**Product Information**

**Phenobarbitone Elixir 15mg/5mL**

**Name of the Drug**
Phenobarbitone

**Chemical Structure**

![Chemical Structure Image](image)

**Description** Phenobarbitone is a barbituric acid derivative. It occurs as colourless crystals or a white odourless crystalline powder. Soluble 1 in 1000 of water and 1 in 10 of alcohol. It is soluble in alcohol, in ether and in solutions of fixed alkali hydroxides and carbonates, it is sparingly soluble in chloroform. Phenobarbitone is 5-ethyl-5-phenylbarbituric acid and has the molecular formula $\text{C}_{12}\text{H}_{12}\text{N}_{2}\text{O}_{3}$ and molecular weight 232.2.

CAS number 50-06-6

Phenobarbitone Elixir contains 15mg phenobarbitone per 5mL (0.3%w/v) in a sweetened sucrose free base. It contains butterscotch flavour, ethanol, glycerol, sorbitol solution (70% non-crystallising) and water.

**Pharmacology**

**Actions** Phenobarbitone is a non selective central nervous system depressant with a long duration of action. The mechanism of action of the barbiturates is not completely known. They may act by enhancing and/or mimicking the synaptic action of gamma-aminobutyric acid (GABA). Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function and produce drowsiness, sedation and hypnosis. Phenobarbitone is reported to have anti-convulsant activity at sub-hypnotic doses.

The anticonvulsant properties are believed to be due to depression of mono-synaptic and poly-synaptic transmission and increasing the threshold for electrical stimulation of the motor cortex.

**Pharmacokinetics**

**Absorption** Phenobarbitone is readily absorbed (about 70-90% of an oral dose) from the gastrointestinal tract. It is relatively lipid insoluble and may require up to an hour or longer to achieve effective concentrations. Absorption is increased if barbiturates are taken well diluted or on an empty stomach. Its duration of action ranges from 10-12 hours.

**Distribution**
Following the absorption phenobarbitone 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, and thus has a slower onset and longer duration of action.

Phenobarbitone is about 45% bound to the plasma proteins.
Therapeutic monitoring of plasma concentrations has been performed as an aid in assessing control of its anticonvulsant activity. The therapeutic range is usually quoted as being 15-40 micrograms per mL (65-170 micromol per L).

**Elimination**
The plasma half-life is about 90-100 hours in adults but is greatly prolonged in neonates. The half-life in children is about 65-70 hours.

Phenobarbitone is metabolised primarily in the liver by the hepatic microsomal enzyme system and is a potent inducer of the CYP_{450} system and thus may accelerate metabolism of other concomitantly administered drugs metabolised by these enzymes see *(Drug Interactions)*. The pharmacokinetics of phenobarbitone is affected by the concomitant administration of other antiepileptics.

Phenobarbitone is hydroxylated by the liver to form p-hydroxyphenobarbitone, an inactive metabolite. About 25-50% of a dose is excreted unchanged in the urine at normal urinary pH. About 75% of the dose is excreted via the kidneys as the p-hydroxy metabolite and its glucuronide and sulfate 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.

**Indication**
Treatment of epilepsy.

**Contraindications**
Not to be administered to patients who are known to be hypersensitive to barbituric acid derivatives. Patients with porphyria, severe respiratory depression or pulmonary insufficiency, renal impairment, hepatic impairment, sleep apnoea, uncontrolled diabetes mellitus, severe anaemia due to folate deficiency, hyperkinetic children, suicidal potential, alcoholism and drug dependency. Not to be used in the presence of uncontrolled pain as paradoxical excitement may be produced. Phenobarbitone should not be administered to elderly patients who exhibit nocturnal confusion or restlessness from sedative hypnotic drugs or to persons who are known to be, or are likely to become, dependent on sedative hypnotic medications.

**Precautions**
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 and 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 30mg 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.

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) (see *Contraindications*). The blood count should be monitored during long term therapy. Patients should be instructed to 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).
Barbiturates should be used with caution in patients with a history of asthma, urticaria or angio-oedema. Mild hypersensitivity reactions have been reported in 1-3% of patients 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 Steven Johnson syndrome (see **Adverse Reactions**). Phenobarbitone should be discontinued in the presence of dermatological reactions or other manifestations of hypersensitivity such as bronchospasm.

Phenobarbitone should be used with caution in the presence of any respiratory difficulty (see **Contraindications**).

