NAME OF THE MEDICINE

Phenobarbitone sodium (CAS -57-30-7) has the following chemical structure:

Its molecular formula is \( C_{12}H_{11}N_2NaO_3 \). The molecular weight is 254.2.

Phenobarbitone (CAS -50–06–6) has the following chemical structure:

Its molecular formula is \( C_{12}H_{12}N_2O_3 \). The molecular weight is 232.2.

DESCRIPTION

Phenobarbitone sodium is a white, odourless, hygroscopic powder, granules or flakes. It is very soluble in water and soluble in alcohol, practically insoluble in chloroform and ether. A 10% solution in water has a pH of not more than 10.2. Store in airtight containers.

Phenobarbitone presents as colourless crystals or a white odourless crystalline powder. It may exhibit polymorphism. It is soluble 1 in 1000 of water and 1 in 10 of alcohol; sparingly soluble in chloroform; soluble in ether. A saturated solution in water has a pH of about 5.
PHENOBARBITONE INJECTION contains phenobarbitone sodium 219 mg (equivalent to phenobarbitone 200 mg) per 1 mL ampoule. It also contains the following excipients: ethanol, propylene glycol and water for injections.

PHENOBARBITONE ASPEN tablets contain phenobarbitone 30 mg per tablet. It also contains the following excipients: lactose, acacia, wheat starch and magnesium stearate.

PHARMACOLOGY

Actions
Phenobarbitone is a long acting barbiturate used as a sedative-hypnotic and as an anticonvulsant in the treatment of epilepsy.

Recent studies have suggested that the sedative-hypnotic and anticonvulsant effects of barbiturates may be related to their ability to enhance and/or mimic the inhibitory synaptic action of gamma-aminobutyric acid (GABA). Phenobarbitone inhibits seizure activity at doses which cause relatively little sedation.

The barbiturates are general central nervous system depressants, the effect ranging from mild sedation to general anaesthesia.

Onset of action after IV dosage is usually within 5 minutes and maximum effects are achieved within 30 minutes. Orally administered phenobarbitone has an onset of action that varies from 20 to 60 minutes. IM injection results in somewhat slower distribution compared with IV administration. The duration of action of parenterally administered phenobarbitone sodium is usually 4-6 hours.

PHARMACOKINETICS

Absorption
About 70-90% of an oral dose is absorbed as in the case of other barbiturates. The oral preparation is relatively lipid insoluble; hence attainment of peak concentrations in the blood may take several hours.

Distribution
Phenobarbitone sodium is rapidly distributed to all tissues and fluids with high concentrations in the brain, kidney and liver. As lipid solubility is low, phenobarbitone is slower than other barbiturates in penetrating the tissues. Phenobarbitone is approximately 40% bound to plasma proteins. The plasma half-life is approximately 90 to 100 hours in adults but is significantly prolonged in neonates. The half-life in children is shorter than in adults (about 65 to 70 hours). Phenobarbitone crosses the placenta and is excreted in breast milk.

Metabolism and excretion
Metabolism is primarily via the hepatic microsomal enzyme system. Phenobarbitone is converted via oxidative hydroxylation to ρ-hydroxyphenobarbitone, an inactive metabolite. Approximately 25% of a dose is excreted unchanged in the urine and about 75% of the dose is excreted via the kidneys as ρ-hydroxyphenobarbitone and its glucuronide and sulphate conjugates. Alkalisation of the urine and/or increasing urinary flow rate substantially increases the rate of excretion of unchanged phenobarbitone. Unmetabolised drug can
accumulate in patients with oliguria or uraemia. Phenobarbitone is a potent inducer of enzymes of the Cytochrome P-450 system (refer to INTERACTIONS WITH OTHER MEDICINES.)

**Therapeutic Monitoring**
When used as an anticonvulsant, monitoring of plasma concentrations has been performed as an aid in assessing control. The therapeutic range is usually quoted as being 15 to 40 micrograms per mL (65 to 170 micromol per litre).

**INDICATIONS**

PHENOBARBITONE INJECTION: Treatment of grand mal and psychomotor epilepsy; sedation.

PHENOBARBITONE ASPEN tablets: Epilepsy; sedation.

