SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenobarbital Colonis 50 mg/5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of suspension contains 50 mg phenobarbital (as phenobarbital sodium).

Excipient(s) with known effect

Each 1 ml of suspension contains 0.50 mg sodium benzoate and approx. 3.42 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

White to off-white homogenous suspension with characteristic lemon odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Phenobarbital oral suspension is an anticonvulsant indicated in adults and children for the treatment of all forms of epilepsy, except absence seizures. It may be used as monotherapy or in combination with another antiepileptic treatment.

4.2 Posology and method of administration

Posology

It may take more than two weeks for the medicine to reach sufficient levels in the bloodstream in order to control seizures. This also applies when the dose is adjusted.

When therapeutic drug monitoring is justified, current clinical practice guidelines for phenobarbital blood level monitoring should be followed.

Adults

2 to 3 mg/kg per day, taken once daily at bedtime.

Paediatric population (by weight)

-Less than 20 kg: 5 mg/kg per day, as one or two divided doses,

-Between 20 and 30 kg: 3 to 4 mg/kg per day, as one or two divided doses,

-Above 30 kg: 2 to 3 mg/kg per day, as one or two divided doses.

Method of administration

For oral use.

A 10 ml graduated oral syringe with intermediate graduations of 0.2 ml and a “Press-In” Bottle Adapter (PIBA) are provided with the product.

1. Shake the bottle well, before use.
2. Open the bottle and at first use insert the “Press-In” Bottle Adapter (PIBA).
3. Insert the syringe into the PIBA and draw out the required volume from the inverted bottle.
4. Remove the filled syringe from the bottle in the upright position.
5. Discharge the syringe contents into the mouth. Repeat steps 3 to 5 as needed to achieve the required dose.
6. Replace the cap on the bottle (PIBA remains in place).
7. Rinse the syringe with water and allow to air dry.

If you are giving Phenobarbital oral suspension to a child:

- Make sure that the child is sitting up or standing.
- Put the syringe into the child’s mouth, placing the barrel-opening in the area between the gums and the inside of the cheek.
- Push the plunger slowly, giving the child time to swallow the medicine as it squirts out. Do not push the plunger too quickly as the medicine may come out too quickly and the child may choke.
- Give the child some water to drink in order to ensure that all the medicine is washed down.

Note

If necessary, Phenobarbital oral suspension can be administered via intragastric feeding tubes (nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes). Tubes should be rinsed with 2 ml of water immediately after administration. For further information see section 6.6.

4.3 Contraindications

- Hypersensitivity to phenobarbital other barbiturates or to any of the excipients listed in Section 6.1.
- Severe respiratory depression.
- Severe hepatic or renal impairment.
- Acute intermittent porphyria.
- Treatment with cobicistat, rilpivirine, telaprevir, cholic acid, delamanid, daclatasvir, dasabuvir, ombitasvir-paritaprevir, ledipasvir, sofosbuvir or voriconazole (see section 4.5).
- In combination with St. John's wort.
- Hyperkinetic children.

4.4 Special warnings and precautions for use

Special warnings

Phenobarbital is not effective in absences and myoclonic seizures which can sometimes be aggravated.

The introduction of an antiepileptic drug may, rarely, be followed by relapse of seizures or the onset of a new form of seizure in the patient, irrespectively of the fluctuations observed in certain epileptic forms. With regard to phenobarbital, the origin of these aggravations can be due to inappropriate choice of medication with respect to the patient's seizure form, a modification of the concomitant antiepileptic treatment or a pharmacokinetic interaction with it, toxicity or overdose. There may be no other explanation than a paradoxical reaction.

Prolonged intake of phenobarbital (100 mg per day for 3 months) may result in the appearance of a dependence syndrome and particular care should be taken in treating patients with a history of drug abuse or alcoholism. Avoid sudden withdrawal to prevent rebound seizures.

Phenobarbital should be used with caution in the young, the elderly, in debilitated patients and in those with depressive disorders.

Suicidal risk

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents for several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic drugs has 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 oral suspension. 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.

Serious skin reactions

Serious skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN or Lyell's syndrome), drug hypersensitivity syndrome with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with phenobarbital treatment.

Patients should be informed of the signs and symptoms of serious skin lesions and be closely monitored. The risk of occurrence of SJS or TEN is greater during the first weeks of treatment.

Treatment should be discontinued at the first emergence of rash, mucosal lesions or any other manifestation of skin hypersensitivity.

Early diagnosis and immediate discontinuation of any suspect medication leads to better results in the management of SJS or TEN. Early cessation is associated with a better prognosis.

If SJS or TEN is developed during phenobarbital treatment, the patient should never take phenobarbital again.

Precautions for use

If hypersensitivity or hepatic disorders occur, treatment with phenobarbital should be discontinued.

