Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Phenobarbital Sodium 60mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 60mg of Phenobarbital sodium.

Each ml of solution contains 0.934g of propylene glycol

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

An anti-convulsant for the treatment of all forms of epilepsy except absence seizures.

4.2 Posology and method of administration

Route of Administration

By intramuscular, subcutaneous or, after dilution with 10 times its own volume of Water for Injection, by slow intravenous administration.

Adults

50-200mg as a single dose by intramuscular, subcutaneous or, after, by intravenous injection. Repeated, if necessary, after 6 hours.

Maximum daily intake 600mg.

Elderly

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

Children

3-5mg per kilogram body weight as a single dose by the intramuscular route.

4.3 Contraindications

- Acute intermittent porphyria.
- Severe renal, hepatic or respiratory dysfunction.
- Known hypersensitivity to barbiturates or any of the ingredients.

4.4 Special warnings and precautions for use

- 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 increased risk for Phenobarbital Sodium.

  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.
- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of phenobarbital sodium.
- 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 sodium 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 sodium, phenobarbital sodium must not be re-started in this patient at any time.
- 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.
- Phenobarbital should be used with caution in the young, elderly, senile or debilitated patient and those with renal impairment, existing liver disease or respiratory depression, (should be avoided if severe).
- Prolonged use may result in dependence of the alcohol-barbiturate type and care must be taken in treating patients with a history of drug abuse or alcoholism.
- Necrosis can occur at the site of subcutaneous injection.
- Withdrawal of the drug or transition to or from another form of anti-convulsant therapy must be gradual to avoid precipitating an increase in frequency of seizures.
- 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).

4.5 Interaction with other medicinal products and other forms of interaction

- Alcohol and other CNS depressants (for example, opiates and benzodiazepines), may have an additive effect.
- Phenobarbital causes hepatic microsomal enzyme induction which increases the rate of metabolism of some drugs and consequently serum concentrations of some drugs may be reduced. These include coumarin anticoagulants, digitoxin, disopyramide, quinidine, leukopritrionine antagonist montelukast, phenytoin, lamotrigine, carbamazepine, phenylbutazone, systemic steroids leading to a reduced effect and oral contraceptives (possibly leading to a contraceptive failure), phenothiazines, tricyclic antidepressants, griseofulvin and voriconozole, rifampicin, chloramphenicol, doxycycline, metronidazole, cyclosporin, calcium channel blocking agents (especially felodipine, verapamil, nimodipine and nifedipine - may require an increase in dosage) and theophylline.
- The plasma concentratioins of indinavir, lopinavir, nelfinavir and saquinavir may be reduced by concomitant administration of phenobarbitol.
- 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.
- The convulsive threshold may be lowered by simultaneous use of antipsychotic drugs. Phenobarbital also accelerates the metabolism of haloperidol.
- 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.
- Concomitant administration with other anti-epileptics (for example sodium valproate) may enhance toxicity without a corresponding increase in antiepileptic effect. Moreover, interactions (such as enhanced effect, increased sedation and reduced plasma concentrations) may complicate monitoring of treatment.
- 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 metabolizing 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 the 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

The use of phenobarbital within the 1st and 3rd trimesters should be avoided unless considered essential.

Phenobarbital can cross the placental barrier and the risk of teratogenicity is increased. Neonatal bleeding may occur due to depletion of foetal vitamin K_1 reserves and prophylactic treatment with vitamin K_1 for the mother before delivery may be necessary. Vitamin K_1 should also be given to the neonate immediately after delivery. Neonates may develop withdrawal symptoms.

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

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.

4.7 Effects on ability to drive and use machines

Phenobarbital may cause drowsiness and therefore affect driving and the handling of machinery.

4.8 Undesirable effects

- Megaloblastic anaemia (due to folate deficiency). Agranulocytosis, aplastic anaemia, and macrocytic anaemia. Frequency: rare but severe effects.
- Mental depression and confusion, memory and cognitive impairment, hyperactivity and behavioural disturbance. Paradoxical excitement, irritability and hyperexcitability may sometimes occur particularly in the elderly and children. Restlessness in the elderly and hyperkinesia in children may also arise. Frequency: not known

- Drowsiness and lethargy. Frequency: not known
- Nystagmus. Frequency: not known
- Ataxia and respiratory depression. Frequency: not known
- Allergic skin reactions, maculopapular, morbilliform or scarlatiniform rashes can occur in a small proportion of patients. Severe reactions such as exfoliate 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
- Osteomalacia, hypokamcaemia and Dupuytren's contracture. Frequency: rare effects associated with continued use of the drug.
- Hepatitis and cholestasis have been associated with barbiturate administration. Frequency: not known

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

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

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

5.2 Pharmacokinetic properties

The plasma half life ($T_{½}$) is about 75 hours in children and about 100 hours in adults. In elderly patients, subjects of overdose and patients with renal or hepatic disease these values may increase.

Phenobarbital is only slowly taken up in body tissues and does not accumulate in body fat. It is about 40% plasma bound.

The plasma level for optimum response is 15-40mg per litre.

Metabolism occurs to a limited extent and this is principally in the liver. Excretion is mainly in the urine. 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. Under normal circumstances approximately 30% of the drug is excreted unchanged. In patients with cirrhosis of the liver this value increases to about 50%.

Phenobarbital crosses the placenta and is secreted in the milk of nursing mothers.

5.3 Preclinical safety data

No additional pre-clinical data of relevance to the prescriber is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Propylene glycol
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Keep the ampoule in the outer carton, in order to protect from light

6.5 Nature and contents of container

Clear Type I glass ampoules sold in cardboard outers of 10 ampoules.

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

For single use only.

Discard unused contents.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0361/005/003

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