1. Name of the medicinal product
Verbital-100 (Phenobarbital tablet BP 100 mg).

2. Qualitative and quantitative composition
Qualitative formula
Each uncoated tablet contains
Phenobarbital BP
Excipients q.s.

Quantitative formula
Each uncoated tablet contains
Phenobarbital BP 100 mg
Excipients q.s.

3. Pharmaceutical form
Oral Solid Dosage form (tablet)

4. Clinical particulars
4.1 Therapeutic indications
Phenobarbital is recommended for all forms of epilepsy (except absence seizures).

4.2 Posology and method of administration
Adults: 60-180mg at night
Child: 5-8mg/kg daily
Elderly: Phenobarbital clearance diminishes in the elderly. Therefore the dose of phenobarbital is usually lower in elderly patients.
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
For oral administration

4.3 Contraindications
Phenobarbital should not be given to patients with:
• Known hypersensitivity to phenobarbital, other barbiturates or other ingredients in the tablet
• Acute intermittent porphyia
• 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:
• Patients with the rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose – galactose malabsorption should not take this medicine
• 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects on Phenobarbital	**Effects of phenobarbital on other medicines**
• Alcohol – concurrent administration with alcohol may lead to an additive CNS depressant effect. This is likely with concurrent administration with other CNS depressants.	Phenobarbital increases the rate of metabolism reducing serum concentrations of the following drugs: • Anti-arrhythmics – disopyramide and quinidine loss of arrhythmia control is possible. Plasma levels of antiarrhymics should be monitored, if

• Antidepressants – including MAOIs, SSRIs and tricyclics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold • Antiepileptics - phenobarbital plasma concentrations increased by oxcarbazepine, phenytoin and sodium valproate. Vigabatrin possibly decreases phenobarbital plasma concentrations. • Antipsychotics – concurrent use of chlorpromazine and thioridazine with phenobarbital can reduce the serum levels of either drug. • Folic acid – if folic acid supplements are given to treat folate deficiency, which can be caused by the use of phenobarbital, the serum phenobarbital levels may fall, leading to decreased seizure control in some patients. (see section 4.6). • Memantine – the effect of Phenobarbital is possibly reduced. • Methylphenidate – plasma concentration of Phenobarbital is possibly increased. • St John's wort (Hypericum perforatum) – the effect of phenobarbital can be reduced by concomitant use of the herbal remedy St John's wort.	phenobarbital is added or withdrawn. Changes in dosage may be necessary. • Antibacterials – chloramphenicol, doxycycline, metronidazole and rifampicin. Avoid concomitant use of telithromycin during and for 2 weeks after Phenobarbital. • Anticoagulants. • Antidepressants – paroxetine, mianserin and tricyclic antidepressants. • Antiepileptics – carbamazepine, lamotrigine, tiagabine, zonisamide, primidone and possibly ethosuxamide. • Antifungals – the antifungal effects of griseofulvin can be reduced or even abolished by concurrent use. Phenobarbital possibly reduces plasma concentrations of itraconazole or posaconazole. Avoid concomitant use of voriconazole. • Antipsychotics – phenobarbital possibly reduces concentration of aripiprazole. • Antivirals – phenobarbital possibly reduces plasma levels of abacavir, amprenavir, darunavir, lopinavir, indinavir, nelfinavir, saquinavir. • Anxiolytics and Hypnotics – clonazepam. • Aprepitant – phenobarbital possibly reduces plasma concentration of aprepitant. • Beta-blockers – metoprolol, timolol and possibly propranolol. • Calcium channel blockers – phenobarbital causes reduced levels of felodipine, isradipine, diltiazem, verapamil, nimodipine and nifedipine and an increase in dosage may be required. • Cardiac Glycosides – blood levels of digitoxin can be halved by concurrent use. • Ciclosporin or tacrolimus. • Corticosteroids. • Cytotoxics – phenobarbital possibly reduces the plasma levels of etoposide or irinotecan. • Diuretics – concomitant use with eplerenone should be avoided.

