

NEW ZEALAND DATA SHEET

1. PRODUCT NAME (strength pharmaceutical form)

Phenobarbitone (PSM), Tablet, 15mg

Phenobarbitone (PSM), Tablets, 30mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance

Phenobarbital 15mg

Phenobarbital 30mg

Excipient(s) with known effect

<For the full list of excipients, see section 6.1.>

3. PHARMACEUTICAL FORM

Oral – tablet

Presentations

Phenobarbitone (PSM) tablets 15 mg: 'White normal convex 5.0 mm tablets'

Phenobarbitone (PSM) tablets 30 mg: 'White normal convex 5.55 mm tablets'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Accepted: Phenobarbital is indicated for use as preoperative medication to help reduce anxiety and facilitate induction of anaesthesia.

Phenobarbital a long acting barbiturate is indicated as long term anticonvulsant therapy for the treatment of generalised tonic-clonic and simple partial (cortical focus) seizures.

Seizures (prophylaxis and treatment) of febrile seizures.

4.2 Dose and method of administration

Phenobarbital is a barbiturate which may be used as an antiepileptic agent to control tonic-clonic (grand mal) and partial (focal) seizures.

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The dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires plasma concentrations of 10 to 40mcg per ml (43 to 172 micromoles per litre).

Up to 350 mg daily in divided doses may be taken.

4.3 Contraindications

Hypersensitivity to barbituric acid derivatives. Phenobarbital is contraindicated in patients with acute intermittent 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. Phenobarbital is also contraindicated in those who have a natural or acquired idiosyncrasy to barbiturates. Not to be administered in the presence of uncontrolled pain as paradoxical excitement may be produced. Phenobarbital 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.

4.4 Special warnings and precautions for use

Paediatric population

Paediatric neurotoxicity:

Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans.

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6).

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Phenobarbital should be used with care in children and elderly patients, in those with acute pain, and in those with mental depression. They should be given cautiously to patients with impaired hepatic, renal, or respiratory function and may be contra-indicated when the impairment is severe. They are also contra-indicated in patients with acute porphyrias.

Care is required when withdrawing Phenobarbital therapy in epileptic patients.

The effects of Phenobarbital and other barbiturates are enhanced by concurrent administration of other CNS depressants including alcohol. Valproic acid has been reported to cause rises in Phenobarbital (and primidone) concentrations in plasma. Phenobarbital and other barbiturates may reduce the activity of many drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes. For further details of the interactions of Phenobarbital see below.

An analysis of reports of suicidality (suicidal behaviour or ideation) from placebo-controlled clinical studies of eleven medicines used to treat epilepsy as well as psychiatric disorders, and other conditions revealed that patients receiving anti-epileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behaviour and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine and continued through 24 weeks. The results were generally consistent among the eleven medicines. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk of suicidality was higher in the patients with epilepsy compared to the patients who were given one of the medicines in the class for psychiatric or other conditions. All patients who are currently taking or starting on any anti-epileptic drugs should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

Health Care Professionals should inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

4.5 Interaction with other medicines and other forms of interaction

There are complex interactions between **antiepileptics**, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Valproate and phenytoin have been reported to cause rises in Phenobarbital (and primidone) concentrations in plasma.

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The effects of Phenobarbital and **other barbiturates** are enhanced by other CNS depressants including alcohol.

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Analgesics:

Dextropropoxyphene 65mg given three times daily to 4 epileptic patients stabilised on Phenobarbital therapy increased serum-phenobarbital concentration by 8 to 29%, but this was not considered of major importance in light of the normally accepted therapeutic range for phenobarbital.

Fenoprofen - Phenobarbital may increase the rate of metabolism of fenoprofen and dosage adjustment of fenoprofen may be required when given with Phenobarbital.

Methadone - Opioid withdrawal symptoms have been reported in patients maintained on methadone when they were given Phenobarbital.

Pethidine – Barbiturates can be expected to have addictive CNS depressant effects. Prolonged sedation with pethidine in the presence of Phenobarbital has also been attributed to induction of N-demethylation of pethidine resulting in the enhanced formation of the potentially neurotoxic metabolite norpethidine.

Paracetamol - Enzyme-inducing antiepileptics such as Phenobarbital also affect the threshold for the use of antidote in the treatment of paracetamol poisoning. The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing drugs such as Phenobarbital.

Antiarrhythmics:

Disopyramide – The clearance of disopyramide may be increased by enzyme inducers such as Phenobarbital.

