NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Phenobarbitone (Noumed), Tablet, 15mg
Phenobarbitone (Noumed), Tablets, 30mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance

Phenobarbital 15mg
Phenobarbital 30mg

Excipient(s) with known effect

Contains gluten, sulfites and sugars (as lactose).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral – tablet

Presentations

Phenobarbitone (Noumed) tablets 15 mg: A white, biconvex, circular tablet.

Phenobarbitone (Noumed) tablets 30 mg: A white, biconvex, circular tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.
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

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% Cl: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

Indication	Placebo Patients with Events/1000 Patients	Drug Patients with Events/1000 Patients	Relative Risk: Incidence of Events in Drug patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing 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).

Asthma, urticaria and angioedema:
Barbiturates should be used with caution in patients with a history of asthma, urticaria or angioedema. 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, Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (refer to section 4.8 Adverse effects (undesirable 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

Corticosteroids, hypoadrenalism and hyperthyroidism:
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 section 4.5 Interactions with other medicines and other forms of interactions).

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

Women of childbearing potential:
Phenobarbital may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenobarbital may increase the risk of congenital malformations and adverse developmental outcomes (see section 4.6).

Phenobarbital should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options. Women of childbearing potential, women planning pregnancy and pregnant women should be fully informed of the potential risk to the fetus if they take phenobarbital during pregnancy.

A pregnancy test to rule out pregnancy should be considered prior to commencing treatment with phenobarbital in women of childbearing potential.

Women of childbearing potential should use highly effective contraception during treatment and for 2 months after the last dose. Due to enzyme induction, phenobarbital may result in a failure of the therapeutic effect of oral contraceptive drugs (see section 4.5 and 4.6).

Women planning a pregnancy should be advised to consult in advance with her physician so that adequate counselling can be provided and appropriate other treatment options can be discussed prior to conception and before contraception is discontinued.

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with phenobarbital.

Use in hepatic impairment:
Phenobarbitone is metabolised in the liver, therefore hepatic dysfunction may theoretically lead to increased blood levels. The dose may need to be reduced.”

Use in renal impairment:
Unchanged phenobarbitone is excreted by the kidneys, therefore a reduction in dose may be required in patients with renal dysfunction.

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.

Paediatric use:
Some children may react with paradoxical excitement.

Paediatric Neurotoxicity
Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

Effects 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.

4.5 Interaction with other medicines and other forms of interaction

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.

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 – 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.

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 increases the metabolism of quinidine and increased doses may be required.
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.

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 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 – 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.

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.
Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitor (eg. Amitriptyline, Fluoxetine, Paroxetine) – 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.
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.
Monoamine oxidase inhibitors (MAOI) – Barbiturate metabolism may be inhibited 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 semicoma for 36 hours in one case study.

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-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 complete 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 a 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 ethoxumide dosages may be necessary to achieve therapeutic drug levels.

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

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 reduces the half-life of zonisamide.

Antifungals:

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

Itraconazole, Ketoconazole – Enzyme inducing drugs such as phenobarbital may decrease plasma concentrations of itraconazole and ketoconazole sufficiently to reduce its efficacy. Fluconazole does not appear to be much affected.

Antibiotics:

Doxycycline – 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.

Antineoplastics:

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

Antiprotozoals:

Metronidazole – Plasma concentrations are increased by phenobarbital, with a consequent reduction in the efficacy 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, such as haloperidol and phenothiazines, may antagonize the antiepileptics activity of phenobarbital by lowering the convulsive threshold.

Chloropromazine – 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 100 mg 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 150 mg daily was required to restore concentrations. The tipranavir/ritonair 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:
Dihydropyramide 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 than 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 give *frusemide* 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 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 phenobarbital have been most frequently implicated. These drugs increase the clearance if both oestrogens and progestogens by enzyme induction, so diminish their effects.

Immunosuppressants:
Cyclosporin and *tacrolimus* – Clearance have been shown to be increased by barbituates.

Theophylline:
Theophylline – Although phenobarbital 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.

