td>
<td>2.0</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Therapeutic inefficiency</td>
<td>2.0</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Pain</td>
<td>1.0</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Drug levels increased/decreased</td>
<td>0.9</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Drug interaction</td>
<td>0.25</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Total adverse events reported</td>
<td>791 (27*) (based on 384 drug reports)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Events leading to death

In relation to the 791 events (384 reports) received by ADRAC on sodium valproate products (brand name not stated in 95 drug reports).

very common: ≥10%
common: ≥1% and < 10%
uncommon: ≥0.1% and < 1%
rare: ≥0.01% and < 0.1%

In Mania

No new or unexpected adverse events have been reported in clinical trials of sodium valproate in mania. The frequencies of adverse events (%) reported on valproate (as divalproex) in the largest controlled clinical trial described under Section 5.1, Pharmacodynamic Properties, CLINICAL TRIALS are summarised in Table 3.

Table 3. Adverse events reported on divalproex in the Bowden et al. study (1994)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>VPA* n = 69</th>
<th>Lithium n = 36</th>
<th>Placebo n = 74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>19</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>Somnolence/sedation/fatigue</td>
<td>19</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Twitching</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>
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% versus 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**

**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, Special Warnings and Precautions for Use, Check the following before use).

Common cases of thrombocytopaenia and anaemia have been reported.

Uncommon cases of leucopenia and pancytopenia 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, Special Warnings and Precautions for Use).

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**

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

**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.
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 Section 4.4, Special Warnings and Precautions for Use).

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, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder have been commonly reported.

**Nervous system disorders**

The true incidence of drowsiness and sedation with VALPRO is difficult to assess, as mostly it was administered in combination with other medicines. VALPRO, 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.

Very common cases of tremor have been reported.

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

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, Special Warnings and Precautions for Use), lethargy, paresthesia and reversible parkinsonism have been reported. Diplopia and depression have occurred rarely and usually in association with other anticonvulsants. Excitement, 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.

Stupor and lethargy sometimes leading to transient coma/encephalopathy, either isolated or in conjunction with recurrence of seizures, may occur and were most often associated with polytherapy, too high a starting dose or too rapid a dose escalation.

**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.
Vomiting is common. Upper abdominal pain, 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. Gastrointestinal 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, Special Warnings and Precautions for Use).

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 the serum amylase estimated promptly; if these levels are elevated the medicine should be withdrawn (see Section 4.4, Special Warnings and Precautions for Use).

**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, Special Warnings and Precautions for Use).

**Skin and subcutaneous tissue disorders**

Hypersensitivity and transient and/or dose related alopecia have been commonly observed. This effect does not appear to be dose related and regrowth may occur, although the hair may become more curly than previously.

Nail and nail bed disorders have been commonly reported.

Hirsutism, acne and male pattern alopecia are uncommon (see **Endocrine disorders**). Angioedema, rash and hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal) are uncommon.

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

Dermatological reactions consistent with immune adverse reactions such as pruritus, urticaria and Stevens Johnson syndrome have been noted. 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**

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

Dysmenorrhoea is common and amenorrhoea is uncommon. There have been rare reports of male infertility and polycystic ovaries.

**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 Suspected Adverse Effects**


**4.9 OVERDOSE**

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

**Symptoms**

Overdosage symptoms 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, nevertheless, a favourable outcome is usual. 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. 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.
For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Class: Anticonvulsant, antipsychotic.

Mechanism of Action

Site and mode of action

The mechanism of action of sodium valproate is not fully known. Its anticonvulsant effect is attributed to the blockade of voltage-dependent sodium channels and increased brain levels of gamma-aminobutyric acid (GABA). The GABA-ergic effect is also believed to contribute towards the anti-manic properties of sodium valproate.

In animals, sodium valproate raises cerebral and cerebellar levels of the inhibitory synaptic transmitter, GABA, possibly by inhibiting GABA degradative enzymes, such as GABA transaminase and/or succinic semi-aldehyde dehydrogenase and/or by inhibiting the re-uptake of GABA by neuronal cells.

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

Sodium valproate 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

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

In Mania

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 drug interactions likely to be relevant to valproate in the management of patients with mania are outlined under Section 4.5, Interactions with Other Medicines and Other Forms of Interactions. 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

Sodium valproate’s efficacy in this therapeutic indication is widely known and recognised.
In mania

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 = 0.004). 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

Absorption of valproic acid from enteric coated tablets given to fasting subjects is delayed, with peak blood levels occurring within 3 to 7 hours. This variability is thought to reflect the delay in tablet dissolution, probably associated with the rate of gastric emptying.