Lidocaine – Studies in healthy subjects and patients with epilepsy suggest that long-term use of drugs such as barbiturates may increase dosage requirements for lidocaine due to induction of drug metabolizing microsomal enzymes.

Quinidine – Quinidine is metabolized by the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and may interact with inhibitors or inducers of this isoenzyme. Phenobarbital increase the metabolism of quinidine and increased doses may be required.

Antibacterials:

Chloramphenicol - Serum concentrations of phenytoin and phenobarbital in a previously stabilized patient were increased when he took chloramphenicol. Subsequent monitoring revealed a similar effect when chloramphenicol was taken with Phenobarbital alone. In turn, Phenobarbital may affect serum concentrations of chloramphenicol. The metabolism of chloramphenicol may be increased by inducers of

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hepatic enzymes such as Phenobarbital. Serum concentrations of chloramphenicol are usually reduced by the hepatic enzyme induction that occurs with Phenobarbital.

Doxycycline – Barbiturate such as Phenobarbital may enhance the metabolism of doxycycline.

Anticoagulants:

Warfarin – Barbiturates such as Phenobarbital diminish the activity of warfarin and other coumarins through increased metabolism.

Antidepressants:

As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of Phenobarbital by lowering the convulsive threshold.

St John's wort - has been shown to induce several drug metabolising enzymes and so might reduce several the blood concentrations of phenobarbital, and increase the seizure risk. There is a possibility of an interaction between St John's wort and antiepileptics such as Phenobarbital.

Amitriptyline – Antidepressants may antagonize the antiepileptic activity of some barbiturates by lowering the convulsive threshold. Barbiturates can increase the metabolism if tricyclic antidepressants and thereby produce lower plasma concentrations.

Interactions of tricyclic antidepressants with barbiturates anaesthetics - resulting in increased sleep time and duration of anaesthesia meant that lower doses of barbiturates should be used.

Bupropion – bupropion may induce seizures and consequently is contra-indicated in patients with epilepsy. Phenobarbital may induce the metabolism of bupropion.

Fluoxetine – Antidepressants may antagonize the activity of antiepileptics by lowering the convulsive threshold. Phenobarbital has been reported to reduce serum concentrations of paroxetine.

Lithium – Severe CNS toxicity despite 'normal' serum lithium concentrations has been described in a patient also taking Phenobarbital.

Mianserin – Reduced plasma concentrations and half-lives of mianserin and desmethylmianserin were seen in 6 patients also receiving antiepileptic therapy consisting of phenytoin with either carbamazepine or Phenobarbital. Mianserin may antagonize the action of antiepileptics by lowering the convulsive threshold.

Antiepileptics:

Interactions may occur if Phenobarbital is given with other antiepileptics, of which probably the most significant is the interaction with valproate.

Valproate increases plasma-phenobarbital concentration by a reported 17 to 48%, and it may be necessary to reduce the dose of Phenobarbital in some patients. The mechanism for the increase appears to be inhibition of the metabolism of Phenobarbital, resulting in reduced clearance, valproate appears to inhibit both the direct N-glucosidation of Phenobarbital and the O-glucuronidation of p-

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hydroxyphenobarbital. However, Phenobarbital reciprocally increases the clearance of valproate, and the valproate dose may also need to be adjusted.

A similar complex interaction exists between Phenobarbital and phenytoin.

Phenytoin can increase plasma concentrations of Phenobarbital in some patients since the two drugs compete for metabolism by the same enzyme system, but other evidence suggests that where this occurs it is rarely of significant magnitude.

Similarly, although Phenobarbital induces the metabolism of phenytoin it is also, as stated, a competitive inhibitor and in practice, the two effects appear to balance out, with rarely any need for dose adjustment. However dosage adjustment of Phenobarbital may be crucial for some patients. Measurement of serum concentrations of phenytoin and Phenobarbital in one patient showed that, in her case, large increases in serum-phenobarbital concentrations resulted from use with phenytoin; the increases were concentration-dependant.

The GABA-agonist, progabide has also been reported to cause a significant increase in Phenobarbital concentrations when the two were given together to healthy subjects. Neurotoxicity, attributed to an increase in plasma concentrations of Phenobarbital, has been seen in one patient taking Phenobarbital and *sodium valproate* when *felbamate* was added to treatment. The dosage of Phenobarbital had already been reduced before treatment with *felbamate* was started. Data from a pharmacokinetic study indicated that the interaction may result from the inhibition of Phenobarbital hydroxylation by *felbamate*.