Anaesthetics, halogenated hydrocarbon:
Halothane and *enflurane* – Barbiturates may increase the metabolism of anesthetic agents leading to increased risk of hepatotoxicity.

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. Co-administration of valproate and phenobarbital increases the risk of valproate-associated encephalopathy and/or increased ammonia levels.

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 if 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-hyroxycholecalciferol concentrations, and elevated alkaline phosphatase.

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:
Alkalinising the urine may diminish the effects of barbiturates due to increased excretion.

Stiripentol:
Phenobarbital should not be used in conjunction with stiripentol (medicinal product used to treat Dravet's syndrome). If co-administration is inevitable, clinical monitoring of phenobarbital serum concentrations with possible dose adjustments is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Category D

Risk related to antiepileptic medical products in general:

Specialist medical advice regarding the potential risks to a fetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment and especially to women planning pregnancy and women who are pregnant.

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant. In pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.

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;
- adequate folic acid supplementation 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.

Risks related to phenobarbital:

Phenobarbital readily crosses the placenta following oral administration and is distributed throughout fetal tissue the highest concentrations being found in the placenta, fetal liver and brain. Animal studies (literature data) have shown reproductive toxicity in rodents (see section 5.3).

Phenobarbital therapy in pregnant women with epilepsy presents a risk to the fetus in terms of major and minor congenital defects including congenital craniofacial and cardia defects, digital abnormalities and less commonly cleft lip and palate. Studies in women with epilepsy who were exposed to phenobarbital during pregnancy identified a frequency of major malformations of 6-7% in their offspring compared to the background rate in the general population of 2-3%. Studies have found the risk of congenital malformations following in-utero exposure to phenobarbital to be dose-dependent, however no dose has been found to be without risk. Therefore, the lowest effective dose should be used.

In neonates:

Data from a registry study suggest an increase in the risk of infants born small for gestational

age or with reduced body length, to women with epilepsy who were exposed to phenobarbital during pregnancy compared to women exposed to lamotrigine monotherapy during pregnancy.

Adverse effects on neurobehavioral development have also been reported. Studies investigating neurobehavioral development have also been reported. Studies investigating neurodevelopmental effects of prenatally administered phenobarbital were mostly small in numbers; however significant negative effects on neurodevelopment and IQ were found following in utero and postnatal exposure. Pre-clinical studies have also reported adverse neurodevelopment effects (see section 5.3).

Haemorrhage at birth and addiction are also a risk. Prophylactic treatment with vitamin K1 for the mother before delivery (as well as the neonate) is recommended and the neonate should be monitored for signs of bleeding.

Use of barbiturates throughout the third trimester of pregnancy may result in physical dependence and subsequent withdrawal symptoms in the neonate such as sedation, hypotonia and sucking disorder. 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.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

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

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.

4.8 Undesirable effects

Undesirable effects are presented below by MedDRA System Organ Class, using the following frequency convention.

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

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 section 4.4 Special warnings and precautions for use regarding withdrawal symptoms). Tolerance to the hypnotic effects may develop. Refer to section 4.6 Overdose for the effects of excessive doses.

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

Psychiatric Disorders	
Very common	Confusion
Common	'Hangover' effects, disorientation, mental confusion, depression, excitement, irritability, hyperexcitability, restlessness, tolerance and dependence, psychic or physical dependence
Uncommon	Depressed moods
Less frequent to rare	Profound shock, lowered body temperature, prolonged coma, depressed or absent reflexes, nystagmus
Nervous System Disorders	
Very common	Drowsiness, lethargy, dizziness, headache, ataxia, cognitive disorders, sedation (appears to lessen with use)
Blood and Lymphatic System Disorders	
Uncommon	Folate deficiency, bone marrow damage, megaloblastic anaemia
Less frequent to rare	Thrombocytopenia, agranulocytosis
Not known	Blood count changes such as leucocytosis, lymphocytosis, leucopenia
Vascular Disorders	
Uncommon	Hypotension, syncope, bradycardia, vasodilatation, circulatory disorders accompanied by arterial hypotension or even shock
Less frequent to rare	Peripheral vascular collapse, feeble heartbeat, circulatory failure
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Significant respiratory depression, bronchospasm or

