

# DATA SHEET

## PHENOBARBITONE BP (15mg and 30mg) TABLETS

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### PRESENTATION

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Phenobarbitone BP 15mg Tablets  
Phenobarbitone BP 30mg Tablets  
15mg White normal convex 5.0mm tablet  
30mg White normal convex 5.6mm tablet

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### USES

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#### ***Actions***

Phenobarbitone 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 Phenobarbitone antiepileptic treatment continues.

#### ***Pharmacokinetics***

Phenobarbitone 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:**

Phenobarbitone 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. Phenobarbitone 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 Phenobarbitone kinetics. Monitoring of plasma concentrations has been performed as an aid in assessing control and the therapeutic range of plasma-phenobarbitone is usually quoted as being 10 to 40 mcg per ml (43 to 172 micromoles per litre)

Phenobarbitone 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.

**Indications**

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

Phenobarbitone 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.

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**DOSAGE AND ADMINISTRATION**

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Phenobarbitone 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 172micromoles per litre). Up to 350mg daily in divided doses may be taken.

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## **CONTRAINDICATIONS**

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Hypersensitivity to barbituric acid derivatives. Phenobarbitone 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. Phenobarbitone 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. Phenobarbitone should not be administered to elderly patients who exhibit nocturnal confusion or restlessness from sedative hypnotic drugs or to persons who are known to be, or are likely to become, dependent on sedative hypnotic medications.

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## **WARNINGS AND PRECAUTIONS**

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Phenobarbitone should be used with care in children and elderly patients, in those in 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 Phenobarbitone therapy in epileptic patients.

The effects of Phenobarbitone and other barbiturates are enhanced by concurrent administration of other CNS depressants including alcohol. Valproic acid has been reported to cause rises in Phenobarbitone (and primidone) concentrations in plasma.

Phenobarbitone 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 Phenobarbitone 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.

## **Use in Pregnancy and Lactation**

### **Pregnancy**

#### Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

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

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of fetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

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

The use in pregnancy of phenobarbitone has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability. Barbiturates can give rise to hypotension, respiratory depression and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration during labour should be avoided.

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

The serum level of phenobarbitone 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**

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

### **Effects on ability to drive and use machinery**

Phenobarbitone 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 Phenobarbitone, should not take charge of vehicles, or machinery where loss of attention could cause accidents.

### **Carcinogenesis, mutagenesis, impairment of fertility**

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

Genotoxicity studies for gene mutations and chromosome aberrations have given mixed results, however tests for DNA damage or repair have been negative. In a 29 year epidemiological study of 9,136 patients who were treated on an anticonvulsant protocol that included phenobarbitone, results indicated a higher than normal incidence of hepatic carcinoma. Previously some of the patients had been treated with 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.

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## ADVERSE EFFECTS

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Adverse effects include the following:

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

The most frequent adverse effect following administration of Phenobarbitone is sedation, but this often becomes less marked with continued administration. Like some other antiepileptic agents Phenobarbitone 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.

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

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## INTERACTIONS

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**Antiepileptics.** Interactions may occur if Phenobarbitone is given with other antiepileptic agents, of which probably the most significant is the interaction with valproic acid. Valproate results in an increase in plasma-phenobarbitone concentration that has been reported to range from 17 to 48%, and it may be necessary to reduce the dose of Phenobarbitone in some patients. The mechanism for the increase appears to be inhibition of the metabolism of Phenobarbitone, resulting in reduced clearance. However, it is worthy of note that Phenobarbitone reciprocally increases the clearance of valproate, thus potentially requiring the valproate dose to be adjusted too.

A similarly complex interaction exists between Phenobarbitone and phenytoin. Phenytoin may cause a rise in plasma concentrations of Phenobarbitone 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 Phenobarbitone induces the metabolism of phenytoin it is also, as stated, a competitive inhibitor and in practice the two affects appear to balance out, with rarely any need for dose adjustment.

The effects of Phenobarbitone and other barbiturates are enhanced by concurrent administration of other CNS depressants including alcohol.

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## OVERDOSAGE

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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 Phenobarbitone 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.

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## **PHARMACEUTICAL PRECAUTIONS**

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Shelf life is 60 months from the date of manufacture. Store below 25°C.

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## **MEDICINE CLASSIFICATION**

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Controlled Drug C5

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## **PACKAGE QUANTITIES**

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Blister packs of 500 tablets.

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## **FURTHER INFORMATION**

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Keep out of reach of children.

This product also contains Magnesium Stearate, Purified Talc, Wheat Starch and Lactose.

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## **NAME AND ADDRESS**

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## **DATE OF PREPARATION**

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March 4<sup>th</sup>, 2009