# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Phenobarbital Activase 60 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Phenobarbital 60 mg.

Excipient(s) with known effect

Lactose monohydrate

Sunset yellow (E110)

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablets

Pale orange, circular, biconvex tablet.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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.

Phenobarbital clearance diminishes in the elderly. Therefore, the dose of Phenobarbital is usually lower in elderly patients.

*Children:* 5 – 8 mg per kg bodyweight daily.

The dose of Phenobarbital should be adjusted to meet the needs of individual patients. This usually requires plasma concentration of 15 to 40 micrograms/ml (65 to 170 micromoles/litre).

Method of administration

Oral; the tablets should be swallowed with water.

## 4.3 Contraindications

- Hypersensitivity to the active substance, other barbiturates or to any of the excipients listed in section 6.1.
- Acute intermittent porphyria.
- Severe respiratory depression.
- Severe renal or hepatic impairment.

## 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. 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.

Care should be used in the following situations:

- Respiratory depression (avoid if severe)
- Young, debilitated or senile patients
- Renal impairment
- Existing liver disease
- 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.

- Prolonged use may result in dependence of the alcohol-barbiturate type. Care should be taken in treating patients with a history of drug abuse or alcoholism.

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

*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

| **Effects on Phenobarbital** | **Effects of phenobarbital on other medicines** |
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| • **Alcohol** – concurrent administrationwith alcohol may lead to an additiveCNS depressant effect. This is likelywith concurrent administration with other CNS depressants.<br>• **Antidepressants** – including MAOIs,SSRIs and tricyclics may antagonisethe antiepileptic activity of phenobarbital by lowering the convulsive threshold<br>• **Antiepileptics** - phenobarbital plasmaconcentrations increased by oxcarbazepine, phenytoin, and sodium valproate. Vigabatrin possibly decreases phenobarbital plasma concentrations.<br>• **Antipsychotics** – concurrent use of | Phenobarbital increases the rate of metabolism reducing serum concentrations of the following drugs:<br>• **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 many be necessary<br>• **Antibacterials** - chloramphenicol, doxycycline, metronidazole and rifampicin. Avoid concomitant use of telithromycin during and for 2 weeks after Phenobarbital.<br>• **Anticoagulants** |

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| chlorpromazine and thioridazine with phenobarbital can reduce the serum levels of either drug.<br>• **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, leadingto decreased seizure control in some patients. (see section 4.6).<br>• **Memantine** – the effect of Phenobarbital is possibly reduced.<br>• **Methylphenidate** – plasma concentration of Phenobarbital is possibly increased.<br>• **St John's wort (Hypericum perforatum) –** the effect of phenobarbital can be reduced by concomitant use of theherbal remedy St John's wort. | • **Antidepressants** – paroxetine, mianserin and tricyclic antidepressants.<br>• **Antiepileptics** – carbamazepine, lamotrigine, tiagabine, zonisamide, primidone and possibly ethosuxamide.<br>• **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.<br>• **Antipsychotics** – phenobarbital possibly reduces concentration of aripiprazole.<br>• **Antivirals** – phenobarbital possibly reduces plasma levels of abacavir, amprenavir, darunavir, lopinavir, indinavir, nelfinavir, saquinavir.<br>• **Anxiolytics and Hypnotics** – clonazepam.<br>• **Aprepitant** – phenobarbital possibly reduces plasma concentration of aprepitant.<br>• **Beta-blockers** – metoprolol, timololand possibly propranolol.<br>• **Calcium channel blockers** – phenobarbital causes reduced levels of felodipine, isradipine, diltiazem, verapamil, nimodipine and nifedipine and an increase in dosage may be required.<br>• **Cardiac Glycosides** – blood levels of digitoxin can be halved by concurrent use.<br>• **Ciclosporin or tacrolimus.**<br>• **Corticosteroids**<br>• **Cytotoxics** – phenobarbital possibly reduces the plasma levels of etoposide or irinotecan.<br>• **Diuretics** – concomitant use with eplerenone should be avoided.<br>• **Haloperidol** - serum levels are approximately halved by concurrent used with phenobarbital.<br>• **Hormone Antagonists** – gestrinone and possibly toremifene.<br>• **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. |

