Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Phenobarbital 60 mg Tablets

2. Qualitative and quantitative composition

Each tablet contains 60 mg of Phenobarbital BP.

Excipients with known effect:
Each tablet contains 29 mg of Lactose BP

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Uncoated Tablet

White to offwhite circular biconvex shaped tablets embossed 'COSMOS' on one side and breakline on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Phenobarbital tablets are indicated for the management of all forms of epilepsy except absence seizures.

4.2 Posology and method of administration

Posology
Adults and the elderly: 60 - 180 mg daily at night.
Caution must be exercised in the treatment of elderly patients with careful monitoring of their condition.
Children: 5 - 8 mg per kg bodyweight daily.

Method of Administration
Oral
The tablets should be swallowed with water.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Prolonged use may result in the dependence of the alcohol-barbiturate type and particular care should be taken in treating

patients with a history of drug abuse or alcoholism.

Avoid sudden withdrawal to prevent rebound seizures.

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 interaction

Phenobarbital increases the rate of metabolism of many drugs by induction of drug-metabolising enzymes in liver microsomes. This may result in a reduction in activity.

The following list is not exhaustive; the metabolism may be increased (and activity decreased) of any drug metabolised by hepatic enzymes, during concomitant use with phenobarbital.

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 – Phenobarbital reduces plasma concentrations of methadone. Opioid withdrawal syndrome has been reported in patients maintained on methadone when phenobarbital was added to their regimen. Opioid analgesics can also be expected to have additive CNS effects. Plasma levels of phenobarbital may be increased when used in conjunction with dextropropoxyphene. Plasma levels of fenoprofen may be reduced by phenobarbital. Enhanced CNS depressant effects with pethidine, including reports of prolonged sedation. Cases of hepatotoxicity have been reported in patients on phenobarbital after taking paracetamol.
Anti-arrhythmics – Clearance of disopyramide, lidocaine, propafenone, dronedarone and quinidine increased, leading to increased dosage requirements.

Antibacterials – Phenobarbital accelerates the metabolism of chloramphenicol, doxycycline and metronidazole and may reduce plasma levels of rifampicin. There is a possibility of increased phenobarbital levels during concomitant use of chloramphenicol. Plasma concentrations of telithromycin are reduced by phenobarbital (avoid concomitant use and use for two weeks after phenobarbital withdrawal). A marked increase in serious skin reactions has been seen in children given cefotaxime and phenobarbital.

Anticoagulants – Metabolism of coumarin anticoagulants increased leading to reduced effect.

Antidepressants – Possible antagonism of effect of phenobarbital by SSRIs, tricyclic and tricyclic-related antidepressants, by lowering of seizure threshold. Increased metabolism and therefore reduced plasma levels of paroxetine, fluoxetine, mianserin, bupropion, MAOIs, tricyclic antidepressants (e.g. imiptamine, amitriptyline) and tricyclic-related antidepressants. Possible increased lithium toxicity. The effect of phenobarbital can be reduced by concomitant use of the herbal remedy St. John's Wort (Hypericum perforatum).

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. Plasma concentration of phenytoin usually reduced, but may be raised. Plasma concentration of ethosuximide possibly reduced. Plasma concentration of phenobarbital increased by oxcarbazepine, phenytoin, valproate, and possibly felbamate, whereas plasma concentrations of oxcarbazepine and its active metabolite, and valproate may be reduced. Plasma concentration of phenobarbital increased by stiripentol and reduced by vigabatrin. As primidone is

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

Antifungals – Phenobarbital possibly reduces plasma concentrations of itraconazole, posaconazole and voriconazole (avoid concomitant use) and may reduce the absorption of griseofulvin.
Antipsychotics – Anticonvulsant effect of phenobarbital antagonised by antipsychotics (lowered seizure threshold). Phenobarbital accelerates metabolism of haloperidol. 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. 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 concentrations of abacavir, amprenavir, darunavir, fosamprenavir, lopinavir, indinavir, nelfinavir and saquinavir. Plasma concentration of phenobarbital possibly increased by indinavir. Manufacturer of etravirine recommends avoidance of phenobarbital. There are potential interactions with ritonavir and tipranavir.