**CONTRAINDICATIONS**

Phenobarbitone is not recommended in the presence of the following conditions:

- a history of porphyria, either acute intermittent or variegata
- hypersensitivity to barbiturates or the excipients in the injection solution or tablets
- severe anaemia (if it is due to folate deficiency)
- severe asthma (if uncontrolled)
- diabetes mellitus (if uncontrolled)
- a history of drug abuse or dependence
- severe hepatic or renal impairment
- hyperkinetic children
- severe depression or suicidal tendencies
- acute or chronic pain (paradoxical excitement may result or other symptoms may be masked).

**PRECAUTIONS**

**Parenteral administration**
Care should be taken during parenteral administration of phenobarbitone to avoid extravasation. Owing to the extreme alkalinity of sodium salts of barbiturates subcutaneous injection or extravasation can lead to tissue necrosis.

**Dependence, tolerance and withdrawal**
Prolonged use may lead to physical dependence and tolerance hence phenobarbitone should not be discontinued abruptly. Symptoms of withdrawal are characterised after several hours by apprehension and weakness, followed by anxiety, headache, dizziness, irritability, tremors, nausea, vomiting, insomnia, visual problems, muscle twitching and tachycardia. Hallucinations, orthostatic hypotension and convulsions may develop after a day or two, sometimes leading to status epilepticus. Sudden withdrawal of phenobarbitone from an epileptic patient should be avoided as it may precipitate status epilepticus.
Phenobarbitone dose should be reduced gradually over a period of days or weeks. For example the total daily dose can be reduced by 30 mg daily as long as no signs of withdrawal occur or alternatively the phenobarbitone dose can be reduced daily by 10% if tolerated by the patient.

**Suicidal Behaviour and Ideation**
Antiepileptic drugs, including phenobarbitone, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any antiepileptic drugs 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 antiepileptic drugs showed that patients randomised to one of the antiepileptic drugs 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 antiepileptic drug-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 antiepileptic drugs was observed as early as one week after starting drug treatment with antiepileptic drugs 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 antiepileptic drugs of varying mechanisms of action and across a range of indications suggests that the risk applies to all antiepileptic drugs 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 antiepileptic drugs.

**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 phenobarbitone or any other antiepileptic drugs must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which antiepileptic drugs 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 antiepileptic drugs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of 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.

**Haematological disease**
Phenobarbitone should be used with caution in patients with a history of haematological disease especially chronic anaemia (folate requirements are increased in patients on long term anticonvulsant therapy). The blood count should be monitored during long term therapy. Patients should be instructed to immediately report symptoms such as sore throat, fever, easy bruising, epistaxis or other signs of infection or bleeding tendency (note that megaloblastic anaemia and thrombocytopenia have been reported rarely).

**Intra-arterial injection**
Intra-arterial injection should be avoided. The consequences range from pain in the region of the artery to pallor, patchy discolouration of the skin and even gangrene.

**Asthma, urticaria and angioedema**
Barbiturates should be used with caution in patients with a history of asthma, urticaria or angio-oedema. Milder hypersensitivity reactions have been reported in 1 to 3% of patients treated with phenobarbitone. These include urticaria, and maculopapular, erythematous and morbilliform rashes which resolve on discontinuation. More serious reactions include serum sickness, exfoliative dermatitis, erythema multiforme and Stevens Johnson syndrome (refer to ADVERSE EFFECTS). Phenobarbitone should be discontinued in the presence of dermatological reactions or other manifestations of hypersensitivity such as bronchospasm.

**Hypotension, cardiovascular disease and respiratory disease**
Parenteral barbiturates should be administered with caution in patients with a history of hypotension, cardiovascular disease or respiratory disease.

**Bone mineral density and fractures**
Chronic administration of phenobarbitone may decrease bone mineral density and increase the risk of fractures. Periodic monitoring of bone mineral density and the use of supplemental calcium and vitamin D are advisable. Patients should be advised to have adequate sunlight exposure, regular weight-bearing exercise, and avoid other risk factors associated with bone disease, such as alcohol use and smoking.