Although rare, rickets and osteomalacia have been reported following prolonged usage of barbiturates due to increased metabolism of vitamin D.

Phenobarbitone should be used with caution in patients with acute or chronic pain, since paradoxical excitement may occur or important symptoms might be masked (see **Contraindications**).

**Use in children** Caution should be exercised when using phenobarbitone in children because the drug may exacerbate existing hyperkinetic behaviour, which is severe enough to necessitate a change to a different barbiturate derivative or another anticonvulsant (see **Contraindications**).

**Use in 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. The incidence of fractures due to falls may be increased.

**Impaired renal function** Phenobarbitone is excreted in the kidneys, therefore a reduction in dose may be required in patients with renal dysfunction.

**Impaired hepatic function** 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 pituitary or adrenal in origin. Patients with hyperthyroidism should be treated with caution as symptoms may be exacerbated through displacement of thyroxine from plasma proteins.

Concurrent use of phenobarbitone with other CNS depressant drugs (eg alcohol, narcotics, tranquillisers and antihistamines) and alcohol may result in additional CNS depressant effects. Caution is recommended and dosage reduction of either or both medications may be needed.

**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.

**Carcinogenicity and Mutagenicity** Phenobarbitone is carcinogenic in mice and 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 epidemiological 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 the patients had been treated with thorotrast, a drug known to cause hepatic carcinomas. When patients who had received thorotrast were included, 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 – drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Barbiturates readily cross the placenta and are distributed throughout foetal tissues. The highest concentrations are found in the placenta and in the foetal liver and brain. Prenatal exposure to barbiturates has been reported to increase the risk of foetal abnormalities and of brain tumours.

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 (5mg) 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 risk of a mother with epilepsy giving birth to a child with an abnormality is about three times that of the general population.

The use of phenobarbitone in pregnancy has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability.

The use of phenobarbitone in pregnancy alone, or in combination with other anticonvulsants, can cause coagulation defects in the newborn infant that may be preventable by the prophylactic administration of Vitamin K to the mother prior to delivery.

The serum level of phenobarbitone may decline during pregnancy requiring adjustments in dosage. Post partum restoration of the original dose will probably be indicated.

Barbiturate withdrawal has been reported in neonates who have been exposed to the drug in utero. Withdrawal may occur 1-14 days after birth, and symptoms include seizures, irritability, disturbed sleep, tremor, hypotonia, vomiting and hyperreflexia.

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.

Interactions Pharmacokinetic interactions Phenobarbitone is an inducer of hepatic microsomal enzymes and is capable of increasing the clearance of many hepatically metabolised drugs. This can result in a decrease in or a loss of effectiveness of other drugs during phenobarbitone use and/or increase in effect and even frank toxicity on discontinuation of phenobarbitone.

Anticoagulants Barbiturates may increase the metabolism of oral anticoagulants resulting in decreased anticoagulant response. Correspondingly, if phenobarbitone is discontinued from a stabilised dosage, the hypoprothrombinaemic response may be greatly increased, potentially resulting in haemorrhagic complications. Prothrombin times should be monitored.
closely if phenobarbitone is added or deleted from a regimen that includes oral anticoagulants.

**Anticonvulsants**

**Carbamazepine** – phenobarbitone usually accelerates the metabolism of carbamazepine, resulting in decreased plasma concentrations.

**Lamotrigine** – phenobarbitone may enhance the metabolism of lamotrigine. Adjustment of lamotrigine dose may be required following withdrawal of phenobarbitone from the therapeutic regimen.

**Phenytoin** – when phenobarbitone is used with phenytoin concentrations of either, or both drugs may be affected. While phenobarbitone may induce the metabolism of phenytoin it may also decrease it because both drugs compete for the same metabolic pathway. Therefore, plasma concentrations of both drugs should be monitored when these are used concomitantly.

**Sodium valproate** – the metabolism of phenobarbitone may be decreased by sodium valproate, resulting in increased CNS depressant effects. Phenobarbitone potentiates the hepatotoxicity of sodium valproate by increasing the metabolism of sodium valproate to form valproate-4-ene, a known hepatotoxin. Therefore, plasma concentrations of sodium valproate and phenobarbitone should be monitored when any change in the therapeutic regimen occurs.

**Corticosteroids** Barbiturates increase the metabolism of corticosteroids, and may exacerbate asthma and other conditions when added to regimens containing corticosteroids. Reduction in serum levels of corticosteroids may compromise their effectiveness in the treatment of steroid responsive disorders such as asthma.

