**1.4 PRODUCT INFORMATION**
**1.4.1 Prescribing information (Summary of Product Characteristics)**
**1. NAME OF THE MEDICINAL PRODUCT**
Phenytoin 100mg Tablets.

**1.1 Strength:**
Phenytoin Sodium 100mg.

**1.2 Pharmaceutical Form:**
Film Coated Tablets.

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
**Each film coated tablet contains:** Phenytoin Sodium BP 100mg.
*Full list of excipients is provided in section 6.1*

**3. PHARMACEUTICAL FORM**
Film Coated Tablets.
White, circular, biconvex film coated tablets plain on both sides. Packed in blisters of 10 x 10's, 100 x 10's in a unit box and in 1000's in HDPE containers with literature insert.

**4. CLINICAL PARTICULARS**
**4.1 Therapeutic indications:**
Phenytoin tablets are indicated for the control of generalized tonic-clonic (grand mal) and complex partial (focal) seizures and prevention and treatment of seizure occurring during or after-neurosurgery of following severe traumatic injury to the head. It is believed to stabilize rather than alleviate the seizure threshold and to limit the spread of seizure activity.

**4.2 Dosage and administration:**
Phenytoin tablets are administered orally with at least half a tumbleful of water either during or after meals in order to lessen gastric irritation. The dose of phenytoin tablets should be adjusted to the needs of individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations.
**Dosage:** ***Adults***
The recommended initial dose of phenytoin tablets in adults is 100mg three times daily progressively increased with care to 600mg daily if necessary; the suggested interval between increments can range from one week to one month. Maintenance dose is 300 to 400mg daily.
***Dosage: Children***
**Initial dose:** 5mg per kg body weight daily in 2 to 3 divided doses.
**Maintenance dose:** 4mg to 8mg per kg body weight daily in divided doses. Young children may require a higher dose per kg body weight than adults due to more rapid metabolism.
Phenytoin tablets may be administered with other antiepileptic agents but single drug therapy is generally preferred unless the patient is suffering from two different forms of epilepsy which require control by different drugs.

**4.3 Method of administration:**
Phenytoin 100mg Tablets are administered orally.

**4.4 Contraindications:**
1. Phenytoin is contraindicated in patients hypersensitive to phenytoin or other hydantoins.
2. Use of phenytoin in pregnancy may result in hypoprothrombinaemia and at times congenital malfunctions in the newborn.

**4.5 Special warnings and precautions for use:**
1.Phenytoin should be used with caution in diabetics and in liver malfunction.
2.Change of phenytoin administration with other antiepileptic drugs during therapy should be gradual.
3.Withdraw treatment if leucopenia develops.
4.Patients/minders should be taught to recognize toxicity signs and advised to seek medical help if hypersensitivity reactions develop.
5. Drugs that inhibit phenytoin metabolism have the potential of raising phenytoin concentration to toxic levels.

**4.6 Paediatric Population:**
**Infants and Children:**
Initially, 5mg/kg/day in two divided doses, with subsequent dosage individualised to a maximum of 300mg daily. A recommended daily maintenance dosage is usually 4 mg/kg to 8 mg/kg.
**Neonates:**
The absorption of phenytoin following oral administration in neonates is unpredictable. Furthermore, the metabolism of phenytoin may be depressed. It is therefore especially important to monitor serum levels in the neonate.

**4.7 Interaction with other medicinal products and other forms of interaction:**
Phenytoin induces the metabolism of a number of drugs which include antibacterials, anticoagulants, corticosteroids, quinidine and oral contraceptives.

**4.8 Additional information on special populations:**
**Patients with Renal or Hepatic Disease:**
Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinemia. Unbound phenytoin concentrations may be more useful in these patient populations (see section 4.4 Special warnings and precautions for use-General).

**4.9 Paediatric Population:**
**Infants and Children:**
Initially, 5mg/kg/day in two divided doses, with subsequent dosage individualised to a maximum of 300mg daily. A recommended daily maintenance dosage is usually 4 mg/kg to 8 mg/kg.
**Neonates:**
The absorption of phenytoin following oral administration in neonates is unpredictable. Furthermore, the metabolism of phenytoin may be depressed. It is therefore especially important to monitor serum levels in the neonate.