Anxiolytics and Hypnotics – Phenobarbital reduces plasma concentrations of clonazepam.

Aprepitant – Plasma concentrations possibly reduced by phenobarbital.

Beta-blockers – Plasma concentration of metoprolol and timolol and possibly propranolol reduced by phenobarbital.

Calcium-channel blockers – Effects of felodipine and isradipine, and possibly dihydropyridines (nimodipine, nifedipine – may require an increase in dosage), diltiazem, and verapamil reduced by phenobarbital.

Cardiac glycosides – Metabolism of digitoxin accelerated by phenobarbital.

CNS depressants (also see Alcohol) – Increased sedative effects when used in combination with anaesthetics, antihistamines, narcotic analgesics and other sedatives/tranquilisers.

Corticosteroids - Plasma levels may be reduced, leading to reduced efficacy.

Cytotoxics – Phenobarbital reduces plasma concentrations of irinotecan and its active metabolite, and possibly plasma concentrations of

doxorubicin, teniposide and etoposide. 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.

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. Furosemide may increase plasma phenobarbital levels, leading to adverse effects.

Hormone Antagonists – Accelerated metabolism of gestrinone and toremifene.

Immunosuppressants – Reduced effect of ciclosporin due to acceleration of metabolism by phenobarbital. Plasma concentrations of tacrolimus possibly reduced by phenobarbital

Leukotriene Receptor Antagonists – Reduced plasma concentration of montelukast.

Lofexidine – increased sedative effect when phenobarbital given with lofexidine.

Memantine – Effects of phenobarbital possibly reduced by memantine.

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.

Sodium Oxybate - Enhanced effects (avoid concomitant use).

Sympathomimetics – Plasma concentrations of phenobarbital possibly increased by methylphenidate.

Theophylline – Phenobarbital accelerates metabolism of theophylline, leading to reduced effect.

Thyroid Hormones – Phenobarbital accelerates metabolism of thyroid hormones (levothyroxine) and may increase requirements in hypothyroidism. Prescribers should be alert for changes in thyroid status if barbiturates are added or withdrawn from patients being treated for hypothyroidism.

Tibolone – Phenobarbital accelerate metabolism of tibolone leading to reduced plasma levels.

Vaccines – Increased phenobarbital levels may occur when used concomitantly with the influenza vaccine.

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.). Pyridoxine (Vitamin B6), folic acid and folinic acid may reduce serum concentrations of phenobarbital.

4.6 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 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.

Pregnancy

Risk related to antiepileptic medicinal products in general

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. 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 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.

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. Phenobarbital therapy in epileptic pregnant women presents a risk to the foetus in-terms of major and minor congenital defects including congenital craniofacial and cardiac defects, digital abnormalities and, less commonly, cleft lip and palate. Studies in women with epilepsy who were exposed to phenobarbital during pregnancy identified a frequency of 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. Animal studies (literature data) have shown reproductive toxicity in rodents (see section 5.3).

Adverse effects on neurobehavioral development have also been reported. Studies investigating neurodevelopmental effects of prenatally administered phenobarbital were mostly small in numbers; however, significant negative effects on neurodevelopment and IQ were found following in utero and postnatal exposure.

Data from a registry study suggest an increase in the risk of infants born small for gestational age or with reduced body length to women with epilepsy who were exposed to phenobarbital during pregnancy compared to women exposed to lamotrigine monotherapy during pregnancy.

Haemorrhage at birth and addiction are also a risk. Prophylactic treatment with vitamin K1 for the mother before delivery (as well as the neonate) is recommended, the neonate should be monitored for signs of bleeding.

Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy (see section 4.5).

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 advisable.

4.7 Effects on ability to drive and use machine

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

4.8 Undesirable effects

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

Blood and lymphatic system disorders
Agranulocytosis, macrocytic anaemia, megaloblastic anaemia, hypoprothrombinaemia, thrombocytopenia. Methaemoglobinaemia in infants nursed by mothers receiving phenobarbital.

Endocrine disorders
Serum concentrations of thyroid hormones may be reduced (see section 4.5).

