SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenobarbital Pharmvit 60 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg Phenobarbital.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet.

Appearance: Pale orange, circular, biconvex tablet or pale orange , circular , biconvex tablet embossed PV on one side and P over 60 on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For all forms of epilepsy except absence seizures.

4.2. Posology and Method of Administration

Adults and the elderly: 60 - 180 mg daily at night.
Children: 5 - 8 mg per kg bodyweight daily.

Elderly: Phenobarbital clearance diminishes in the elderly. Therefore the dose of phenobarbital is usually lower in elderly patients.

The dose of phenobarbital should be adjusted to meet the needs of individual patients. This usually requires plasma concentration of 15 to 40 micrograms/ml (65 to 170 micromoles/litre).

Caution must be exercised in the treatment of elderly patients with careful monitoring of their condition.

Administration: Oral; the tablets should be swallowed with water.

4.3. Contraindications

1. Known hypersensitivity to barbiturates.
2. Hypersensitivity to any of the ingredients in this medicine.
3. Acute intermittent porphyria.
4. Severe respiratory depression.
5. Severe impairment of renal and hepatic function.

4.4 Special warnings and precautions for use

Phenobarbital should be used with caution in the young, debilitated or senile patients and those with renal impairment, existing liver disease or respiratory depression (should be avoided if severe).

Prolonged use may result in the dependence of the alcohol-barbiturate type and particular care should be taken in treating patients with a history of drug abuse or alcoholism.

Avoid sudden withdrawal to prevent rebound seizures.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Phenobarbital.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Steven-Johnson syndrome and toxic epidermal necrolysis

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of phenobarbital. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Phenobarbital treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of phenobarbital, phenobarbital must not be re-started in this patient at any time.

Phenobarbital may interfere with some laboratory tests including metyrapone test, phenlolamine tests and serum bilirubin estimation

Care should be used in the following situations:

• Patients with the rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose – galactose malabsorption should not take this medicine

• Respiratory depression (avoid if severe)

• Young, debilitated or senile patients

• Renal impairment

• Existing liver disease

• Sudden withdrawal should be avoided as severe withdrawal syndrome (rebound insomnia, anxiety, tremor, dizziness, nausea, fits and delirium) may be precipitated

• Acute chronic pain – paradoxical excitement may be induced or important symptoms masked.

• Prolonged use may result in dependence of the alcohol-barbiturate type. Care should be taken in treating patients with a history of drug abuse or alcoholism.

4.5. Interactions with other Medicaments and other forms of Interaction

Effects on Phenobarbital

• Alcohol – concurrent administration with alcohol may lead to an additive CNS depressant effect. This is likely with concurrent administration with other CNS depressants.

• Antidepressants – including MAOIs, SSRIs and tricyclics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold

• Antiepileptics - phenobarbital plasma concentrations increased by oxcarbazepine, phenytoin and sodium valproate. Vigabatrin possibly decreases phenobarbital plasma concentrations.

• Antipsychotics – concurrent use of chlorpromazine and thioridazine with phenobarbital can reduce the serum levels of either drug.

• Folic acid – if folic acid supplements are given to treat folate deficiency, which can be caused by the use of phenobarbital, the serum phenobarbital levels may fall, leading to decreased seizure control in some patients. (see section 4.6).

• Memantine – the effect of Phenobarbital is possibly reduced.

• Methylphenidate – plasma concentration of Phenobarbital is possibly increased.

• St John's wort (Hypericum perforatum) – the effect of phenobarbital can be reduced by concomitant use of the herbal remedy St John's wort.

Effects of phenobarbital on other medicines

Phenobarbital increases the rate of metabolism reducing serum concentrations of the following drugs:

• Anti-arrhythmics – disopyramide and quinidine loss of arrhythmia control is possible. Plasma levels of antiarrhymics should be monitored, if phenobarbital is added or withdrawn. Changes in dosage may be necessary.

• Antibacterials – chloramphenicol, doxycycline, metronidazole and rifampicin. Avoid concomitant use of telithromycin during and for 2 weeks after Phenobarbital.

• Anticoagulants.

• Antidepressants – paroxetine, mianserin and tricyclic antidepressants.

• Antiepileptics – carbamazepine, lamotrigine, tiagabine, zonisamide, primidone and possibly ethosuxamide.

• Antifungals – the antifungal effects of griseofulvin can be reduced or even abolished by concurrent use. Phenobarbital possibly reduces plasma concentrations of itraconazole or posaconazole. Avoid concomitant use of voriconazole.

• Antipsychotics – phenobarbital possibly reduces concentration of aripiprazole.

• Antivirals – phenobarbital possibly reduces plasma levels of abacavir, amprenavir, darunavir, lopinavir, indinavir, nelfinavir, saquinavir.