**4.10 Fertility, Pregnancy and Lactation:**
**Pregnancy**
Risk related to antiepileptic medicinal products in general
When possible, 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 breakthrough seizures that could have serious consequences for the woman and the unborn child. As a general principle, monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

**Risk related to phenytoin**
**Phenytoin crosses the placenta in humans.**
Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Studies have shown that phenytoin exposure during pregnancy is associated with an approximate 6% frequency of major malformations, which is higher than the frequency in the general population of 2-3%. Malformations such as orofacial clefts, cardiac defects, craniofacial defects, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Foetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy.
Neurodevelopmental disorders have been reported among children born to women with epilepsy who took phenytoin alone or in combination with other AEDs during pregnancy. Studies related to neurodevelopmental risk in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded. A small number of studies have found an increase of serious adverse outcomes compared to control subjects including foetal hydantoin syndrome and below average IQ.
There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. However, the respective role of antiepileptic drugs and other factors in the increased risk is not determined.
Phenytoin should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking phenytoin during pregnancy.

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see section 4.2). However, postpartum restoration of the original dosage will probably be indicated.
If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and the treatment with Phenytoin Sodium film-coated tablets is continued, the lowest effective dose of phenytoin should be used. If a woman is planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If a woman becomes pregnant while taking phenytoin, she should be referred to a specialist to reassess phenytoin treatment and consider alternative treatment options.

**In women of childbearing potential**
Phenytoin 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. The woman should be fully informed of and understand the risk of potential harm to the foetus if phenytoin is taken during pregnancy and therefore the importance of planning any pregnancy. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with Phenytoin.
Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, Phenytoin Sodium film-coated tablets may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see section 4.5). At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

**Women planning to become pregnant and in pregnant women**
In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception. Phenytoin should not be discontinued prior to reassessment of the treatment. When possible, patients should be informed of the potential harm to the foetus. If based on a careful evaluation of the risks and the benefits, phenytoin treatment is continued during the pregnancy, it is recommended to use the lowest effective dose and to institute specialized prenatal monitoring, oriented on the possible occurrence of the described malformations.

**In neonates**
Haemorrhagic syndrome has been reported in neonates born from epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother during the last gestational month and to the neonate after birth.

**Post-natal monitoring/children**
In case of exposure during pregnancy, children should be closely monitored in relation to neurodevelopmental disorders in order to provide specialized care as soon as possible, if necessary.

**Breast-feeding**
It is not known whether phenytoin is excreted in human milk. Following administration of oral phenytoin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast-feeding is not recommended for women receiving Phenytoin sodium tablets.

**Fertility**
In animal studies, phenytoin had no direct effect on fertility.

**4.11 Effects on ability to drive and use machines:**
Because of the side effect profile, administration of phenytoin is likely to have an effect on the ability to drive and use machines. Patients must therefore be advised against operating machinery or driving after administration of phenytoin.

**4.12 Undesirable effects:**

**Commonly encountered side effects:**

1.Anorexia, headache, dizziness, transient nervousness, insomnia and gastrointestinal disturbances such as nausea, vomiting and constipation.

2. Tenderness and hyperplasia of gums in young patients.

3. Acne, hirsutism and coarsening of facial features in adolescents and women.

4. Mild hypersensitivity reactions commonly with skin rashes, often morbilliform and which may be accompanied with fever.

**Occasionally encountered side effects:**

1. Symptoms of rare severe hypersensitivity reactions such as lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis.

2. Other conditions that may represent hypersensitivity reactions are: eosinophilia, lymphadenopathy, blood disorders such as a plastic anaemia, leucopenia, thrombocytopenia and agranulocytosis.

**Side effects that may be encountered with prolonged treatment:**

1. Subtle effects on mental function and cognition may be produced especially in children.

2. Rickets and osteomalacia may occur in those inadequately exposed to sunlight.

3. Mild peripheral neuropathies

4. Megaloblastic anaemia.

**Toxic manifestations**

1. These manifest often as cerebellar, vestibular and ocular effects; notable are nystagmus, diplopia and ataxia; mental confusion (Sometimes severe), dyskinesia, and exacerbations of seizure frequency may occur.

