SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenobarbital Sodium 30mg/ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 30mg of Phenobarbital Sodium

Excipient with known effect

Propylene Glycol: 90.000%v/v

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for Injection

Clear, colourless, solution practically free from particles

pH = 10.0 – 11.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults

50 - 200mg as a single dose by intramuscular, subcutaneous or, after dilution 1 in 10 with Water for Injection, by intravenous injection, repeated, if necessary, after 6 hours.

Paediatric population

3 - 5mg per kg body weight as a single dose by intramuscular injection.

Method of administration
Intramuscular, subcutaneous or intravenous injection

4.3 Contraindications

Hypersensitivity to phenobarbital, other barbiturates or to any of the excipients listed in section 6.1

Severe respiratory depression.

Acute intermittent porphyria.

Severe impairment of renal or hepatic function.

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 an 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.

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 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), pregnancy, breastfeeding and porphyria.

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.

Intravenous use must be preceded by dilution as described in section 4.2. Subcutaneous injection can cause tissue necrosis.

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.

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

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 their 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 their doctor immediately if they become pregnant or think they might be pregnant while on treatment with phenobarbital.

Excipient warning

The maximum daily dose of propylene glycol should be calculated based on the product containing 0.9g of propylene glycol per ml of undiluted product.

Propylene glycol in high doses may cause central nervous system side-effects, lactic acidosis, kidney and liver toxicity, increase in plasma osmolarity, and haemolytic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 - Phenobarbital has been shown to accelerate the metabolism of levothyroxine and liothyronine. Prescribers should be alert for changes in thyroid status if barbiturates are added or withdrawn from patients being treated for hypothyroidism.
- Tibolone
- Tropisetron
- Vitamins – barbiturates possibly increase requirements for vitamin D

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

4.6 Fertility, pregnancy and lactation

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 oestrogen, 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 their 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 their doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with phenobarbital.

Pregnancy

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 foetus in terms of major and minor congenital defects such as congenital craniofacial, digital abnormalities and, less commonly, cleft lip and palate. . 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.

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.

The risk of teratogenic effects developing appears to be greater if more than one antiepileptic drug is administered. 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.

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.

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). Folic supplementation during pregnancy can help to counteract the risk of neural tube defects.

4.7 Effects on ability to drive and use machines

Phenobarbital may impair the mental and/or physical abilities of the patient. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Antiepileptic hypersensitivity syndrome may occur. Symptoms include fever, rash, lymphadenopathy and hepatitis.

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

Metabolism and nutritional disorders: osteomalacia, rickets.

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

Musculoskeletal, connective tissue and bone disorders: Frequency not known: Dupuytren's contracture, frozen shoulder, arthralgia, osteomalacia, 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.

Reproductive system and breast disorders
Frequency not known: Peyronie's disease.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for Yellow card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms. These include drowsiness, dysarthria, ataxia, nystagmus and disinhibition. There may also be coma, hypotension, hypotonia, hyporeflexia, hypothermia, and 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 of solution for injection is given,or erroneously taken by mouth, 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

ATC Code: N03A A02 (antiepileptics, barbiturates and derivatives).

Phenobarbital is a long-acting barbiturate, which because of its depressant effect on the motor cortex, is used in the treatment of epilepsy. Phenobarbital has a widespread depressant action on cerebral function.

It has selective anticonvulsant activity and, used in hypnotic doses, it alters the stages of sleep in a dose dependent manner.
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

Metabolism
The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. The half-life is increased in the elderly and in neonates and is prolonged by renal and hepatic disorders. There is a considerable interindividual variation in Phenobarbital kinetics. Phenobarbital is only partly metabolised in the liver.

It is about 40% plasma bound.

Elimination

Excretion is mainly in the urine (and is increased in alkaline urine) with about 30% of the drug unchanged. The remainder is inactivated in the liver.

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 and Water for Injection.

6.2 Incompatibilities

None stated.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Protect from light.

Do not store above 25°C

6.5 Nature and contents of container

Clear type 1 Ph Eur glass ampoules each containing sufficient product to allow removal of 1ml. Sold in cardboard outers of 10 ampoules.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 01883/6188R

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