**Impaired renal function**
Unchanged phenobarbitone is excreted by the kidneys, therefore a reduction in dose may be required in patients with renal dysfunction.
Corticosteroids, hypoadrenalism and hyperthyroidism
Phenobarbitone is metabolised in the liver, therefore hepatic dysfunction may theoretically lead to increased blood levels. The dose may need to be reduced.

The systemic effects of exogenous and endogenous corticosteroids may be diminished by phenobarbitone. The drug should be administered with caution in patients with borderline hypoadrenalism regardless of whether it is the pituitary or adrenal in origin. Patients with hyperthyroidism should be treated with caution as symptoms may be exacerbated through the displacement of thyroxine from plasma proteins.

CNS depressants
Concurrent use of phenobarbitone with other CNS depressant drugs and alcohol can lead to potentiation of the CNS depressants effects of either these substances or phenobarbitone (refer to Interactions with other medicines).

Withdrawal of these drugs should be slow and cautious, as the condition “Severe abstinence syndrome” (grand mal seizures, delirium) may occur.

Driving and operating machinery
Patients should be warned that barbiturates may impair their ability to perform potentially hazardous activities requiring mental alertness and physical coordination such as driving and operating machinery.

The sedative action of phenobarbitone in epileptic patients can be reduced by using a lower dose supplemented by phenytoin or primidone.

Use in children
Some children may react with paradoxical excitement.

Use in the elderly
Phenobarbitone and other barbiturates should be administered cautiously to the elderly; reduced dosage should be employed until tolerance is assessed. Age related hepatic and/or renal impairment may require reduction in dosage. Elderly patients may react with excitement, confusion or mental depression. The risk of barbiturate induced hypothermia may be increased especially with high doses or in acute overdose.

Carcinogenicity, mutagenicity, impairment of fertility
Phenobarbitone sodium is carcinogenic in mice and in rats after lifetime administration. In mice, it produced benign and malignant liver cell tumours; in rats, benign liver cell tumours were observed. Phenobarbitone was negative in a 26 week bioassay in p53 heterozygous mice.

Genotoxicity studies for gene mutations and chromosome aberrations have given mixed results, however, tests for DNA damage or repair have been negative.

In a 29 year epidemiologic study of 9,136 patients who were treated on an anticonvulsant protocol that included phenobarbitone, results indicated a higher than normal incidence of hepatic carcinoma. Previously, some of these patients had been treated with thorotrast, a drug known to produce hepatic carcinomas. When patients who had received thorotrast were excluded, there was a non-significant increase in the number of liver tumours, and, unlike the mouse liver tumours, were mostly associated with cirrhosis.
Use in pregnancy (Category D)
The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive prepregnancy counselling with regard to the risk of fetal 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;
- folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

The use in pregnancy of primidone, phenobarbitone or methylphenobarbitone has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability. Their use in pregnancy alone, or in combination with other anticonvulsants, can cause coagulation defects in the newborn infant which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.

Barbiturates readily cross the placenta and are distributed throughout foetal tissues. The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. Some of this risk is due to the anticonvulsant drugs taken. There is a lack of data permitting any statement that women taking primidone, phenobarbitone or methylphenobarbitone are at any different risk of having a baby with an abnormality from women taking other anticonvulsants.

Use of barbiturates throughout the third trimester of pregnancy may result in physical dependence and subsequent withdrawal symptoms in the neonate. In infants experiencing long term exposure in utero, the acute withdrawal syndrome of seizures and hyperirritability has been reported to occur up to 14 days after birth. Use of the barbiturates during labour may cause respiratory depression in the neonate. Elimination of phenobarbitone is slow in the newborn especially in premature infants.

Use in lactation
Phenobarbitone is not recommended in breast feeding mothers. Phenobarbitone is distributed into breast milk and use by breast feeding mothers may cause CNS depression in the infant.

INTERACTIONS WITH OTHER MEDICINES

Phenobarbitone is metabolised via the cytochrome P450 system within the gut wall and the liver. Therefore most of its interactions with other medicines are due to the competition between phenobarbitone and other medicines for the specific isoenzymes within this system.

Induction
Phenobarbitone is a potent inducer of the isoenzymes CYP3A4, CYP1A2 and CYP2C. Discontinuation of phenobarbitone may result in enhanced effects of concomitant medications or even their potential toxicity. Upon phenobarbitone commencement
appearance of overt signs of drug interactions due to enzyme induction occurs in approximately one week.