Reduce the dosage in renal insufficiency, hepatic insufficiency (biological monitoring is advised, because of the risk of hepatic encephalopathy), in the elderly and in alcoholics.

There is still some debate on the effects of antiepileptics, including Phenobarbital, on bone metabolism. It is therefore recommended that Vitamin D supplementation is considered in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of Vitamin D or calcium. In children subjected to long-term treatment with phenobarbital, the addition of a prophylactic treatment for rickets: vitamin D2 (1200 to 2000 IU/day) or 25-OH-vitamin D3 is recommended.

Patients are advised to avoid alcohol while using this medicine. The concomitant administration of barbiturates and alcohol may lead to an additive CNS depressant effect, serious respiratory depression and a lowering of the lethal dose (see section 4.5).

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.

The risk-benefit ratio should be carefully reassessed at regular intervals during treatment, at puberty, and urgently in women of childbearing potential treated with phenobarbital, planning pregnancy or are pregnant.

Phenobarbital Colonis 50 mg/5 ml oral suspension contains sodium benzoate and sodium.

This medicinal product contains 0.5 mg sodium benzoate in each 1 ml of suspension.

Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to four weeks old).

This medicinal product contains 3.42 mg sodium in each 1 ml of suspension, equivalent to 0.17 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Patients treated concomitantly with valproate (or divalproate or valpromide) 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

Contraindication for concomitant use

- The effect of phenobarbital can be reduced by concomitant use of the herbal remedy St. John's wort (Hypericum perforatum). Risk of decreased plasma concentrations and anticonvulsant efficacy (see section 4.3).
- *Cholic acid* - antagonistic effect of phenobarbital (see section 4.3).

Precautions for concomitant use

- *Alcohol* - the concomitant administration of barbiturates and alcohol may lead to an additive CNS depressant effect, may produce very serious respiratory depression and a lowering of the lethal dose of phenobarbital (see section 4.4).
- *Analgesics* - plasma levels of phenobarbital may be increased when used in conjunction with dextropropoxyphene.
- *Antibacterials* - there is a possibility of increased phenobarbital levels during concomitant use of chloramphenicol.
- *Antidepressants* - including MAOIs, SSRIs and tricyclics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold.

Imipramine antidepressants promote the onset of generalized seizures. Clinical monitoring and possible increase in doses of antiepileptics.

- *Antiepileptics* - phenobarbital plasma concentrations increased by oxcarbazepine, phenytoin, stiripentol, felbamate and valproate.

Felbamate: Clinical monitoring, control of plasma concentrations of phenobarbital with dosage adjustment if necessary.

Phenytoin: In case of previous treatment with phenobarbital or primidone and addition of phenytoin, increase in plasma concentrations of phenobarbital which may lead to toxic signs (inhibition of metabolism by competition).

As primidone is substantially converted into phenobarbital within the body elevated phenobarbital levels will arise if they are given concurrently.

Vigabatrin possibly decreases phenobarbital plasma concentrations.

Perampanel: Significant reduction (up to two-thirds) of perampanel concentrations.

- *Antipsychotics* - anticonvulsant effect of phenobarbital antagonised by antipsychotics (lowered seizure threshold). Concurrent use of chlorpromazine and thioridazine with phenobarbital can reduce the serum levels of either drug.
- *Antivirals* - plasma concentration of phenobarbital possibly increased by indinavir.
- *Chlorpropamide* - the metabolism of phenobarbital can be decreased when combined with chlorpropamide.
- *Diuretics* - furosemide may increase plasma phenobarbital levels, leading to adverse effects.
- *Folic acid* - decreased plasma concentrations of phenobarbital, by increasing its metabolism, of which folate is one of the cofactors. 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). Clinical monitoring, control of plasma concentrations, and adjustment, if necessary, of the dosage of phenobarbital during folic supplementation and after its discontinuation.
- *Memantine* - the effect of Phenobarbital is possibly reduced.
- *Phenylbutazone* - the metabolism of phenobarbital can be decreased when combined with phenylbutazone.
- *Pyridoxine* (Vitamin B6) - may reduce serum concentrations of phenobarbital.
- *Sympathomimetics* - plasma concentrations of phenobarbital possibly increased by methylphenidate.
- *Vaccines* - increased phenobarbital levels may occur when used concomitantly with the influenza vaccine.

Effects of phenobarbital on other medicines

Contraindication for concomitant use

- *Antimycobacterials* - decrease in plasma concentrations of delamanid and bedaquiline by increasing its hepatic metabolism by the enzyme inducer (see section 4.3).
- *Antivirals* - Significant decrease in plasma concentrations of rilpivirine due to increase in its hepatic metabolism by the enzyme inducer. Risk of very significant decrease in telaprevir concentrations. Decreased plasma concentrations of daclatasvir by increasing its hepatic metabolism by the enzyme inducer. Decrease in plasma concentrations of dual therapy with ombitasvir-paritaprevir by increase in its hepatic metabolism by the enzyme inducer. Significant decrease in the plasma concentrations of ledipasvir by increasing its hepatic metabolism by the enzyme-inducing anticonvulsant. Risk of decrease in plasma concentrations of dasabuvir by the enzyme inducer. Risk of reduction in plasma concentrations of

sofosbuvir by reduction of its intestinal absorption by the enzyme inducer. (see section 4.3).