Overall absorption is not significantly altered by co-administration with milk products, but is delayed if the drug is taken with food. The extent of absorption, however, is not affected. Because of delayed dissolution, 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.

Distribution

Distribution of sodium valproate is rapid and most likely restricted to the circulation and rapidly exchangeable extracellular water. Cerebrospinal fluid (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.

Sodium valproate 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. Sodium valproate may displace phenobarbitone or phenytoin from plasma protein binding sites.

Saliva levels of sodium valproate 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

The metabolism of sodium valproate is complex. The major elimination pathway is via glucuronidation (40 to 60%). The remainder is largely metabolised via oxidation pathways, beta-oxidation accounting for 30 to 40% and omega-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. Only 1 to 3% of the ingested dose is found to be excreted unchanged in the urine. 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 drug for long periods. In cases of overdose, long half-lives up to 30 hours have been reported. Antipsychotic agents or antidepressants including monoamine oxidase inhibitors (MAOIs), tricyclics and selective serotonin reuptake inhibitors (SSRIs) coadministered with sodium valproate may result in competitive metabolism or enzyme inhibition, thereby increasing valproate levels (see Section 4.5, Interactions with Other Medicines and Other Forms of Interactions).

**5.3 PRECLINICAL SAFETY DATA**

**Genotoxicity**

**Toxicology**

No significant toxic effects were seen in rats receiving 270 mg/kg/day for three 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**

Sodium valproate 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. However, reproductive studies carried out in rats with similarly high doses in both sexes have not shown any evidence of impaired fertility. The relevance of these findings to man is not clear.

**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.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 LIST OF EXCIPIENTS**

Maize starch, magnesium stearate, sodium starch glycollate, microcrystalline cellulose, colloidal anhydrous silica, purified talc, hypromellose, diethyl phthalate, cellacephate, macrogol 400, Opadry Violet OY-6721 (includes colours titanium dioxide CI 77891, indigo carmine CI 73015, erythrosine CI 45430, sunset yellow FCF CI 15985). The tablets are gluten free.

**6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

**6.3 SHELF LIFE**
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
VALPRO tablets are hygroscopic and must be kept in protective foil until taken.

Store in a dry place below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
VALPRO 200 mg and VALPRO 500 mg are packed in Al/Al blister packs of 100's or 200's.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES
Sodium valproate is a white, odourless, crystalline powder with a saline taste. It is quite dissimilar to other established anticonvulsants such as barbiturates, hydantoins, succinamides, oxazolidinediones and acetylsalicylic acid in that it has no nitrogen or aromatic moiety.

Active ingredient: Sodium valproate

Chemical name: Sodium di-n-propylacetic acid

Molecular formula: \( \text{C}_8\text{H}_{15}\text{O}_2\text{Na} \)

Molecular weight: 166.2

Chemical Structure:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{COONa} \\
\text{H}_3\text{C} & \quad \text{H}
\end{align*}
\]

CAS number: 1069-66-5

7 MEDICINE SCHEDULE (POISONS STANDARD)
S4 (Prescription Only Medicine)

8 SPONSOR
Alphapharm Pty Limited/Mylan Health Pty Limited
Level 1, 30 The Bond
30 – 34 Hickson Road
Millers Point NSW 2000
ABN 93 002 359 739

www.mylan.com.au
9 DATE OF FIRST APPROVAL

14/10/1993

10 DATE OF REVISION

04/10/2018

Summary Table of Changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of New Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>Reformatted the PI in line with the revised Australian form for providing product information format.</td>
</tr>
<tr>
<td>4.2</td>
<td>Updated warning information related to female patients. Updated warning information on the use of estrogen containing products.</td>
</tr>
<tr>
<td>4.4</td>
<td>Updated information on the suggestive signs and detection of hepatic dysfunction. As well as updated information on suicidal behaviour and ideation, the use of estrogen containing products.</td>
</tr>
<tr>
<td>4.5</td>
<td>Updated information on the potential effects of other medicines on valproate including medicines with extensive protein binding and estrogen containing products.</td>
</tr>
<tr>
<td>4.6</td>
<td>Updated information on valproate therapy during pregnancy.</td>
</tr>
<tr>
<td>4.8</td>
<td>Updated information on gastrointestinal disorders (vomiting) and renal and urinary disorders (urinary incontinence).</td>
</tr>
</tbody>
</table>