• Anxiolytics and Hypnotics – clonazepam.

• Aprepitant – phenobarbital possibly reduces plasma concentration of aprepitant.

• Beta-blockers – metoprolol, timolol and possibly propranolol.

• Calcium channel blockers – phenobarbital causes reduced levels of felodipine, isradipine, diltiazem, verapamil, nimodipine and nifedipine and an increase in dosage may be required.

• Cardiac Glycosides – blood levels of digitoxin can be halved by concurrent use.

• Ciclosporin or tacrolimus.

• Corticosteroids.

• Cytotoxics – phenobarbital possibly reduces the plasma levels of etoposide or irinotecan.

• Diuretics – concomitant use with eplerenone should be avoided.

• Haloperidol- serum levels are approximately halved by concurrent used with phenobarbital.

• Hormone Antagonists – gestrinone and possibly toremifene.

• Methadone – levels can be reduced by concurrent use of phenobarbital and withdrawal symptoms have been reported in patients maintained on methadone when phenobarbital has been added. Increases in the methadone dosage may be necessary.

• Montelukast.

• Oestrogens – reduced contraceptive effect.

• Progestogens – reduced contraceptive effect.

• Sodium oxybate – enhanced effects, avoid concomitant use.

• Theophylline – may require an increase in theophylline dose.

• Thyroid hormones-may increase requirements for thyroid hormones in hypothyroidism.

• Tibolone

• Tropisetron

• Vitamins – barbiturates possibly increase requirements for vitamin D

Phenobarbital may interfere with some laboratory tests including metyrapone test, phenlolamine tests and serum bilirubin estimation.

4.6. Fertility, pregnancy and lactation

Risk related to antiepileptic medicinal products in general
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 breakthrough seizures that could have serious consequences for the woman and the unborn child. As a general principle, monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs appear to be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Risk 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. Phenobarbital therapy in epileptic pregnant women presents a risk to the fetus in terms of major and minor congenital defects including congenital craniofacial and cardiac 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.

Adverse effects on 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.
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.

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, the neonate should be monitored for signs of bleeding.
Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy (see section 4.5).

The use of phenobarbital in pregnancy, especially the first and third trimesters should be avoided unless it is considered to be essential.. Phenobarbital can cross the placental barrier and there is an increased risk of teratogenicity. The risk of teratogenic effects developing appears to be greater if more than one antiepileptic drug is administered. Neonatal bleeding may occur and prophylactic treatment with vitamin K1 for the mother before delivery (as well as for the neonate) is recommended.

The risk to the mother, however is greater if phenobarbital is withheld and seizure control is lost. The risk: benefit balance, in this case, favours continued use of the drug during pregnancy at the lowest possible level to control seizures.

Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy. Folic acid supplementation during pregnancy can help to reduce the risk of neural defects to the infant.

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. Adverse effects on neurobehavioral development have also been reported.

Phenobarbital is excreted into breast milk and there is a small risk of neonatal sedation. Breast-feeding is therefore not advisable.

4.7. Effects on Ability to Drive and Use Machines

Phenobarbital may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery. If patients are affected they should not drive or operate machinery.

4.8. Undesirable Effects

• *Blood and the lymphatic system disorders:* megaloblastic anaemia (due to folate deficiency), agranulocytosis, thrombocytopenia.

• *Metabolism and nutritional disorders:* osteomalacia have been associated with barbiturate administration, rickets.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenobarbital. The mechanism by which phenobarbital affects bone metabolism has not been identified.

• *Psychiatric disorders:* paradoxical reaction (unusual excitement), hallucinations, restlessness and confusion in the elderly, mental depression, memory and cognitive impairment, drowsiness, lethargy.

• *Nervous system disorders:* hyperactivity, behavioural disturbances in children, ataxia, nystagmus.

• *Cardiac disorders:* hypotension.

• *Respiratory disorders:* respiratory depression.

• *Hepato-bilary:* hepatitis, cholestasis.

• *Skin and subcutaneous tissue disorders:* allergic skin reactions (maculopapular morbilliform or scarlatiniform rashes), other skin reactions such as exfoliative dermatitis, erythema multiforme and toxic epidermal necrolysis are extremely rare.

Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

Frequency: very rare

• *General disorders and administration site conditions:* antiepileptic hypersensitivity syndrome (features include fever, rash, lymphadenopathy, lymphocytosis, eosinophilia, haematological abnormalities, hepatic and other organ involvement including renal and pulmonary systems which may become life threatening).

4.9. Overdose

Toxicity varies between patients; tolerance will develop with chronic use. Features of poisoning are to be expected after ingestion of 1g in adults.