Vigabatrin has been reported to lower plasma concentrations of Phenobarbital in some patients, although dosage changes were not necessary in these patients.

High dose of *oxcarbamazepine* may increase the plasma concentrations of phenobarbital but this was thought unlikely to be clinically significant, conversely strong inducers of cytochrome P450 coenzymes, such as phenobarbital may reduce the plasma concentrations of the active metabolite of *oxcarbamazepine*.

Carbamazepine – The metabolism of carbamazepine is enhanced by enzyme inducers such as Phenobarbital. Interactions of varying degrees of clinical significance have been reported between carbamazepine and other antiepileptics. Serum concentrations of carbamazepine are reported to be reduced by Phenobarbital, but without loss of seizure control; this reduction is probably due to induction of carbamazepine metabolism.

Diazepam – Phenobarbital is an inducer of hepatic drug metabolizing enzymes. Therefore, in patients receiving long term therapy of these drugs the metabolism of benzodiazepines may be enhanced.

Ethosuximide – since ethosuximide has a limited spectrum of antiepileptic action, patients with mixed seizure syndromes may require addition of other antiepileptics, Phenobarbital has been shown to increase the clearance of ethosuximide and thus reduce plasma concentration. This interaction is likely to be clinically relevant and higher ethosuximide dosages may be necessary to achieve therapeutic drug levels.

Lamotrigine - The metabolism of carbamazepine is enhanced by enzyme inducers such as Phenobarbital. Phenobarbital markedly induce the elimination of lamotrigine.

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Tiagabine - The hepatic metabolism of tiagabine is accelerated by antiepileptics that include enzymes of the cytochrome P450 system such as Phenobarbital. Plasma concentrations of tiagabine may be reduced up to threefold by use with Phenobarbital.

Zonisamide – There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Use with drugs that induce or inhibit the cytochrome P450 isoenzyme CYP3A4 may alter plasma concentrations of zonisamide. Phenobarbital reduce the half-life of zonisamide.

Antifungals:

Griseofulvin - Phenobarbital has been reported to decrease the gastrointestinal absorption of griseofulvin.

Itraconazole – Enzyme inducing drugs such as Phenobarbital may decrease plasma concentrations of itraconazole sufficiently to reduce its efficacy.

Antineoplastics:

Teniposide – Clearance of teniposide was markedly increased by Phenobarbital; the resultant decrease in systemic exposure to the antineoplastic might reduce its efficacy, and increased dosage would be needed in patients receiving this drugs to guarantee equivalent exposure.

Antiprotozoals:

Metronidazole – Plasma concentrations are increased by Phenobarbital, with a consequent reduction in the efficiency of metronidazole.

An increase in the rate of metabolism of metronidazole, resulting in treatment failure, was reported in a patient taking Phenobarbital. In a retrospective survey of patients who had not responded to treatment with metronidazole 80% were found to be on long term phenobarbital therapy. Up to 3 times the usual dose was required to produce a parasitological cure for giardiasis in such patients.

Antipsychotics:

With all antiepileptics, antipsychotics may antagonize the antiepileptics activity of Phenobarbital by lowering the convulsive threshold.

Chlorpromazine – Phenobarbital are potent enzyme inducers and may decrease plasma concentrations of antipsychotics or their active metabolite when used together. The clinical effect of any interaction has not been consistent; worsening; improvement, or no change in psychotic symptoms have all been noted.

Antivirals:

A patient stabilised on Phenobarbital 100mg daily has an episode of seizures 4 weeks after starting HAART therapy with abacavir, didanosine, ritonavir-boosted tipranavir, and enfuvirtide. The patient's Phenobarbital plasma concentrations had fallen from 16 to 8 micrograms/mL and an increase in the Phenobarbital dosage to 150mg daily was

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required to restore concentrations. The tipranavir/ritonavir component of HAART therapy was considered to be responsible.

HIV- protease inhibitors – Reduced plasma concentrations of HIV-protease inhibitors may be anticipated if the enzyme inducer Phenobarbital is given concurrently.

Beta blockers:

Anxiolytics and Antipsychotics – Plasma concentrations of some beta blockers may be reduced by barbiturates.