- *Antifungals* - Voriconazole: Risk of reduced efficacy of voriconazole due to increased hepatic metabolism by the enzyme inducer. Avoid concomitant use of voriconazole.

Precautions of concomitant use

- *Albendazole* - significant decrease in plasma concentrations of albendazole and its active metabolite by the enzyme inducer, with risk of reduced efficacy.

Clinical monitoring of the therapeutic response and possible adjustment of the dosage of albendazole during treatment with the enzyme inducer and after its discontinuation.

- *Analgesics* - opioid analgesics can be expected to have additive CNS effects. Pethidine: Enhanced CNS depressant effects with pethidine, including reports of prolonged sedation.

Fentanyl: Decreased plasma concentrations of fentanyl by increasing its hepatic metabolism by the anticonvulsant. Prefer another opioid.
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. Increased risk of respiratory depression, which can be fatal in the event of overdose. Regular clinical monitoring and adjustment of methadone dosage.
Fenoprofen: Plasma levels of fenoprofen may be reduced by phenobarbital.
Paracetamol: Cases of hepatotoxicity have been reported in patients on phenobarbital after taking paracetamol.

- *Androgens (androstanolone, norethandrolone, testosterone)* - risk of reduction in plasma concentrations of the androgen and consequently in its efficacy, by increasing its hepatic metabolism by the enzyme inducer.

Clinical and biological monitoring during the combination and 1 to 2 weeks after stopping the enzyme inducer.

- *Anti-arrhythmics* - disopyramide, lidocaine, propafenone, dronedarone, hydroquinidine and quinidine loss of arrhythmia control is possible. Decreased plasma concentrations and efficacy of quinidines and propafenone (increased hepatic metabolism). Clinical monitoring, electrocardiogram (ECG) and control of plasma concentrations; if necessary, adaptation of the dosage of the antiarrhythmic during treatment with the enzyme inducer and after its discontinuation.

- *Antibacterials* - chloramphenicol, doxycycline, metronidazole and rifampicin. Decrease in plasma concentrations of doxycycline and metronidazole by increasing its hepatic metabolism. Clinical monitoring and possible adaptation of the dosage of doxycycline and metronidazole during treatment with the enzyme inducer and after its discontinuation. Avoid concomitant use of telithromycin during and for 2 weeks after Phenobarbital. A marked increase in serious skin reactions has been seen in children given cefotaxime and phenobarbital.

- *Antithrombotic agents* - metabolism of coumarin anticoagulants increased leading to reduced effect. Decreased plasma concentrations of apixaban, dabigatran, rivaroxaban with risk of reduced therapeutic effect. Significant decrease in plasma concentrations of ticagrelor due to increase in its hepatic metabolism by the enzyme-inducing anticonvulsant, with risk of reduced therapeutic effect.

- *Antidepressants* - increased metabolism and therefore reduced plasma levels of paroxetine, fluoxetine, mianserin, bupropion, MAOIs, tricyclic antidepressants (e.g. imipramine, amitriptyline, amitriptylinoxide) and tricyclic-related antidepressants. Possible increased lithium toxicity. Risk of ineffectiveness of antidepressant treatment with sertraline.
- *Antiepileptics* - interactions between antiepileptics are complex. Concomitant administration of phenobarbital with other antiepileptics may enhance toxicity (increased sedative effects are possible with phenytoin and sodium valproate) without a corresponding increase in antiepileptic effect. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Plasma concentrations of carbamazepine, clonazepam, diazepam, lamotrigine, tiagabine and zonisamide reduced.
Carbamazepine: Gradual decrease in plasma concentrations of carbamazepine and its active metabolite with no apparent change in antiepileptic efficacy. Caution in interpreting plasma concentrations.
Lamotrigine: The combination of phenobarbital and lamotrigine may induce reduced efficacy and haematological toxicity such as leucopenia and thrombocytopenia.
Tiagabine: An increase in tiagabine dosage may be necessary.

Plasma concentration of phenytoin usually reduced, but may be raised. In case of previous treatment with phenytoin and addition of phenobarbital or primidone, there are unpredictable variations: a) the plasma concentrations of phenytoin are most often reduced (increased metabolism) without this reduction adversely affecting the anticonvulsant activity. When stopping phenobarbital or primidone, possibility of toxic effects of phenytoin; b) sometimes the concentrations of phenytoin can be increased (inhibition of metabolism by competition).