	laryngospasm
Less frequent to rare	Apnoea
Immune System Disorders	
Common	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.
Uncommon	Intolerance reactions (fever, hepatic disorders, hepatitis, lymph node swelling, leucocytosis (increase in the number of white blood cells), lymphocytosis, increased sensitivity to light (photosensitisation), severe skin reactions e.g. exfoliative dermatitis, erythema multiforme (see also "*Skin and subcutaneous tissue disorders*"
Not known	Allergic cross-reactions with other antiepileptics
Skin and Subcutaneous Tissue Disorders	
Uncommon	Injection site reactions, erythroderma, urticaria and angioedema
Less frequent to rare	Stevens Johnson syndrome, toxic epidermal necrolysis and local necrosis following extravasation after intravenous or subcutaneous injection
Not known	Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), pemphigus vulgaris (severe skin disease with formation of blisters)
Renal and Urinary Disorders	
Uncommon	Renal damage
Less frequent to rare	Renal failure
Gastrointestinal Disorders	
Uncommon	Nausea, vomiting, diarrhoea, constipation, upper abdominal discomfort
Not known	Gingival enlargement
Hepatobiliary Disorders	
Uncommon	Hepatitis, jaundice
Metabolic and Nutritional Disorders	
Uncommon	Hypocalcaemia
Less frequent or rare	Osteomalacia, rickets
Musculoskeletal and Connective Tissue Disorders	
Very rare	Dupuytren's contracture, which usually occurs bilaterally, frequently accompanied by thickening of the finger joints and proliferation of connective tissue on the soles of the feet, periarthritis humeroscapularis ("frozen shoulder")
Less frequent or rare	Reduce bone mineral density, increase the risk of fractures, osteoporosis
Not known	General joint pain
Reproductive System and Breast Disorders	

Very common	Disorders of sexual function (reduced libido, impotence)
General Disorders and Administration Site Conditions	
Very common	Tiredness (sleepiness, weariness, muziness, prolonged reaction time)
Investigations	
Not known	Reduction of serum concentrations of thyroid hormones, in particular on combined treatment with other antiepileptics, reduction in folic acid levels.
Neonates Exposed to Phenobarbitone *In Utero*	
Common	Drug dependency, symptoms resembling Vitamin K deficiency

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

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.

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 arousal 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions: Phenobarbital is a long-acting 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. 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.

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-anaesthetic 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 anaesthetic 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:

Phenobarbital is readily absorbed from the gastro-intestinal tract, although it is relatively lipid-insoluble and may require and 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 172micromoles 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.

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.

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

Carcinogenicity
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 thorotrast, a drug known to cause hepatic carcinomas. When patients who had received thorotrast 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, magnesium stearate, purified talc, and wheat starch.

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.

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

Blister packs of 500 tablets.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Controlled Drug C5

8. SPONSOR

Noumed Pharmaceuticals Limited
Auckland, New Zealand
Freephone 0800 527 545

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

05 December 2024

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
4.4 Special warnings and precautions for use	Updated information to align with international prescription information.
4.5 Interaction with other medicines and other forms of interaction	Updated information to align with international prescription information.
4.6 Fertility, pregnancy and lactation	Updated information to align with international prescription information. Information relating to carcinotoxicity moved to Section 5.3.
4.8 Undesirable effects	Updated information to align with international prescription information. Added instructions for reporting suspected adverse reactions.
4.9 Overdose	Updated information on treatment to align with international prescription information. Added contact number for National

	Poisons Centre.
5.1 Pharmacodynamic properties	Updated recent studies on sedative-hypnotic and anticonvulsant effects of barbiturates to align with international prescription information.
5.3 Preclinical safety data	Updated information on genotoxicity and carcinogenicity to align with international prescription information.