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| | • **Montelukast.**<br>• **Oestrogens** – reduced contraceptive effect.<br>• **Progestogens** – reduced contraceptive effect.<br>• **Sodium oxybate –** enhanced effects, avoid concomitant use.<br>• **Theophylline** – may require an increase in theophylline dose.<br>• **Thyroid hormones** - may increase requirements for thyroid hormones in hypothyroidism.<br>• **Tibolone**<br>• **Tropisetron**<br>• **Vitamins** – barbiturates possibly<br>• increase requirements for vitamin D. |

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.

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 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 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 appears 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 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 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 lamotrigine monotherapy during pregnancy.

Pre-clinical studies have also reported adverse neurodevelopment effects (see section 5.3).

Haemorrhage at birth and addiction are also a risk. Prophylactic treatment with vitamin K1 for the mother before delivery (as well as 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.

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.

Breast-feeding

Phenobarbital is excreted into breast milk and there is a small risk of neonatal sedation. Breast feeding is therefore not advisable.

## 4.7 Effects on ability to drive and use machines

Phenobarbital may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery. Patients should be advised to make sure they are not affected before undertaking any potentially hazardous tasks.

## 4.8 Undesirable effects

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

*Musculoskeletal and connective tissue disorders:* 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 and breast disorders:* Peyronie's disease.

*Psychiatric disorders:* Paradoxical reaction (unusual excitement), hallucinations, restlessness and confusion in the elderly, mental depression, memory and cognitive impairment, drowsiness, lethargy.

*Nervous systems disorders:* Hyperactivity, behavioural disturbances in children, ataxia, nystagmus.

*Cardiac disorders:* Hypotension

*Respiratory disorders:* Respiratory depression

*Hepato-biliary disorders:* 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).

Frequency: very rare.

*General disorders and administration site conditions:* Antiepileptic hypersensitivity syndrome (features include fever, rash, lymphadenopathy, lymphocytosis, eosinophilia, haematological abnormalities, hepatic and other organ involvement including renal and pulmonary systems which may become life threatening).

**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

Drowsiness, coma, respiratory depression, dysarthria, ataxia, nystagmus, disinhibition, cardiovascular collapse, cardiac arrest, hypotonia, hyporeflexia, hypotension and hypothermia.

Barbiturates decrease gut motility, which may lead to slow onset and worsening of symptoms or cyclical improvement and worsening of symptoms.

Management

Consider activated charcoal (50g for an adult, 10-15g for a child under 5 years) if more than 10mg/kg body weight of phenobarbital has been ingested within 1 hour, provided the airway can be protected. Repeat dose activated charcoal is the best method of enhancing elimination of phenobarbital in symptomatic patients. In severe hypotension dopamine or dobutamine can be used. Treat rhabdomyolysis with urinary alkalinisation. Haemodialysis or haemofiltration may be required for cases of acute renal or severe hyperkalaemia.

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

Pharmacotherapeutic group: Barbiturates and derivatives, ATC code: N03A A02

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 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 Ca2+ 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

Absorption - Phenobarbital is readily absorbed from the gastrointestinal tract although it is relatively lipid-insoluble; peak concentrations are reached in about 2 hours after oral administration.

Distribution - Phenobarbital is about 45 to 60% bound to plasma proteins. Phenobarbital crosses the placental barrier and is distributed into breast milk.

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. There is considerable interindividual variation in phenobarbital kinetics. Phenobarbital is only partly metabolised in the liver.

Elimination – About 25% of a dose is excreted in the urine unchanged at normal urinary pH.

### 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

Maize starch
Lactose monohydrate
Sodium laurilsulfate
Sodium starch glycolate (Type A)
Magnesium stearate
Stearic acid
Sunset yellow (E110)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed.
Store in the original container.

### 6.5 Nature and contents of container

Polypropylene tablet containers with low density polyethylene caps.

Pack sizes: 28, 1000 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited,
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Nicosia.
Cyprus

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0082

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/11/2011

## 10 DATE OF REVISION OF THE TEXT

27/01/2022