Plasma concentration of ethosuximide possibly reduced.

Plasma concentrations of oxcarbazepine and its active metabolite, and valproate may be reduced.

Decreased plasma concentrations and efficacy of felbamate.

Cenobamate: In a study conducted in healthy subjects, the concomitant administration of cenobamate at a dose of 200 mg/day and phenobarbital at a dose of 90 mg/day did not result in clinically significant changes in cenobamate exposure, but led to an increase in phenobarbital exposure (an increase in C_{max} by 34% and in AUC by 37%). No adjustment of the cenobamate dose is necessary. Phenobarbital concentrations should be monitored during the titration of cenobamate. Depending on the individual response, it may be necessary to reduce the dose of phenobarbital.

- *Antifungals* - the antifungal effects of griseofulvin can be reduced or even abolished by concurrent use. Phenobarbital possibly reduces plasma concentrations and efficacy of itraconazole.

Posaconazole: Phenobarbital possibly reduces plasma concentrations and efficacy of posaconazole. Clinical monitoring. If possible, control of plasma concentrations of posaconazole and possible adjustment of its dosage.

- *Antipsychotics* - phenobarbital accelerates metabolism of haloperidol. Haloperidol serum levels are approximately halved by concurrent use with phenobarbital. Plasma concentrations of both drugs reduced when phenobarbital given with chlorpromazine. Possible interaction with other phenothiazines (mesoridazine, thiodorazine). Plasma levels of aripiprazole possibly reduced by phenobarbital. Very significant decrease in plasma concentrations of quetiapine

due to increase in its hepatic metabolism by the enzyme inducer, with risk of ineffectiveness. The clinical effect of interactions with antipsychotics has not been consistent; worsening, improvement or no change in psychotic symptoms have all been noted.

- *Antivirals* - phenobarbital possibly reduces plasma levels of amprenavir, atazanavir, darunavir, fosamprenavir, lopinavir, indinavir, nelfinavir, saquinavir. Risk of reduced efficacy of the protease inhibitors lopinavir, ritonavir, boceprevir by increasing its hepatic metabolism by the enzyme inducer. Decrease in plasma concentrations of simeprevir by increase in its hepatic metabolism by the enzyme inducer. There are potential interactions with ritonavir and tipranavir. Regular clinical and biological monitoring of ritonavir-boosted protease inhibitors especially at the start of the combination.

Phenobarbital possibly reduces plasma levels of abacavir. Manufacturer of etravirine recommends avoidance of phenobarbital. Decrease in plasma concentrations of dolutegravir due to increase in its metabolism by the enzyme inducer. In the absence of co-administration with a strong CYP3A4 inhibitor, decrease in maraviroc concentrations by the enzyme inducer. The maraviroc dose should be increased to 600 mg twice daily in this situation. *R*isk of reduced efficacy of cobicistat due to increased metabolism by the enzyme inducer.

- *Antihypertensives for pulmonary hypertension* - risk of decreased bosentan plasma concentrations. Decreased plasma concentrations of macitentan by increasing its metabolism by the enzyme inducer.
- *Anxiolytics and Hypnotics* - phenobarbital reduces plasma concentrations of clonazepam.
- *Aprepitant* - phenobarbital possibly reduces plasma concentration of aprepitant.
- *Beta-blockers* - metoprolol, timolol and possibly propranolol. Plasma concentration of timolol reduced by phenobarbital. Decrease in the plasma concentrations of metoprolol and propranolol with a reduction in their clinical effects (acceleration of their hepatic metabolism).
- *Calcium channel blockers* - phenobarbital causes reduced levels of felodipine, isradipine, diltiazem, dihydropyridines, bepridil, verapamil, nimodipine and nifedipine and an increase in dosage may be required. Clinical monitoring and possible adaptation of the dosage of the calcium antagonist during treatment with the enzyme inducer and after its discontinuation.
- *Cardiac Glycosides* - blood levels of digitoxin can be halved by concurrent use. Decrease in the efficacy of digitoxin (increase in its hepatic metabolism).

Clinical monitoring, ECG and possibly control of digitoxinaemia. If necessary, adapt the dosage of digitoxin during the combination and after stopping phenobarbital or prefer digoxin, which is less metabolized by the liver.

- *CNS depressants* - increased sedative effects when used in combination with anaesthetics, antihistamines, narcotic analgesics and other sedatives/tranquilisers. Other CNS depressants: morphine derivatives (analgesics, cough suppressants and substitution treatments); neuroleptics; barbiturates; benzodiazepines; anxiolytics other than benzodiazepines (eg meprobamate), hypnotics; sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine); sedating H1 antihistamines; central antihypertensives; others: baclofen, thalidomide. Increased central depression. Impaired alertness can make driving vehicles and using machines dangerous. In addition, for morphine derivatives (analgesics, cough suppressants and substitution treatments), benzodiazepines:

Increased risk of respiratory depression, which can be fatal in the event of overdose. Risk of reduction in plasma concentrations of midazolam by the anticonvulsant.