Calcium-channel blockers:

Dihydropyridine calcium channel blockers – Nifedipine – The effects of dihydropyridine calcium-channel blockers may be reduced by enzyme-inducing antiepileptics such as Phenobarbital.

Verapamil – Phenobarbital is a hepatic enzyme inducing drug and has been reported to increase the clearance of oral and intravenous verapamil and to reduce oral bioavailability in healthy subjects. Plasma protein binding of verapamil was also reduced. Dosage adjustment of verapamil may be needed in patients also taking Phenobarbital.

Cardiac glycosides:

Digitoxin – Phenobarbital may greatly accelerate the metabolism of digitoxin. Since digitoxin is significantly metabolized in the liver it may be affected by drugs that induce microsomal enzymes, including antiepileptics such as Phenobarbital.

Ciclosporin:

Ciclosporin – Use with the antiepileptic Phenobarbital which is an inducer of hepatic cytochrome P450, has been associated with a reduction in blood ciclosporin trough concentrations.

Corticosteroids:

Concurrent use of barbiturates may enhance the metabolism and reduce the effects of systemic corticosteroids.

Corticosteroids – reduced efficacy of corticosteroids has been noted in asthmatics, arthritic, renal transplant, and other patients who also received Phenobarbital.

Diuretics:

Serum-phenobarbital concentrations were raised in 8 to 10 epileptic patients taking Phenobarbital and additional antiepileptics when given *furosemide* 40mg three times daily for 4 weeks. This might have been the cause of drowsiness in 5 to 14 patients. 3 of whom had to stop *furosemide*.

Levothyroxine:

Enzyme induction by drugs such as barbiturates enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. Therefore patients on

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thyroid replacement therapy may require an increase in their dose of thyroid hormone if these drugs are also given and a decrease if the enzyme-inducing drug is withdrawn.

Montelukast:

Licensed product information recommends caution when potent inducers of the cytochrome P450 isoenzyme CYP3A4 such as Phenobarbital are given with montelukast.

Montelukast – Peak serum concentrations after a single dose of montelukast 10mg were reduced by 20% in 14 healthy subjects who took Phenobarbital 100mg daily for 14 days, and area under the serum concentration-time curve was reduced by 38%. However, it was not thought that montelukast doses would need adjustment if given with Phenobarbital.

Sex hormones:

Sex hormones – oral contraceptives – Oral contraceptive failure and breakthrough bleeding have been reported in numerous cases during antiepileptic therapy. Barbiturates such as phenobarbitone has been most frequently implicated. These drugs increase the clearance of both oestrogens and progestogens by enzyme induction, so diminish their effects.

Theophylline:

Theophylline – Although Phenobarbitone was not found to have any significant effect on the pharmacokinetics of a single dose of theophylline given intravenously, enhanced theophylline clearance has been seen in patients after longer periods of treatment with Phenobarbital. The magnitude of the changes in theophylline elimination appears to be smaller with Phenobarbital than phenytoin.

Vaccines:

Influenza vaccinations can cause prolonged rises in serum-phenobarbital concentrations in some patients.

Vitamins:

Pyridoxidine reduced serum-phenobarbital concentrations in 5 patients. Plasma concentrations of Phenobarbital and primidone are possibly reduced by folic acid and folinic acid.

Vitamin D – There are many reports indicating effects of antiepileptics on bone and on calcium and vitamin D metabolism. Therapy with Phenobarbital has been associated with reduction in serum-calcium concentration to hypocalcaemic values, significant reduction in 25-hydroxycholecalciferol concentrations, and elevated alkaline phosphatase.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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Category D

Risk summary statement:

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Preclinical data

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

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 giving birth to a child with an abnormality as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive pre pregnancy counselling with regard to the risk of foetal abnormalities;
- AEDs should be continued during pregnancy and mono therapy 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.

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

Barbiturates can give rise to hypotension, respiratory depression and hypothermia in the new born infant. Continuous treatment during pregnancy and administration during labour should be avoided.

The use of Phenobarbital in pregnancy alone, or in combination with other anticonvulsants, can cause coagulation defects in the new born infant which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.

The serum level of Phenobarbital may decline during pregnancy requiring adjustments in dosage. Postpartum 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 to 14 days after birth and symptoms include seizures, irritability, disturbed sleep, tremor, hypotonia, vomiting and hyperreflexia.

Lactation:

Phenobarbital is not recommended in breastfeeding mothers. Phenobarbital is distributed into breast milk and use by breastfeeding mothers may cause CNS depression.