	• Haloperidol- serum levels are approximately halved by concurrent used with phenobarbital. • Hormone Antagonists – gestrinone and possibly toremifene. • Methadone – levels can be reduced by concurrent use of phenobarbital and withdrawal symptoms have been reported in patients maintained on methadone when phenobarbital has been added. Increases in the methadone dosage may be necessary. • Montelukast. • Oestrogens – reduced contraceptive effect. • Progestogens – reduced contraceptive effect. • Sodium oxybate – enhanced effects, avoid concomitant use. • Theophylline – may require an increase in theophylline dose. • Thyroid hormones-may increase requirements for thyroid hormones in hypothyroidism. • Tibolone • Tropisetron • Vitamins – barbiturates possibly increase requirements for vitamin D

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

4.6 Pregnancy and lactation

Phenobarbital therapy in epileptic pregnant women presents a risk to the fetus in terms of major and minor congenital defects such as congenital craniofacial, digital abnormalities and, less commonly, cleft lip and palate. The risk of teratogenic effects developing appears to be greater if more than one antiepileptic drug is administered. The risk to the mother, however is greater if phenobarbital is withheld and seizure control is lost. The risk: benefit balance, in this case, favours continued use of the drug during pregnancy at the lowest possible level to control seizures.

Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy. Folic acid supplementation during pregnancy can help to reduce the risk of neural defects to the infant.

Phenobarbital readily crosses the placenta following oral administration and is distributed throughout fetal tissue, the highest concentrations being found in the placenta, fetal liver and brain. Adverse effects on neurobehavioral development have also been reported.

Haemorrhage at birth and addiction are also a risk. Prophylactic treatment with vitamin K^1 for the mother before delivery (as well as the neonate) is recommended, the neonate should be monitored for signs of bleeding.
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 a car 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 the lymphatic system disorders:* megaloblastic anaemia (due to folate deficiency), agranulocytosis, thrombocytopenia.
•*Metabolism and nutritional disorders:* 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.
•*Psychiatric disorders:* paradoxical reaction (unusual excitement), hallucinations, restlessness and confusion in the elderly, mental depression, memory and cognitive impairment, drowsiness, lethargy.
•*Nervous system disorders:* hyperactivity, behavioural disturbances in children, ataxia, nystagmus.
•*Cardiac disorders:* hypotension.
•*Respiratory disorders:* respiratory depression.
•*Hepato-bilary:* hepatitis, cholestasis.
•*Skin and subcutaneous tissue disorders:* allergic skin reactions (maculopapular morbilliform or scarlatiniform rashes), other skin reactions such as exfoliative dermatitis, erythema multiforme.
Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported.
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).
• *Blood and the lymphatic system disorders:* megaloblastic anaemia (due to folate deficiency), agranulocytosis, thrombocytopenia.
•*Metabolism and nutritional disorders:* osteomalacia, rickets.

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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.

Features:

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

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 alkalinistion. 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 severe barbiturate poisoning who fail to improve, or who deteriorate despite good supportive care.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC CODE: N03A A02

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 Ca^{2+} influx into depolarised synaptosomes. It raises brain serotonin levels, and inhibits noradrenaline **(**norepinephrine) reuptake into synaptosomes. These additional biochemical actions may contribute towards the anticonvulsant effects of the drug.

5.2 Pharmacokinetic properties

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 in 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

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate
Maize Starch
Microcrystalline cellulose
P.V.P.K.-30
Colloidal silicon dioxide

Purified talc
Magnesium stearate
Sodium starch glycolate
Crosscarmellose sodium
Purified water

6.2 Incompatibilities
Incompatible with macrogol.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at a temperature not exceeding 30° C. Protect from light & moisture.

6.5 Nature and contents of container
Verbital-100 is supplied in blister of 10 tablets, 10 such blister in 1 carton (10x10)

6.6 Special precautions for disposal and other handling
Not applicable.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES
Marketing Authorisation Holder
Abacus Pharma (A) Ltd.
BP 4344, B1 -85
K.CT Market
Kigali, Rwanda

Manufacturing Site:
Verve Human Care Laboratories
15-A, Pharmacity,
Selaqui, Dehradun-248011
India

8. MARKETING AUTHORISATION NUMBER
Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION
Not Applicable

10. DATE OF REVISION OF THE TEXT
Not Applicable

11. DOSIMETRY (IF APPLICABLE)
Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
Not Applicable