- *Corticosteroids (gluco-, mineralo-)* - decreased plasma concentrations and efficacy of corticosteroids by increasing their hepatic metabolism: the consequences are particularly significant in Addisonians treated with hydrocortisone and in the event of transplantation.

Risk of reduced efficacy of hydrocortisone (increased metabolism); the consequences are serious when hydrocortisone is administered as replacement therapy or in the event of transplantation.
Clinical and biological monitoring; adaptation of the dosage of corticosteroids during treatment with the enzyme inducer and after its discontinuation.

- *Cytotoxics* - phenobarbital reduces plasma concentrations of irinotecan and its active metabolite, and possibly plasma concentrations of doxorubicin, teniposide and etoposide. Risk of failure of cytotoxic treatment with irinotecan. Phenobarbital may enhance the effects of cyclophosphamide. Phenobarbital may increase the risk of hypersensitivity reactions with procarbazine. Avoidance of barbiturates is advised by manufacturer of Gefitinib. Risk of reduction in plasma concentrations of eribulin by the enzyme inducer. Risk of increased neurotoxicity of ifosfamide by increasing its hepatic metabolism by phenobarbital. Decrease in plasma concentrations and in the effectiveness of the tyrosine kinase inhibitors (axitinib, bosutinib, crizotinib, dabrafenib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, ruxolitinib, sorafenib, sunitinib, vandetanib), by increasing their metabolism by the enzyme inducer. Decreased plasma concentrations of regorafenib due to increased metabolism by the enzyme inducer. Risk of decreased vemurafenib concentrations, with reduced efficacy. Risk of significant reduction in plasma concentrations of vismodegib by increasing its hepatic metabolism by the enzyme inducer. The combination of phenobarbital and anti-cancer drugs metabolized via enzymes (cytochrome P-450 and UDP glycosyltransferases) may induce a risk of reduced exposure to anti-cancer drugs. Bortezomib, cabazitaxel, docetaxel: Decreased concentrations of the cytotoxic by increasing its metabolism by the enzyme inducer, with risk of reduced efficacy.
- *Deferasirox* - risk of decreased plasma concentrations of deferasirox. Monitor serum ferritin during and after treatment with the enzyme inducer. If necessary, adjustment of the deferasirox dosage.
- *Diuretics* - phenobarbital reduces plasma concentrations of eplerenone (avoid concomitant use). Increased risk of osteomalacia (see section 4.8) when phenobarbital used in conjunction with carbonic anhydrase inhibitors.
- *Hormone Antagonists* - accelerated metabolism of gestrinone and toremifene. Notable decrease in plasma concentrations of abiraterone, with risk of reduced efficacy.
- *Immunosuppressants* - reduced effect of ciclosporin due to acceleration of metabolism by phenobarbital. Plasma concentrations of tacrolimus, everolimus, sirolimus, possibly reduced by phenobarbital. Plasma concentrations of immunosuppressants should be monitored.
- *Ivacaftor* - significant decrease in ivacaftor concentrations, with risk of loss of efficacy.

- *Ivabradine* - risk of reduced efficacy of ivabradine, by increasing its metabolism by the enzyme inducer. Clinical monitoring and dose adjustment of ivabradine during the combination and after discontinuation of the enzyme inducer.
- *Leukotriene Receptor Antagonists* - reduced plasma concentration of montelukast. Risk of reduced efficacy of montelukast due to increased hepatic metabolism. Clinical monitoring and possible adaptation of the dosage of the antiasthmatic.
- *Lofexidine* - increased sedative effect when phenobarbital given with lofexidine.
- *Oestrogens (oral, transdermal and nasal routes) and progestogens (non-contraceptive)* - decreased effectiveness of oestrogen or progestin. Clinical monitoring and possible adjustment of the dosage of oestrogen or progestogen during treatment with the enzyme inducer and after its discontinuation.
- *Praziquantel* - very significant decrease in plasma concentrations of praziquantel, with risk of treatment failure, due to increase in its hepatic metabolism by the enzyme inducer.
- *Quinine* - risk of loss of efficacy of quinine by increasing its hepatic metabolism by the enzyme inducer. Clinical monitoring and adjustment of quinine dosage during treatment with the enzyme inducer and after its discontinuation.
- *Ranolazine* - risk of significant decrease in ranolazine concentrations.
- *Sex hormones* - increased clearance of oestrogens and progestogens, possibly leading to oral contraceptive failure and breakthrough bleeding. Avoidance of phenobarbital advised by the manufacturer of Ulipristal. *R*isk of reduction in the effect of ulipristal, by increasing its hepatic metabolism by the enzyme inducer. Prefer a therapeutic alternative with little or no metabolism.
- *Sodium oxybate* - enhanced effects, avoid concomitant use.
- *Theophylline (base and salts) and aminophylline* - decrease in plasma concentrations and activity of theophylline by increasing its hepatic metabolism by the enzyme inducer. Clinical monitoring, if necessary, of theophyllinemia. Possible adaptation of the theophylline dosage during treatment with the enzyme inducer and after its discontinuation.
- *Thyroid hormones* - by extrapolation of other well-characterized inducers: Risk of clinical hypothyroidism in hypothyroid patients, by increased metabolism of T3 and T4. Monitoring of serum concentrations of T3 and T4 and adjustment, if necessary, of the dosage of thyroid hormones during treatment with the enzyme inducer and after its discontinuation. 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* - phenobarbital accelerates the metabolism of tibolone leading to reduced plasma levels.
- *Tolbutamide* - the metabolism of tolbutamide can be increased when combined with phenobarbital.
- *Tropisetron* - phenobarbital increases the rate of metabolism reducing serum concentrations of tropisetron.
- *Vitamins* - antiepileptic therapy, including treatment with phenobarbital, is associated with folic acid deficiency, possibly by increased metabolism. Phenobarbital possibly increases the requirements for Vitamin D (see 4.4 – Special warnings and precautions for use.).