The major medicines affected by induction of the CYP-450 isoenzymes by phenobarbitone are:

**Analgesics**
**Paracetamol** - The therapeutic effects of paracetamol may be decreased due to enzyme induction of CYP3A4 and subsequent increased metabolism of the drug. This may also lead to increased risk of hepatotoxicity.

**Opioid analgesics** - Dosage of these analgesics may need to be increased due to increased metabolism. Withdrawal symptoms may develop due to lowered plasma levels. In a well documented interaction between phenobarbitone and methadone, there was a 50% reduction in methadone concentrations with signs of narcotic withdrawal. Methadone levels must be monitored if phenobarbitone is introduced.

**Antidepressants**
**Tricyclic antidepressants** and **selective serotonin reuptake inhibitor** plasma levels may be lowered resulting in compromised efficacy through the possible induction of isoenzyme CYP2D6.

**Anti-arrhythmics**
Such as **quinidine** and **disopyramide**: Concurrent barbiturate use may reduce serum levels to ineffective concentrations due to induction of CYP3A4.

**Digoxin** - Induction may result in decreased blood levels of digoxin when taken with barbiturates. Careful monitoring of dosage is required if barbiturates are given in patients on digoxin therapy.

**Anticoagulants**
Phenobarbitone may increase the metabolism of coumarin anticoagulants such as **warfarin** resulting in a substantial decrease in anticoagulant activity. Initiation of barbiturate therapy in patients stabilised on anticoagulants must be accompanied by monitoring of anticoagulant activity and adjustment of anticoagulant dose if required. Patients maintained on both a coumarin and barbiturates have a risk of bleeding if the barbiturate is discontinued and the dose of the anticoagulant is not adjusted. The long half-life of phenobarbitone must be taken into account when commencing and ceasing treatment. Combination with **phenindione** should be treated in the same manner.

**Antifungal agents**
Poor clinical response to antifungals such as **itraconazole** and **ketoconazole** results from enzyme induction of isoenzyme CYP3A4 by phenobarbitone. **Fluconazole** does not appear to be much affected. The absorption of **griseofulvin** may be decreased resulting in decreased serum concentrations.

**Antibiotics**
The half-life of **doxycycline** may be decreased by phenobarbitone due to induction of metabolism. The dosage and/or dosing interval of doxycycline may need to be adjusted. **Metronidazole** metabolism is enhanced resulting in reduced plasma levels.
**Calcium channel blockers**

Efficacy may be compromised when combining these agents with phenobarbitone. A reduction in efficacy has been documented with nifedipine via induction of CYP3A4.

**Antipsychotics**

*Haloperidol* and the *phenothiazines* lower the seizure threshold and hence combination with phenobarbitone may compromise the efficacy of phenobarbitone. Phenobarbitone may induce the metabolism of haloperidol and phenothiazines through cytochrome enzyme induction.

**Chemotherapeutic agents**

Clearance of etoposide has been shown to increase by 170% when given with phenobarbitone. Be alert for the need to increase etoposide dose if used concurrently with phenobarbitone.

**Corticosteroids**

Reduction in serum levels of corticosteroids may compromise their effectiveness in the treatment of steroid-responsive disorders such as asthma.

**Oral Contraceptives**

Reductions in serum levels with breakthrough bleeding and lowered contraceptive efficacy may occur when these agents are combined with phenobarbitone.

**Immunosuppressants**

*Cyclosporin* and *tacrolimus* have been shown to have clearance increased by barbiturates.

The effect on corticosteroids, oral contraceptives and immunosuppressants is via CYP3A4 induction.

**Protease inhibitors**

Increased metabolism by the action of phenobarbitone on CYP3A4 may result in reduced plasma levels.

**Theophylline**

Induction of isoenzyme CYP1A2 by phenobarbitone may result in lowered plasma levels and loss of efficacy. Serum theophylline levels should be monitored because theophylline has a narrow therapeutic index.

**Anaesthetics, halogenated hydrocarbon**

Barbiturates may increase the metabolism of anaesthetic agents such as halothane and enflurane leading to increased risk of hepatotoxicity.