**Oral Contraceptives** Barbiturates may accelerate the metabolism of both the oestrogenic and progestogenic components of the contraceptive, resulting in decreased effectiveness that may or may not be signalled by breakthrough bleeding. Another form of contraception is advisable if phenobarbitone is given on a regular basis.

**Antidepressants** Phenobarbitone may increase the metabolism of tricyclic antidepressants and selective serotonin reuptake inhibitor through the possible induction of CYP\textsubscript{2}D6, resulting in a lack of effect. Plasma TCA or SSRI levels should be monitored if possible, especially if the patient is not responding to standard dosages of antidepressants.

**Monoamine oxidase inhibitors** MAIOs may inhibit barbiturate metabolism, resulting in increased CNS depressant effects. A reduction in phenobarbitone dosage may be necessary. Phenobarbitone should be avoided in patients who are on tranylcypromine because concomitant use of barbiturate and tranylcypromine has been reported to result in semicomatose for 36 hours in one case study.

**Opioid analgesics** Phenobarbitone may increase the metabolism of opioid analgesics such as methadone leading to a decreased plasma level and opioid withdrawal symptoms. Methadone levels must be monitored if phenobarbitone is introduced.

**Paracetamol** The therapeutic effects of paracetamol may be reduced due to enzyme induction of CYP\textsubscript{3}A4 and subsequent increased metabolism of the drug to its toxic metabolite, leading to increased hepatotoxicity. Chronic use of phenobarbitone may increase the risk of hepatotoxicity with single toxic doses or prolonged high doses of paracetamol.

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

**Cardiovascular** Barbiturates have been reported to increase the metabolism (due to the induction of CYP\textsubscript{3}A4) and correspondingly reduce the effectiveness of digoxin, antiarrhythmics (eg quinidine, disopyramide, and mexiletine), β-blockers (e.g. propanolol) and calcium channel blockers (e.g. nifedipine).

**Antifungals** Poor clinical response to antifungals such as itraconazole and ketoconazole results from enzyme induction of CYP\textsubscript{3}A4 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. Barbiturates have been shown to increase the metabolism and correspondingly reduce the effectiveness of chloramphenicol.
Disulfiram Concurrent administration may result in inhibition of metabolism of barbiturates and an increased incidence of barbiturate toxicity. Flu vaccine Concurrent use of flu vaccine and phenobarbitone may increase the serum concentration of the barbiturate, and dosage adjustments may be necessary. Chemotherapeutic agents Clearance of etoposide has been shown to increase by 170% when given with phenobarbitone. Be alert for the need to increase the etoposide dose if used concurrently with phenobarbitone. Immunosuppressants Cyclosporin and tacrolimus have been shown to have clearance increased by barbiturates. Protease Inhibitors Increased metabolism by the action of phenobarbitone on CYP3A4 may result in reduced plasma levels. Theophylline Induction of CYP1A2 may result in lowered plasma levels and loss of efficacy. Serum theophylline levels should be monitored as 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 anhydrate inhibitors. Urinary alkanisers Alkanising the urine may diminish the effects of barbiturates due to increased excretion. Hypericum perforatum (St John’s Wort) Concomitant 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. Serum barbiturate levels may increase when the administration of St John’s Wort is stopped, thus resulting in a need to adjust the dose of barbiturate. Pharmacodynamic interactions Concurrent administration of phenobarbitone with other drugs may result in increased effect of the other drugs or the barbiturate itself. CNS depressant Excessive CNS depressant effects may result from concurrent administration of barbiturates and other CNS depressants such as alcohol, benzodiazepines, phenothiazines, antihistamines, anaesthetics and opioids. Amphetamines Concurrent use with phenobarbitone may result in delays in the intestinal absorption of phenobarbitone. Tricyclic antidepressants Concomitant use of phenobarbitone and tricyclic antidepressants may result in additive respiratory depressant effects. Tricyclic antidepressants may decrease seizure control: epileptic patients receiving phenobarbitone should be watched closely when tricyclic antidepressants are administered and the dose of phenobarbitone should be adjusted if necessary. Anaesthetics Ketamine anaesthesia following administration of a barbiturate has been reported to produce profound respiratory depression. Carbonic anhydrate inhibitors Concurrent administration of carbonic anhydrate inhibitors with phenobarbitone may enhance osteopaenia induced by phenobarbitone. Patients receiving concurrent therapy should be monitored for early signs of osteopaenia, and carbonic anhydrate inhibitor should be discontinued, with appropriate treatment initiated if required. Hypothermia producing medicines Concurrent use of hypothermia producing medicines with phenobarbitone in high doses or acute overdose may increase the risk of hypothermia. Effects on Laboratory Tests Phenobarbitone may interfere with diagnostic test results when the following agents are used: 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 possible due to induction of glucuronyl transferase, the enzyme responsible for the conjugation of bilirubin.
Adverse reactions