- *Vitamin K antagonists* - decreased (or rarely, increased with phenytoin) the effect of vitamin K antagonist. More frequent monitoring of INR. Possible adaptation of the dosage of vitamin K antagonist, during treatment with phenobarbital and 8 days after its discontinuation.

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 epilepsy and antiepileptic medicinal products

Medical advice regarding the potential risks to the foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential treated with antiepileptics, and especially to women planning pregnancy or are pregnant. As a general principle, monotherapy is preferred for treating epilepsy during pregnancy whenever possible, since treatment with multiple antiepileptic drugs (AEDs) appears to be associated with a higher risk of congenital malformations compared to monotherapy, depending on the AEDs used. Sudden discontinuation of AED therapy should be avoided in pregnant women being treated for epilepsy, as this may lead to convulsions with serious consequences for the woman and the foetus.

Risks related to phenobarbital

Phenobarbital readily crosses the placenta following oral administration and is distributed throughout foetal tissue, the highest concentrations being found in the placenta, foetal liver and brain. Maternal and neonatal concentrations are similar. Animal studies (literature data) have shown reproductive toxicity in rodents (see section 5.3).

Birth defects

Data from meta-analysis and observational studies have shown a risk of major birth defects approximately 2-3 times higher than in the general population (which is 2-3%). The risk depends on the dose; however, no dose has been shown to be safe. Therefore, the lowest effective dose should be used. Phenobarbital monotherapy is associated with increased risk of congenital defects, including cleft lip and palate and cardiovascular malformations. Other malformations involving various body systems including cases of hypospadias, facial dysmorphic features, neural tube defects, craniofacial dysmorphia (microcephaly), and digital abnormalities have also been reported.

Data from an observational study suggest an increased risk of infants born with reduced, than expected for gestational age, body weight and length compared to women exposed to lamotrigine monotherapy during pregnancy.

Neurodevelopmental disorders

Neurodevelopmental disorders have been reported in infants exposed to phenobarbital during pregnancy. Study results relating to the risk of neurodevelopmental disorders in children exposed to phenobarbital during pregnancy are contradictory and a risk cannot be excluded. Preclinical studies have also reported neurodevelopmental adverse effects (see section 5.3). 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. Phenobarbital should not be used during pregnancy unless the potential benefit outweighs the risks, after evaluating other appropriate 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. Regular monitoring of plasma concentrations is recommended for dose adjustment. The woman should be fully informed of and understand the risks related to the use of phenobarbital during pregnancy.

Patients taking phenobarbital should be adequately supplemented with folic acid prior to conception and during pregnancy. Certain antiepileptic drugs, such as phenobarbital, have been reported to decrease serum folate levels. This deficiency may contribute to increased incidence of birth defects in children born by mothers treated for epilepsy. Therefore, for women exposed to phenobarbital and who are planning a pregnancy or who are pregnant, folic acid supplementation may be administered at a dosage of 5 mg/d prior to pregnancy and up to 2 months after the date of conception.

Special prenatal monitoring focused on the malformations described above must be instituted.

Screening for malformations will be the same whether the patient has been treated with folic acid or not.