**Vitamin D**

The effects of Vitamin D may be reduced by barbiturates including phenobarbitone because of accelerated metabolism by hepatic microsomal enzymes. Vitamin D supplementation may be required in patients on long-term anticonvulsant therapy with phenobarbitone to prevent osteomalacia. The effect of phenobarbitone on Vitamin D may be enhanced by the concomitant use of carbonic anhydrase inhibitors.

**Beta-blockers**

The plasma concentration of some beta-blockers e.g. propranolol may be reduced by barbiturates.
Anticonvulsants
Variable effects are seen on the activity of phenytoin when combined with barbiturates. When phenobarbitone is used with phenytoin, concentrations of either or both medicines may be affected. Even though phenobarbitone may induce phenytoin metabolism, it may also decrease it because both medicines compete for the same metabolic pathway. It is recommended that plasma concentrations of both drugs be monitored when they are used concomitantly. Phenobarbitone may accelerate the metabolism of carbamazepine resulting in decreased plasma concentration. Phenobarbitone may enhance the metabolism of lamotrigine. Adjustment of lamotrigine dose may be required following withdrawal of phenobarbitone.

Inhibition
Several drugs inhibit the isoenzymes CYP3A4, CYP1A2 and CYP2C which can lead through competition to decreased metabolism of phenobarbitone. This in turn leads to elevated blood levels of the medicine, respiratory depression and lowering of the lethal dose of phenobarbitone. The effects of inhibition can usually be seen immediately rather than delayed as in induction.

Medicines which inhibit these isoenzymes and could lead to accumulation of phenobarbitone are:

Antidepressants
Monoamine oxidase (MAO) inhibitors may inhibit barbiturate metabolism resulting in increased CNS depressant effects. A reduction in phenobarbitone dosage may be indicated. Concomitant use of barbiturate and tranylcypromine has been reported to result in semicona for 36 hours in one case study.

Selective serotonin reuptake inhibitors (SSRI) may inhibit a number of important cytochrome P450 isoenzymes (CYP1A2, CYP2C9/10, CYP2C19, CYP2D6 and CYP3A3/4) although they differ in their potency. Combination with phenobarbitone may result in increased plasma levels and enhanced activity of phenobarbitone.

Disulfiram
Concurrent administration of disulfiram with barbiturates may result in inhibition of metabolism of barbiturates and an increased incidence of barbiturate toxicity.

Valproic acid/sodium valproate
The metabolism of phenobarbitone may be decreased by valproic acid/sodium valproate resulting in increased CNS depressant effects. Phenobarbitone may potentiate the hepatotoxicity of valproic acid/sodium valproate by increasing the metabolism of this drug to form valproate-4-ene, a known hepatotoxin. It is recommended that plasma concentrations of valproate and phenobarbitone be monitored when any change in the therapeutic regimen occurs.

Other Interactions
Amphetamines
Concurrent use with phenobarbitone may result in delays in the intestinal absorption of phenobarbitone.
**CNS depressants**
Phenobarbitone is a potent CNS depressant so will tend to enhance or potentiate the effects of other CNS depressants. This includes other *sedatives* and *hypnotics, antihistamines, tranquillisers* and *alcohol*.

**Ketamine**
Concurrent use of *ketamine*, especially in high doses or when rapidly administered with barbiturates may result in hypotension and/or respiratory depression, and prolonged recovery time. *Ketamine* and barbiturates are chemically incompatible hence must not be mixed in the same solution.

**Urinary alkalinisers**
Alkalising the urine may diminish the effects of barbiturates due to increased excretion.

**St John’s Wort (Hypericum perforatum)**
Concurrent use of barbiturates and *St John’s Wort* may result in decreased serum barbiturate levels resulting in diminished efficacy. In patients who are taking barbiturates and *St John’s wort*, the serum barbiturate levels should be closely monitored and the administration of *St John’s Wort* should be stopped. The serum barbiturate levels may increase when the administration of *St John’s Wort* is stopped, therefore resulting in a need to adjust the dose of the barbiturate.

