Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Phenobarbital 30 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg Phenobarbital as the active substance.

Excipient(s) with known effect
Each tablet contains 18.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Round, white, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an anticonvulsant for the treatment of all forms of epilepsy except absence seizures.

4.2 Posology and method of administration

The dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires plasma concentrations of 10-40 µg/ml (40-160 µmol/litre).

Adults:
The recommended dose by mouth is 60-180mg daily usually taken at night.

Paediatric population:
5-8 mg/kg/day.

Elderly
The use of Phenobarbital must be the subject of a clinical risk/benefit assessment. Dose schedules may need to be reduced.

Method of administration
Oral.

4.3 Contraindications

1. Acute intermittent porphyria.
2. Severe impairment of renal, hepatic or respiratory function.
3. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings:
Prolonged administration of barbiturates may induce psychic dependence and even addiction in some individuals. A severe withdrawal syndrome may occur.

Withdrawal or transition to another type of anti-epileptic therapy should be gradual to avoid rebound seizures.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic 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.

The use of phenobarbital during labour and delivery is not recommended due to the risk to the foetus. In a life threatening situation a risk/benefit assessment must be made. If phenobarbital is used under these circumstances the presence of resuscitation equipment is recommended.

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 suspected 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 restarted in this patient at any time.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance and the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions:

1. Barbiturates should only be used with great caution and at reduced dosage in infants, the elderly or malnourished, or in those with marked renal or hepatic dysfunction, shock or respiratory depression or Addison's disease.
2. A cumulative effect may occur with the barbiturates leading to features of chronic poisoning including headache, depression, slurred speech.
3. Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking phenobarbital due to the risk of decreased plasma concentrations and reduced clinical effects of phenobarbital (see 4.5 Interactions).

Women of childbearing potential
Phenobarbital may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenobarbital may increase the risk for congenital malformations approximately 2- to 3-fold (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 should be fully informed of the potential risk to the foetus 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 containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods (see sections 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.

4.5 Interaction with other medicinal products and other forms of interactions

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

Concomitant administration of phenobarbital and antipsychotics (e.g haloperidol, chlorpromazine and thioridazine) may result in antagonism of the anticonvulsant effect and lowering of the convulsive threshold. Phenobarbital also accelerates the metabolism of haloperidol.

Concomitant administration of phenobarbital and antidepressants may also result in antagonism of the anticonvulsant effect and lowering of the convulsive threshold. Metabolism of mianserin and tricyclic antidepressants such as nortriptyline may be accelerated.

The plasma concentrations of indinavir, lopinavir, nelfinavir and saquinavir may be reduced by concomitant administration of phenobarbital.

Phenobarbital therapy may increase vitamin D requirements.

The effect of phenobarbital may possibly be reduced by memantine.

The metabolism of toremifene may be accelerated by phenobarbital.

Telithromycin should not be given during or within 2 weeks of discontinuation of treatment with phenobarbital due to reduced plasma concentrations of the antibiotic.

The plasma concentration of tropisetron is reduced by concomitant use of phenobarbital.

Folic acid or folinic acid may possibly reduce plasma concentrations of phenobarbital.

Phenobarbital has been shown to reduce the response to thyroxine. Prescribers should be alert for changes in thyroid status if barbiturates are added or withdrawn from patients being treated for hypothyroidism.

Valproic acid (anti-epileptic) has been reported to cause rises in phenobarbital (and primidone) concentrations in plasma. Concomitant administration of phenobarbital and other anti-epileptics may increase the toxicity of phenobarbital without a corresponding increase in the anti-epileptic effect. Phenobarbital often lowers the plasma concentration of carbamazepine, clonazepam, lamotrigine, phenytoin (but may also raise), and valproate. It sometimes lowers plasma concentration of ethosuximide.

Patients treated concomitantly with valproate and phenobarbital should be monitored for signs of hyperammonemia. In half of the reported cases hyperammonaemia was asymptomatic and does not necessarily result in clinical encephalopathy.