Before delivery/in newborns

Enzyme-inducing antiepileptics may cause in newborns of treated mothers:

- Haemorrhagic syndrome during childbirth or in the first days of life. Prevention by oral vitamin K1 in the mother in the month preceding childbirth and IM or slow IV administration of vitamin K1 in the newborn at birth appear effective. A normal haemostasis assessment in the mother does not preclude haemostasis abnormalities in the newborn. The neonate should be monitored for signs of bleeding.
- Disturbances in calcium phosphate metabolism and bone mineralization, which can be prevented by vitamin D supplementation during the 3rd trimester.
- Withdrawal symptoms may occur in the newborn, including sedation, hypotonia and sucking disorder when phenobarbital is used during the third trimester of pregnancy.
- Rarely: moderate withdrawal syndrome (abnormal movements, poor sucking).

Post-natal follow-up/In children

In case of exposure during pregnancy, close monitoring of the neurobehavioral development of the child should be instituted and appropriate management should be applied as soon as possible, if necessary.

Breast-feeding

Phenobarbital is excreted into breast milk and there is a small risk of neonatal sedation and methaemoglobinaemia in nursing infants. Breast-feeding is therefore not recommended.

Fertility

No human data on the effect of phenobarbital on fertility are available.

4.7 Effects on ability to drive and use machines

Phenobarbital may cause drowsiness and dizziness. It 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

The following adverse effects have been associated with use of phenobarbital. The most frequent adverse effect is sedation.

The classification of adverse events according to their frequency is based on the following conventions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known
Blood and lymphatic system disorders						pancytopenia, aplastic anaemia, folate deficiency anaemia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia, hypoprothrombinaemia, methaemoglobinaemia (in infants nursed by mothers receiving phenobarbital)
Endocrine disorders						reduced thyroid hormones serum concentration
Metabolism and nutrition disorders						folate deficiency, hypocalcaemia, hypophosphataemia, abnormal Vitamin D metabolism, vitamin K deficiency
Psychiatric disorders		abnormal behaviour, agitation, aggression (particularly in children)	mood altered, sleep disorders/ insomnia			dependence, delirium, depression, hallucination, paradoxical excitement, restlessness, suicidal ideation, withdrawal syndrome, hyperactivity (particularly in children)
Nervous system disorders		drowsiness, cognitive impairment, memory impairment	ataxia, dizziness, headache	attention deficit		dyskinesia, Grand Mal convulsion, irritability, lethargy, nystagmus, sedation, behavioural disturbances in children
Vascular disorders						hypotension
Respiratory, thoracic and mediastinal disorders						respiratory depression
Gastrointestinal disorders		nausea, vomiting				
Hepato-biliary disorders		increased GGT, increased transaminases and/or alkaline phosphatases				hepatitis, cholestasis
Skin and subcutaneous tissue disorders		allergic dermatitis (morbiliform or scarlatiniform maculo-papular rashes)				fixed pigmented erythema, erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known
						exanthematous pustulosis (AGEP), photosensitivity, purpura
Musculoskeletal and connective tissue disorders		Dupuytren's disease	arthralgia (shoulder-hand syndrome or rheumatism)			Ledderhose's syndrome, Peyronie's disease, decreased bone mineral density, osteopenia, osteoporosis, osteomalacia, fractures, rickets, frozen shoulder, fibromas, general joint pain
Pregnancy, puerperium and perinatal conditions						neonatal sedation, neonatal drug dependence and withdrawal syndrome, neonatal bleeding due to vitamin K deficiency
Congenital, familial and genetic disorders						cleft lip and palate, congenital malformations, other developmental abnormalities
General disorders and administration site conditions						antiepileptic hypersensitivity syndrome (including fever, rash, lymphadenopathy, lymphocytosis, eosinophilia, liver and other organ involvement)

Serious effects affecting the hepatic and/or cutaneous systems as well as hypersensitivity reactions require discontinuation of treatment.

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 MHRA Yellow Card in the Google Play or Apple App Store.

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.

Symptoms

The toxic effects of overdosage include nausea, vomiting, headache, obnubilation, mental confusion or even coma accompanied by a characteristic neurovegetative syndrome (irregular bradypnea, tracheobronchial stenosis, hypotension), drowsiness, prolonged coma, respiratory depression and cardiovascular depression, with

hypotension and shock leading to renal failure. The duration and depth of cerebral depression varies with the dose and tolerance of the patient. Absent bowel sounds are a sign of severe poisoning. Hypothermia is common, with associated pyrexia during recovery. Characteristic erythematous or haemorrhagic blisters occur in about 6 % of patients. Death is usually due to respiratory and circulatory failure. The chronic effects of phenobarbital on neurological and psychic functions closely resemble those of alcohol. The symptoms of chronic poisoning include disorientation, mental confusion, ataxia, dizziness, depression and skin rashes.

Treatment

The aim in treating poisoning with phenobarbital is to maintain respiration, treat shock and prevent further absorption of the drug. Supportive measures alone may be sufficient if symptoms are mild.