Metabolism and nutrition disorders
Folate deficiency, hypocalcaemia, hypophosphataemia, abnormal Vitamin D metabolism (see section 4.4), vitamin K deficiency.

Psychiatric disorders
Abnormal behaviour, aggression and hyperactivity (particularly in children), agitation, confusional state, delirium, dependence. depression, hallucination, insomnia, mood altered, paradoxical excitement, restlessness, suicidal ideation (see section 4.4), withdrawal syndrome.

Nervous system disorders
Ataxia, cognitive impairment, dizziness, drowsiness, Grand Mal convulsion. headache, irritability, lethargy, memory impairment, nystagmus, sedation.

Vascular disorders
Hypotension.

Respiratory, thoracic and mediastinal disorders
Respiratory depression.

Hepato-biliary disorders
Cholestasis, abnormal hepatic function, hepatitis.

Skin and subcutaneous tissue disorders
Exfoliative dermatitis, drug eruption, erythema multiforme, macropapular rash, mobilliform rash, photosensitivity, purpura, scarlatiniform rash, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders

Bone metabolism disorder, Dupuytren's contracture, frozen shoulder, Ledderhose's syndrome, Peyronie's disease, fibromas, general joint pain, 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.

Pregnancy, puerperium and perinatal conditions
Neonatal sedation, neonatal drug dependence and withdrawal syndrome, neonatal bleeding due to vitamin K deficiency.

Congenital and familial/genetic disorders
Cleft lip and palate, congenital anomaly

General disorders and administration site conditions
Antiepileptic hypersensitivity syndrome (including fever, rash, lymphadenopathy, lymphocytosis, eosinophilia, liver and other organ involvement). Symptoms generally occur between 1 and 8 weeks after first exposure, or within 1 day of rechallenge in sensitised individuals, with potential cross reactivity to other antiepileptics.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

The toxic effects of overdosage include 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. The aims in treating poisoning with phenobarbital are 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 10mg/kg, with the aim of preventing absorption and aiding elimination. Analeptics should generally be avoided. However a single dose of nikethamide may be given in an emergency. If within 4 hours 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. Apomorphine – induced emesis evacuates the stomach more rapidly and reliably than doses of ipecacuanha. After lavage, a saline cathartic should be administered and repeated every 1 to 2 hours, as long as bowel sounds are present. The prime objective of treatment is to maintain vital functions 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 fusion) may enhance the excretion of the drug from the kidneys. The potentially fatal dose of phenobarbital is 6 to 10g. 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 or charcoal haemoperfusion may be used to dispose of the poison. Charcoal haemoperfusion is the treatment of choice for the majority of patients with very severe barbiturate poisoning who fail to improve, or who deteriorate despite good supportive care.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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 afterdischarges, shortens the period of afterdischarge, and suppresses the spread of seizures

5.2 Pharmacokinetic properties

Oral absorption of phenobarbital is complete but slow, peak plasma concentrations occur several hours after a single dose. It is about 40% bound to plasma proteins and bound to a similar extent in tissues. The volume of distribution is approximately 0.9 lkg-1. About 25% of phenobarbital is eliminated by pH-dependent renal excretion, the remainder is inactivated by the hepatic microsomal enzymes.
The major metabolite is the para hydroxyphenyl derivative, which is inactive and is excreted in the urine partly as the sulphate conjugate.

Phenobarbital has a plasma half-life of up to about 75 hours in children and 100 hours in adults. This is increased in the elderly, in overdosage and in renal or hepatic disease.

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

Lactose BP
Maize Starch BP
Potassium Sorbate BP
Purified Water BP
Sodium Lauryl Sulphate BP
Colloidal Anhydrous Silica BP
Magnesium Stearate BP

6.2 Incompatibilities

None

6.3 Shelf-Life

3 Years

6.4 Special Precautions for storage

Store in a dry place below 30°C. Protect from light.

6.5 Nature and Content of container

PVDC/ALU blister packing

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder

COSMOS LIMITED

8. Marketing Authorization Number

CTD11159

9. Date of first authorization/renewal of the authorization

20/12/2023

10. Date of revision of the text

13/05/2025