The most frequent adverse effect following the administration of phenobarbitone is sedation that often becomes less marked with continued administration. Phenobarbitone may induce 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 number of neurological symptoms culminating in seizures and delirium (refer to Precautions regarding withdrawal symptoms). Tolerance to the hypnotic effect may develop. Refer to Overdosage for the effects of excessive doses.

The following adverse reactions have been reported with the use of phenobarbitone:

**Neurological**
- **Common** drowsiness, sedation (appears to lessen with use)
- **Uncommon** agitation, confusion, hyperkinesia, ataxia, CNS depression, nightmares, nervousness, psychiatric disturbance, hallucinations, insomnia, anxiety, dizziness, thinking abnormality, subtle mood changes, impairment of concentration, judgment, memory and fine motor skills. Disturbances of sleep, vertigo, headache and depression.

**Cardiovascular**
- **Uncommon** hypotension, syncope, bradycardia, vasodilation
- **Rare** peripheral vascular collapse, feeble heart beat, circulatory failure

**Respiratory**
- **Uncommon** severe respiratory depression, apnoea, bronchospasm or laryngospasm

**Haematological**
- **Uncommon** folate deficiency or hypocalcaemia, megaloblastic anaemia and lymphocytosis
- **Rare** thrombocytopenia, agranulocytosis

**Digestive system**
- **Uncommon** nausea, vomiting, diarrhoea and constipation

**Dermatological**
- **Very Common** 1-3% incidence of relatively mild skin reactions in the form of maculopapular, morbilliform and scarlatiniform rashes: skin blisters (bullae) in patients with barbiturate overdose, evidence of connective tissue changes.
- **Uncommon** erythoderma, hypersensitivity reactions such as angiodema and skin rashes
- **Rare** exfoliative dermatitis, erythema multiforme (or Stevens-Johnson syndrome) and toxic epidermal necrolysis

**Hepatic**
- **Uncommon** liver damage
- **Rare** toxic hepatitis and jaundice

**Metabolic**
- **Uncommon** increased vitamin D requirements possibly due to increased vitamin D metabolism, hypocalcaemia
- **Rare** rickets and osteomalacia

**Neonates exposed to phenobarbitone in utero**
- **Common** drug dependency, symptoms resembling vitamin K deficiency

**Other**
- **Uncommon** fever and menstrually related mood disorder

Dosage and administration

The dose of phenobarbitone must be adjusted to the individual giving consideration to the patient’s age, weight and condition.

Plasma concentrations required to control epilepsy are usually about 15 to 40 micrograms/mL (65 to 170 micromoles per L). Drug levels should be monitored so as to keep within the therapeutic range.
**Recommended dosage**

- **Adult:** 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 individualized. Geriatric and debilitated patients may exhibit excitement, confusion or depression with usual therapeutic doses, thus lower doses are recommended. Phenobarbitone should be withdrawn slowly in order to avoid precipitating seizures or status epilepticus.

**Overdosage**

Overdosage of barbiturates produce 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: apnoea, 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 of overdosage is primarily 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 is an effective barbiturate absorbent when administered within 30 minutes following ingestion of the drug. 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 the coma. The patients vital signs and fluid intake should be monitored closely. Analapeutic drugs should not be administered because these may produce paroxysmal cerebral activity which may result generalized seizures. In addition, it has been demonstrated that analeptics are incapable of stimulating respiration and exerting an arousal effect in patients with severe barbiturate poisoning and CNS depression. If renal function is normal forced diuresis may be of benefit. In addition alkalisation 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.

**Presentation**

AUST R 21187: Phenobarbitone Elixir, 15mg phenobarbitone/5mL, 100mL and 500mL bottle.

**Storage**

Store below 30°C

**Poisons Schedule**

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**Name and Address of Sponsor**

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**Date of approval**

This Product Information was approved by the Therapeutic Goods Administration on 8th March 2004.
END OF PRODUCT INFORMATION