Oral doses of activated charcoal can be considered in those presenting within 1 hour of ingesting more than 10 mg/kg, with the aim of preventing absorption and aiding elimination. Analeptics should generally be avoided. If within 1 hour of ingestion, gastric aspiration or lavage may be of benefit in adults. The stomach should be emptied by lavage with warm water to leave the stomach empty, but only after precautions have been taken to avoid aspiration. The prime objective of treatment is to maintain vital functions while the majority of the drug is metabolised by hepatic enzymes. The potentially fatal dose of phenobarbital is 6 to 10 g. Attention should be paid to maintenance of a patient’s airway and to the prevention of hypostatic pneumonia. Measures should be taken to prevent further loss of body heat.

In severe acute intoxication circulatory collapse is a major threat. Dehydration is often severe. Hypovolemia must be corrected and if necessary, the blood pressure can be supported with dopamine.

Should renal failure occur, haemodialysis may be used to dispose of the poison.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics,

ATC code: N03AA02

Mechanism of action

Phenobarbital's mechanism of action increases the amount of time chloride channels are open, consequently depressing the Central Nervous System. This action occurs by acting on GABA-A receptor subunits. When phenobarbital binds to these receptors, the chloride ion gates open and stay open, allowing a steady flow of these ions into neuronal cells. This action hyperpolarizes the cell's membrane, thereby increasing the threshold for the action potential. This increase in action potential is the reason why this drug is effective in the treatment of seizures.

Pharmacodynamic effects

The barbiturates reversibly depress the activity of all excitable tissues. Not all tissues are affected at the same dose or concentration and when barbiturates are given in

sedative or hypnotic doses there is very little effect on skeletal, cardiac or smooth muscle.

Phenobarbital is a barbiturate drug which has selective anticonvulsant activity and is used to control tonic-clonic seizures in the treatment of epilepsy. In a dose that has only minor effects on the reticular system, phenobarbital elevates the threshold for the initiation of after discharges, shortens the period of after discharge, and suppresses the spread of seizures. Phenobarbital also exhibits sedative and hypnotic effects.

Clinical efficacy and safety

Phenobarbital has been compared with the established AEDs primidone, phenytoin, and carbamazepine in several major randomized trials and a number of smaller studies conducted in adults and children. The available meta-analyses concluded in high efficacy percentage of phenobarbital when compared to other AEDs

Like other AEDs, phenobarbital is associated with a range of dose-dependent and idiosyncratic drug reactions. Those of most interest is phenobarbital's propensity to produce sedative, behavioural, and mood effects especially in children (see section 4.8).

5.2 Pharmacokinetic properties

Absorption

Oral absorption of phenobarbital is complete but slow. Approximately 80% of orally administered phenobarbital is absorbed from the gastrointestinal tract. Peak plasma concentrations occur in about 8 hours in adults and in about 4 hours in children.

Distribution

Phenobarbital is partially bound to plasma proteins (50% in adults and 60% in children) and bound to a similar extent in tissues. The volume of distribution is approximately 0.9 Lkg^{-1}. Phenobarbital is distributed to all tissues, especially in the brain due to its lipophilicity; it crosses the placenta and passes into breast milk.

Biotransformation

The major metabolite of phenobarbital is the para hydroxyphenyl derivative, which is inactive and is excreted in the urine partly as the sulphate conjugate.

Elimination

About 25 % of phenobarbital is eliminated by pH-dependent renal excretion and the remainder is inactivated by the hepatic microsomal enzymes.

Phenobarbital has a plasma half-life of 40 to 70 hours in children and 50 to 140 hours in adults. This is increased in the elderly, in overdosage and in renal or hepatic disease.

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

Linearity/non-linearity

Phenobarbital follows linear pharmacokinetics.

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

Glycerol (E422)
Citric acid (E330)
Sodium hydroxide (E524)
Microcrystalline cellulose and carmellose sodium
Xanthan gum (E415)
Lemon flavour (including propylene glycol (E1520))
Sucralose (E955)
Polysorbate 80 (E433)
Sodium benzoate (E211)
Simethicone 30% emulsion
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening use within 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Amber, type III glass bottle safely closed with a child resistant screw cap with tamper evident closure.

Each bottle contains 150 ml of this medicinal product.

An HDPE/PP 10 ml graduated oral syringe with intermediate graduations of 0.2 ml and an LDPE “press in” syringe/bottle adapter are also provided.

6.6 Special precautions for disposal

Instructions for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes.

1. Ensure the enteral feeding tube is free from any obstructions before administering this medicine.
2. Flush the tube with 10 ml of boiled cooled water.
3. Administer the required dose of Phenobarbital oral suspension into the tube using a suitable measuring device.
4. Immediately flush the tube again with 2 ml of boiled cooled water.

Compatibility has only been demonstrated with 6 Fr and larger size tubes.

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Colonis Pharma Limited
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WC1B 3HH
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