**Effect on laboratory tests**
The following changes in laboratory determinations have been reported in patients using phenobarbitone:

- Absorption of radioactive *cyanocobalamin* may be impaired.
- *Metyrapone* may have its metabolism enhanced thus decreasing the observed response.
- False positives may be returned from *Phentolamine tests*.
- *Serum bilirubin concentrations* may be decreased possibly due to induction of glucuronyl transferase, the enzyme responsible for the conjugation of bilirubin.

**ADVERSE EFFECTS**
The most frequent adverse effect following administration of phenobarbitone is sedation which often becomes less marked with continued administration. Phenobarbitone may produce mood changes and impairment of cognition and memory. Continued use of barbiturates even in therapeutic doses may result in psychological or physical dependence. Abrupt withdrawal may lead to a series of neurological symptoms culminating in seizures and delirium (refer to precautions regarding withdrawal symptoms). Tolerance to the hypnotic effects may develop. Refer to the OVERDOSAGE section for the effects of excessive doses.
The following adverse effects have been reported with the use of phenobarbitone:

<table>
<thead>
<tr>
<th>Neurological</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Drowsiness, sedation (appears to lessen with use), lethargy, ‘hangover’, disorientation, mental confusion, dizziness, depression, excitement, confusion, irritability, hyperexcitability, restlessness, tolerance and dependence, psychic or physical dependence</td>
</tr>
<tr>
<td><strong>Less frequent to rare</strong></td>
<td>Profound shock, lowered body temperature, prolonged coma, depressed or absent reflexes, ataxia, nystagmus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematological</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Folate deficiency</td>
</tr>
<tr>
<td><strong>Less frequent to rare</strong></td>
<td>Megaloblastic anaemia, thrombocytopenia, agranulocytosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hypotension, syncope, bradycardia, vasodilatation</td>
</tr>
<tr>
<td><strong>Less frequent to rare</strong></td>
<td>Peripheral vascular collapse, feeble heart beat, circulatory failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Significant respiratory depression, bronchospasm or laryngospasm (especially if given IV)</td>
</tr>
<tr>
<td><strong>Less frequent to rare</strong></td>
<td>Apnoea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dermatological and hypersensitivity reactions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>1-3% incidence of relatively mild skin reactions in the form of maculopapular, morbilliform and scarlatiniform rashes; skin blisters (bullae) in patients who have overdosed.</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Injection site reactions, erythroderma, urticaria and angio-oedema</td>
</tr>
<tr>
<td><strong>Less frequent to rare</strong></td>
<td>Exfoliative dermatitis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis and local necrosis following extravasation after intravenous or subcutaneous injection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genitourinary</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Less frequent to rare</strong></td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Nausea, vomiting, diarrhoea, constipation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
<td>Hepatitis, jaundice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic and nutritional</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td><strong>Less frequent or rare</strong></td>
<td>Osteomalacia, rickets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Less frequent or rare</strong></td>
<td>Reduce bone mineral density, increase the risk of fractures, osteoporosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonates exposed to phenobarbitone in utero</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Drug dependency, symptoms resembling Vitamin K deficiency</td>
</tr>
</tbody>
</table>
DOSAGE AND ADMINISTRATION

PHENOBARBITONE INJECTION

PHENOBARBITONE INJECTION is for single use in one patient only. Discard any residue.

PHENOBARBITONE INJECTION has been administered by intramuscular (IM) or slow IV injection.

Intravenous administration requires a delivery of a diluted (1/10) solution in water for injections at a rate not exceeding 60 mg/minute to reduce the risk of significant respiratory depression and circulatory collapse. Extravasation of solution, especially if concentrated, may cause tissue damage. Adequate provisions for supporting respiration and circulation should be present if the intravenous route is contemplated.

The subcutaneous route should be avoided as it may cause tissue necrosis. Phenobarbitone dosage reduction is recommended in the elderly and in patients with decreased renal or hepatic function. The solution should be inspected for discolouration or the presence of particulate matter.

The sponsor recommends that PHENOBARBITONE INJECTION be given by the intramuscular route.

The following dosage regimen is a guide only.

Anticonvulsant

Adults
Intramuscular, 100 to 300 mg, repeated if necessary up to a total dose of 600 mg during a 24 hour period.