Features:

Drowsiness, dysarthria, ataxia, nystagmus and disinhibition. There may also be coma, cardiovascular collapse, cardiac arrest, hypotension, hypotonia, hyporeflexia, hypothermia, hypotension and respiratory depression. The duration and depth of cerebral depression varies with the dose and tolerance of the patient.
Barbiturates decrease gut motility, which may lead to slow onset and worsening of symptoms or cyclical improvement and worsening of symptoms.

Management:
Supportive measures alone may be sufficient if symptoms are mild. If within four hours of ingestion, gastric aspiration or lavage may be of benefit in adults. The prime objective of treatment is to maintain vital functions while the majority of the drug is metabolised by hepatic enzymes.
Consider activated charcoal (50g for an adult, 10-15g for a child under 5 years) if more than 10mg/kg body weight of phenobarbital has been ingested within 1 hour, provided the airway can be protected. Repeat dose activated charcoal is the best method of enhancing elimination of phenobarbital in symptomatic patients. In severe hypotension dopamine or dobutamine can be used. Treat rhabdomyolysis with urinary alkalinistion. Haemodialysis or haemofiltration may be required for cases of acute renal or severe hyperkalaemia.
Charcoal haemoperfusion is the treatment of choice for the majority of patients with severe barbiturate poisoning who fail to improve, or who deteriorate despite good supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ATC CODE: N03A A02

Phenobarbital is a long-acting barbiturate, which because of its depressant effect on the motor cortex, is used in the treatment of epilepsy. The barbiturates reversibly depress the activity of all excitable tissues.
The ability of phenobarbital to exert maximum anticonvulsant action at doses below those required for hypnosis, determine its clinical use as an anti-epileptic. It limits the spread of seizure and elevates the seizure threshold.

Phenobarbital has a widespread depressant action on cerebral function. It has sedative effects and has some protective action against all varieties of human partial and generalised epilepsy, with the exception of absence seizures. Phenobarbital is also effective in preventing seizures in the corresponding experimental animal models of epilepsy. In different studies phenobarbital appears to have had inconsistent effects in suppressing experimental epileptic foci, and epileptic after-discharges, but it inhibits synaptic transmission, at least in the spinal cord. The drug's probable biochemical mechanism of action is through prolonging the opening time of Cl^- ion channels in postsynaptic neuronal membranes. This effect causes membrane hyperpolarisation and thus impairs nerve impulse propagation. Phenobarbital also decreases intraneuronal Na^+ concentrations, and inhibits Ca^{2+} influx into depolarised synaptosomes. It raises brain serotonin levels, and inhibits noradrenaline **(**norepinephrine) reuptake into synaptosomes. These additional biochemical actions may contribute towards the anticonvulsant effects of the drug.

5.2. Pharmacokinetic Properties

Absorption – phenobarbital is readily absorbed from the gastrointestinal tract, although it is relatively lipid – insoluble; peak concentrations are reached in about 2 hours after oral administration. By the oral route the rate determining step in absorption from the empty stomach is dissolution and dispersal of the drug in the gastrointestinal tract.

Distribution – It is 45 to 60% bound to plasma proteins and bound to a similar extent in tissues including the brain. Phenobarbital crosses the placental barrier and is distributed into breast milk. The volume of distribution is approximately 0.5 litres per kilogram.

Metabolism – The plasma half-life of phenobarbital is about 100 hours in adults, somewhat longer in neonates while it is shorter and more variable in children. There is considerable interindividual variation in phenobarbital kinetics. Phenobarbital in only partly metabolised in the liver.

Elimination –The pKa of phenobarbital is 7.3 and up to 25% of a dose is eliminated by pH dependent renal excretion of the unchanged drug at normal urinary pH. The amount excreted increases with increased alkalinity of the urine. The remainder is inactivated by hepatic microsomal enzymes. Although the drug competes with other weak acids for binding to plasma albumin the only clinically important displacement is that of thyroxine. The absorption of dicumarol and griseofulvin are decreased by phenobarbital.

5.3. Preclinical safety data

No preclinical safety data available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Maize starch, lactose monohydrate, sodium laurilsulfate, sodium starch glycollate, magnesium stearate, stearic acid, sunset yellow (E110).

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

3 years.

6.4. Special Precautions for Storage

Do not store above 25°C.
Keep the container tightly closed.
Store in the original container.

6.5. Nature and contents of container

Polypropylene tubes with low density polyethylene caps.

Pack sizes: 28 and 1,000 tablets.

6.6. Instruction for use and handling (, and disposal)

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Pharmvit Limited
Unit 13, Metropolitan Trading Estate
Derby Road
Greenford
Middlesex UB6 8UJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04556/0049

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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