Because of the ability of phenobarbital to induce the oxidising enzyme systems found in hepatic endoplasmic reticulum, any drug which undergoes metabolism by this system is a potential candidate for an interaction with phenobarbital or similar barbiturates. Effects on the metabolism of drugs from a variety of classes have been reported, these include: anticoagulants e.g. warfarin, antibiotics e.g. doxycycline, metronidazole, rifampicin, chloramphenicol, beta blockers which undergo hepatic metabolism e.g. propranolol, verapamil, nimodipine, nifedipine, prednisolone, dexamethasone, cimetidine, methadone and pethidine (may require an increase in dosage), systemic steroids and oral contraceptives (possibly leading to a contraceptive failure), anti-arrhythmics e.g. disopyramide and quinidine, anti-fungals e.g. griseofulvin, voriconozole and itraconazole, digitoxin, high doses of theophylline, leukopritionine antagonist montelukast, phenylbutazone, phenothiazines, cyclosporin.

The effect of phenobarbital can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum)*. This is due to induction of drug metabolising enzymes by St. John's wort. Herbal preparations containing St.

John's wort should therefore not be combined with phenobarbital. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St. John's wort, check the anticonvulsant levels and stop St. John's wort. Anticonvulsant levels may increase on stopping St. John's wort. The dose of anticonvulsant may need adjusting.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general

Specialist medical advice regarding the potential risks to a foetus 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.

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.

Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Risks related to phenobarbital

Phenobarbital crosses the placenta. Animal studies (literature data) have shown reproductive toxicity in rodents (see section 5.3).

Data from meta-analysis and observational studies showed a risk of major malformations about 2 to 3 times higher than the baseline risk of major malformations in the general population (which is 2-3%). The risk is dose-dependent; however, no dose has been found to be without risk. Phenobarbital monotherapy is associated with an increased risk of major congenital malformations, including cleft lip and palate and cardiovascular malformations. Other malformations involving various body systems including cases of hypospadias, facial dysmorphic features, neural tube effects, craniofacial dysmorphia (microcephaly) and digital abnormalities have also been reported.

Data from a registry study suggest an increase in the risk of infants born small for gestational age or with reduced body length, compared to lamotrigine monotherapy.

Neurodevelopmental disorders have been reported among children exposed to phenobarbital during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to phenobarbital during pregnancy are contradictory and a risk cannot be excluded. Pre-clinical studies have also reported adverse neurodevelopment effects (see section 5.3).

Phenobarbital should not be used during pregnancy unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options.

If, following re-evaluation of treatment with phenobarbital, no other treatment option is suitable, the lowest effective dose of phenobarbital should be used. The woman should be fully informed of and understand the risks related to the use of phenobarbital during pregnancy.

When used in the third trimester of pregnancy, withdrawal symptoms may occur in the neonate, including sedation, hypotonia and sucking disorder.

Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy.

Breast-feeding

Phenobarbital crosses the placenta and small amounts are found in the milk of nursing mothers. The risk of sedation in the infant is probably small however breastfeeding is not recommended.

Women of childbearing potential/Contraception

Phenobarbital should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

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 with phenobarbital 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 containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods while on treatment with phenobarbital, e.g. two complementary forms of contraception including a barrier method, oral contraceptive containing higher doses of estrogen, or a non-hormonal intrauterine device (see section 4.5).

Women of childbearing potential should be informed of and understand the risk of potential harm to the foetus associated with phenobarbital use during pregnancy and the importance of planning a pregnancy.

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

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant.

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.

4.7 Effects on ability to drive and use machines

This product may cause drowsiness or incoordination. Patients who take the medication should not drive or operate machinery unless it has been shown not to affect their physical or mental ability.

4.8 Undesirable effects

The most frequent adverse effect following administration of phenobarbital is sedation, but this often becomes less marked with continued administration.

As with other antiepileptic agents phenobarbital may produce subtle mood changes and impairment of cognition and memory which may not be apparent without testing. Mental depression may occur.

Undesirable effects associated with phenobarbital are listed using the MedDRA System organ classification below.