Paediatric
Initial – Intramuscular 10 to 20 mg per kg body weight as a single loading dose.

Maintenance – Intramuscular 1 to 6 mg per kg body weight per day.

Status Epilepticus

Adults
Intramuscular, 10 to 20 mg per kg of body weight, repeated if necessary until seizures are controlled or a total dose of 1 to 2 g is given.

Paediatric
Intramuscular, 15 to 20 mg per kg of body weight, repeated if necessary at a dose of 5 to 10 mg per kg every 20 minutes until seizures are controlled or a total dose of 40 mg per kg is given.

Plasma concentrations of phenobarbitone for the control of epilepsy are usually in the range 15 to 40 micrograms per mL (65 to 170 micromoles per L). Drug levels should be monitored so as to keep within the therapeutic range.

Sedative

Adults
Intramuscular, 30 to 120 mg a day in two or three divided doses.
**Paediatric**
Intramuscular, 1 to 3 mg per kg of body weight a day if needed.

**PHENOBARBITONE ASPEN tablets**

**Anticonvulsant**

*Adults*
60 to 240 mg per day in 2 to 3 divided doses.

*Paediatric*
1 to 6 mg per kg per day in 2 to 3 divided doses.

Phenobarbitone may be given as a single daily dose as it has a long half-life. Doses must be individualised.

**Sedative**

*Adults*
30 to 120 mg per day in 2 to 3 divided doses.

*Paediatric*
1 to 2 mg per kg 2 to 3 times a day.

Alternatively phenobarbitone may be given as a single daily dose.

Geriatric and debilitated patients may exhibit excitement, confusion or depression with usual therapeutic doses. Lower doses are recommended.

**OVERDOSAGE**

**Clinical Features**
Overdosage of barbiturates produces CNS depression ranging from sleep to profound coma to death; respiratory depression which may progress to Cheyne-Stokes respiration, central hypoventilation, and cyanosis; cold, clammy skin and/or hypothermia or later fever, areflexia, tachycardia, hypotension, and decreased urine formation. Pupils are usually slightly constricted but may be dilated in severe poisoning. Patients with severe overdosage often experience typical shock syndrome; apnea, circulatory collapse, respiratory arrest, and death may occur. Complications such as pneumonia, pulmonary oedema, or renal failure may also prove fatal. Other complications which may occur are congestive heart failure, cardiac arrhythmias, and urinary tract infections. Some patients have developed bullous cutaneous lesions which heal slowly.

**Treatment**
Treatment of overdosage is mainly supportive including maintenance of an adequate airway and assisted respiration and oxygen administration if needed. Standard treatment for shock should be administered if necessary. Activated charcoal may reduce absorption of phenobarbitone 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 a nasogastric tube, once the airway is protected. Multiple-dose, nasogastric administration of activated charcoal has been used effectively to treat...
phenobarbitone overdose; activated charcoal enhances the elimination of the drug and shortens the duration of coma. The patient’s vital signs and fluid intake should be monitored closely. Analeptic drugs should not be administered because they may produce paroxysmal cerebral activity which may result in generalised seizures. In addition, it has been demonstrated that analeptics are incapable of stimulating respiration and exerting an arousing effect in patients with severe barbiturate poisoning and profound CNS depression. If renal function is normal, forced diuresis may be of benefit. In addition, alkalinisation of the urine increases renal excretion of phenobarbitone. Peritoneal dialysis or haemodialysis may be useful in severe barbiturate intoxication and/or if the patient is anuric or in shock.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

PHENOBARBITONE INJECTION containing phenobarbitone sodium 219 mg/1 mL (equivalent to phenobarbitone 200 mg/1 mL) is a clear colourless solution in a clear glass ampoule containing 1 mL of solution. 5 ampoules per pack.

PHENOBARBITONE ASPEN tablets contain phenobarbitone 30 mg. They are white, round uncoated biconvex tablets with a scoreline on one side and plain on the other side. Available in white HDPE bottles with a polypropylene child-resistant closure of 200 tablets.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Aspen Pharma Pty Ltd
34-36 Chandos Street,
St Leonards NSW 2065
Australia

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

20 October 2011

DATE OF MOST RECENT AMENDMENT

27 April 2015