Fertility:

Carcinogenesis, mutagenesis, impairment of fertility:

Phenobarbital 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.

Phenobarbital 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 Phenobarbital, results indicated a higher than normal incidence of hepatic carcinoma. Previously some of the patients had been treated with thiorast, a drug known to cause hepatic carcinomas. When patients who had received thiorast had been included, there was a non-significant increase in the number of liver tumours and, unlike the mouse liver tumours, were mostly associated with cirrhosis.

4.7 Effects on ability to drive and use machines

Phenobarbital causes drowsiness and is likely to impair the patient's ability to concentrate and react constituting a risk in the ability to drive and use machines. Patients taking Phenobarbital, should not take charge of vehicles, or machinery where loss of attention could cause accidents.

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4.8 Undesirable effects

Adverse effects include the following:

- *Suicidal Behaviour*
- *Suicidal Ideation*
- *Emergence or worsening of existing depression*

The most frequent adverse effect following administration of Phenobarbital is sedation, but this often becomes less marked with continued administration. Like some other antiepileptic agents Phenobarbital may produce subtle mood changes and impairment of cognition and memory, which may not be apparent without testing.

Prolonged administration may occasionally result in folate deficiency or hypocalcaemia; rarely, megaloblastic anaemia or osteomalacia have been reported.

At high dose nystagmus and ataxia may occur and the typical barbiturate-induced respiratory depression may become severe. Overdosage may result in coma, severe respiratory and cardiovascular depression, hypotension and shock leading to renal failure, and death. Hypothermia may occur, with associated pyrexia during recovery. Skin blisters (bullae) reportedly occur in about 6% of patients with barbiturate overdose.

Owing to their extreme alkalinity necrosis has followed subcutaneous injection or extravasation of sodium salts of barbiturates. Intravenous injections can be hazardous and cause hypotension, shock, laryngospasm, and apnoea.

Phenobarbital and other anticonvulsants that have been shown to induce the CYP450 enzymes are thought to affect bone mineral metabolism directly by increasing the metabolism of vitamin D3. This may lead to vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcaemia, and hypophosphataemia in chronically treated epileptic patients.

Hypersensitivity reactions occur in a small proportion of patients; skin reactions are reported in 1 to 3% of patients receiving Phenobarbital, and are most commonly maculopapular, morbilliform, or scarlatiniform rashes. More severe reactions such as exfoliative dermatitis, erythema multiform (or Stevens-Johnson syndrome), and toxic epidermal necrolysis are extremely rare. Hepatitis and disturbances of liver function have been reported.

Paradoxical excitement, irritability and hyperexcitability may sometimes occur, particularly in children or the elderly.

Neonatal drug dependence and symptoms resembling vitamin K deficiency have been reported in infants born to mothers who received Phenobarbital during pregnancy.

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Congenital malformations have been reported in children of women who received Phenobarbital during pregnancy but the casual role of the drug is a matter of some debate.

4.9 Overdose

Overdosage of barbiturates produce CNS depression ranging from sleep to profound coma to death; respiratory depression which may progress to Cheyne-Stoke 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.

In an overdose of a barbiturate, the stomach may be emptied by lavage. The prime objectives of management are then intensive symptomatic and supportive therapy with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions and to the maintenance of the electrolyte balance. Standard treatment for shock should be administered if necessary.

Several methods aimed at the active removal of a barbiturate with a long elimination half-life such as Phenobarbital have been employed and include forced diuresis, haemodialysis, peritoneal dialysis, and charcoal haemoperfusion, but with the possible exception of charcoal haemoperfusion the hazards of such procedures are generally considered to outweigh any purported benefits.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions: Phenobarbital is a barbiturate used mainly for its antiepileptic properties. It is given by mouth or parenterally, as the base or the sodium salt. It induces liver enzymes and alters the metabolism of a number of other drugs.

Sedation is common but tends to become less of a problem as Phenobarbital antiepileptic treatment continues.

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5.2 Pharmacokinetic properties

Phenobarbital acts as a nonselective depressant of the central nervous system capable of producing all levels of CNS mood alteration from excitation to mild sedation, hypnosis and deep coma. In sufficiently high doses, barbiturates induce anaesthesia.

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).

Sedative-hypnotic - Barbiturates depress the sensory cortex, decrease motor activity, alter cerebral function, and produce drowsiness, sedation and hypnosis. Although the mechanism of action has not been completely established, the barbiturates appear to have a particular effect at the level of the thalamus where they inhibit ascending conduction in the reticular formation, thus interfering with the transmission of impulse to the cortex.