Blood and Lymphatic system disorders:
Agranulocytosis, megaloblastic anaemia, aplastic anaemia, thrombocytopenia and macrocytic anaemia

Vascular disorders:
Hypotension

Ear and labyrinth disorders:
Vertigo

Eye disorders:
Nystagmus

Hepatobilary disorders:
Hepatitis, cholestasis

Metabolism and nutrition disorders:
Folate deficiency, hypocalcaemia

Musculoskeletal and connective tissue disorders:
Osteomalacia, Dupuytren's contracture
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 has not yet been identified.

Nervous System Disorder:
Unsteadiness, incoordination, sedation, ataxia

Psychiatric disorders:
Mood changes, sedation, depression, paradoxical excitement, restlessness, impairment of cognition and memory

Respiratory, thoracic and mediastinal disorders:
Respiratory depression

Immune system disorders:
Hypersensitivity/anaphylactic reaction

Skin and subcutaneous tissue disorders:
Allergic skin reactions (maculopapular, morbilliform or scarlatiniform rashes). Other skin conditions include exfoliative dermatitis
Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS), Drug rash with Eosinophilia and Systemic Symtoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4). Frequency: Very rare

Paediatric and elderly population:
Paradoxical excitement, irritability and hyperexcitability may sometimes occur particularly in the elderly and children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

These include drowsiness, coma, hypotension, hypothermia, respiratory and cardiovascular depression. The duration and depth of cerebral depression varies with the dose and the tolerance of the patient.

Treatment

Supportive measures alone may be sufficient if symptoms are mild. If an overdose is taken by mouth and within 4 hours of ingestion, gastric aspiration or lavage may be of benefit to adults. The prime objective of treatment is to maintain vital functions, respiration, cardiovascular and renal functions and the electrolyte balance while the majority of the drug is metabolised by hepatic enzymes. Given normal renal function, forced alkaline diuresis (maintaining the urinary pH at approximately 8 by intravenous infusion) may enhance the excretion of the drug from the kidneys.
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

Pharmacodynamic Group: Barbiturates and derivatives
ATC code: N03AA

Phenobarbital is a long acting barbiturate with hypnotic and anti-convulsant properties. It has a depressant effect on the motor cortex.

Barbiturates act throughout the CNS, although not with equal potency in all regions. The mesencephalic reticular activating system is particularly sensitive to these drugs. In whatever region of the neuraxis, nonanaesthetic doses preferentially suppress polysynaptic responses. Facilitation is diminished and inhibition is usually enhanced.

5.2 Pharmacokinetic properties

Barbiturates are readily absorbed from the gastro-intestinal tract and most act within 30 minutes of ingestion, although the relatively lipid insoluble phenobarbital may require an hour or longer.

Phenobarbital is only about 40% bound to plasma proteins and is only partly metabolised in the liver. The plasma level for optimum response is 15-40mg per litre. About 25% of a dose is excreted in the urine unchanged. In patients with cirrhosis of the liver this value increases to about 50%. The rate is slow due to the re-adsorption of unchanged drug by kidney tubules. Excretion is increased by increasing the urine flow rate and/or the pH of the urine. It has a plasma half-life (T½) of about 75 hours in children and 100 hours in adults; this is increased in the elderly, in overdosage, and in renal or hepatic disease.

Phenobarbital crosses the placental barrier and small amounts are excreted in breast milk.

5.3 Preclinical safety data

Published studies reported teratogenic effects (morphological defects) in rodents exposed to phenobarbital. Cleft palate is reported consistently in all preclinical studies but other malformations are also reported (e.g. umbilical hernia, spina bifida, exencephaly, exomphalos plus fused ribs) in single studies or species.

In addition, although data from the published studies are inconsistent, phenobarbital given to rats/mice during gestation or early postnatal period was associated with adverse neurodevelopment effects, including alterations in locomotor activity, cognition and learning patterns

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Maize starch
Lactose Monohydrate
Sodium laurilsulfate
Magnesium stearate
Stearic acid
Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.
Keep container tightly closed.
Protect from light.

6.5 Nature and contents of container

Polypropylene tubes with low density polyethylene caps. High density polyethylene film is used as packing material.

Pack sizes: 21, 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
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8 MARKETING AUTHORISATION NUMBER

PA0126/019/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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