Anticonvulsant – Barbiturates are believed to act by depressing monosynaptic and polysynaptic transmission in the CNS. They also increase the threshold for electrical stimulation of the motor cortex.

Antihyperbilirubinemic - Phenobarbital lowers serum bilirubin concentrations probably by induction of glucuronyl transferase, the enzyme which conjugates bilirubin.

Other actions/effects:

Barbiturates have little analgesic action at sub-anesthetic doses and may increase reaction to painful stimuli.

Although Phenobarbital, mephobarbital, and metharbital are the only barbiturates effective as anticonvulsants in sub-hypnotic doses, all of the barbiturates exhibit anticonvulsant activity in anesthetic doses.

Barbiturates are respiratory depressants; the degree of respiratory depression is dose-dependent.

Barbiturates have been shown to reduce the rapid eye movement (REM) phase of sleep or dreaming stage. Also, Stages III and IV sleep (slow-wave sleep, SWS) are decreased.

Animal studies have shown that barbiturates cause reduction in the tone and contractility of the uterus, ureters, and urinary bladder; however, concentrations required to produce this effect in humans are not attained with sedative-hypnotic doses.

Barbiturates have been shown to induce liver microsomal enzymes, thereby increasing and altering the metabolism of other medications or compounds.

Absorption:

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Phenobarbital is readily absorbed from the gastro-intestinal tract, although it is relatively lipid-insoluble and may require an hour or longer to achieve effective concentrations. Phenobarbital is about 45% bound to plasma proteins and is only partly metabolised in the liver. About 25% of a dose is excreted in the urine unchanged at normal urinary pH. The plasma half-life is about 90 to 100 hours in adults but is greatly prolonged in neonates, and shorter (about 65 to 70 hours) in children. There is considerable inter-individual variation in Phenobarbital kinetics. Monitoring of plasma concentrations has been performed as an aid in assessing control and the therapeutic range of plasma-Phenobarbital is usually quoted as being 10 to 40 mcg per ml (43 to 172 micromoles per litre). Phenobarbital crosses the placental barrier and small amounts are excreted in breast milk.

The rate of absorption is increased if barbiturates are taken well diluted or on an empty stomach.

Distribution:

Rapidly distributed to all tissues and fluids with high concentrations in the brain, liver, and kidneys.

Lipid solubility is the primary factor in distribution within the body. The more lipid soluble the barbiturate, the more rapidly it penetrates all tissues of the body; phenobarbital has the lowest lipid solubility and secobarbital the highest.

Biotransformation:

Hepatic, primarily by the hepatic microsomal enzyme system. About 75% of a single oral dose of mephobarbital is metabolized to Phenobarbital in 24 hours.

Metharbital is metabolized to barbital.

Onset of action:

Oral – Varies from 20 to 60 minutes.

Therapeutic serum concentration:

Anticonvulsant – Phenobarbital: 10 to 40 mcg per mL (43 to 172 micromoles/L).

Note: The optimal blood Phenobarbital concentration should be determined by response in seizure control and the appearance of toxic effects.

To achieve blood concentrations considered therapeutic in children, higher-per-kg dosages of Phenobarbital and most other anticonvulsants generally are required.

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5.3 Preclinical safety data

Animal toxicology and/or pharmacology

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, Purified talc, Wheat starch, Lactose

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

60 months from the date of manufacture when stored below 25°C.

NEW ZEALAND DATA SHEET

6.4 Special precautions for storage

Store below 25°C. Store in original package.
Keep out of reach of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Blister packs of 500 tablets.

6.6 Special precautions for disposal <and other handling>

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Controlled Drug C5

8. SPONSOR

PSM Healthcare Limited, t/a API Consumer Brands
14-16 Norman Spencer Drive
PO Box 76 401
Manukau City
AUCKLAND 2241
Telephone 0508 776746

9. DATE OF FIRST APPROVAL

31/12/1969

10. DATE OF REVISION OF THE TEXT

April 2017

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
All sections	Update to the SPC-style format only (required as part of any changes to the data sheet from 1 March 2017)
All sections	Minor changes as indicated in CMN form.
4.4, 4.6 and 5.3	As per Medsafe request (dated 18/04/2017) to update data sheet for use in children – Neurotoxicity and effects on brain development.