2. Toxic phenytoin concentrations often lead to hyperglycaemia.

3. Overdosage leads to hypotension, coma and respiratory depression.

**4.13 Overdose:**

In all cases of overdose or of accidental or non-accidental poisoning, the patient must be admitted to a hospital as soon as possible in order to monitor the course of symptoms efficiently and to initiate appropriate therapy with monitoring of vital functions. Symptoms: the lethal dose in children is not known. The mean lethal dose in adults is between 2 and 5 g. The initial symptoms of overdose are nystagmus, ataxia and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech and nausea and vomiting. On the cardiovascular level, the following symptoms can also be observed: hypotension, sinus bradycardia and transient sinus cardiac arrest. The patient can become comatose and death can follow from respiratory and circulatory depression. Although there are marked variations between individuals with respect to toxic plasma levels of phenytoin, nystagmus usually appears at serum levels of 20 µg/ml, ataxia at 30 µg/ml and dysarthria and lethargy at >40 µg/ml. In the event of an overdose, however contradictory this may be, epileptic seizures can occur. Treatment: the treatment of overdose is non-specific since there is no antidote. The usual measures in the event of poisoning or overdose should be applied. In the case of poisoning, gastric lavage, forced diuresis, activated charcoal, oxygen, vasopressors and assisted ventilation can be used. It is also possible to switch to haemodialysis in the event of severe poisoning. Immediately: forced diuresis and haemoperfusion. In the event of persistent hypotension or persistent bradyarrhythmia, intravenous injection of 0.3 to 0.5 mg atropine should be used, repeated, if necessary, at 15-minute intervals, without exceeding a dose of 1.5 to 2 mg in adults and 0.5 mg to 1 mg in children (mean dose in children: from 10 to 20 µg/kg). Haemodialysis or haemoperfusion can also be considered in the event of severe poisoning.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties:**

**Pharmacotherapeutic Group:** Nervous System, Antiepileptics, Hydantoin Derivatives.

**ATC Code:** N03AB02.

Phenytoin tablets contain Phenytoin Sodium which is an antiepileptic drug. The primary site of action of action of Phenytoin Sodium appears to be the motor cortex were spread of seizure activity is inhibited. Phenytoin Sodium tends to stabilize the threshold against hyperexcitability caused by excessive stimulation by promoting sodium efflux from neurons, thus reducing post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centres responsible for the tonic phase of tonic-clonic (grand mal) seizures.

**5.2 Pharmacokinetic properties:**

Phenytoin is slowly but almost completely absorbed from the gastrointestinal tract and is extensively metabolised in the liver to inactive metabolites. It is widely distributed throughout the body and is extensively bound (about 90%) to plasma proteins. Phenytoin undergoes enterohepatic recycling and is excreted in the urine, mainly as its hydroxylated metabolite, in either free or conjugated form.

**5.3 Preclinical safety data:**

Phenytoin causes embryofetal death, growth retardation and behavioural dysfunctions and is teratogenic in rats, mice, and rabbits. The most common teratogenic effects are craniofacial defects including cleft palate and hydrocephalus, renal defects,

limb abnormalities and cardiovascular defects. The teratogenic effects of phenytoin in rodents occur at doses and exposure similar to the therapeutic dose. Two-year carcinogenicity studies in mice and rats showed an increased number of hepatocellular adenomas in mice, but not rats, at plasma concentrations relevant for humans. The international agency for research on cancer (iarc) classifies phenytoin as possibly carcinogenic to humans (group 2b). Genetic toxicity studies showed that phenytoin was not mutagenic in bacteria. Phenytoin shows clastogenic potential in some in vitro and in vivo studies, while other studies did not confirm such findings.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients:

- Dicalcium Phosphate
- White Corn Starch
- Sodium Lauryl Sulphate
- Polysorbate 80
- Purified Water
- Microcrystalline Cellulose pH 101
- Sodium Starch Glycolate
- Purified Talc
- Magnesium Stearate
- Hydroxypropyl Methylcellulose (5 Cps)
- Titanium Dioxide
- Monopropylene Glycol
- Polyethylene Glycol 6000
- Acetone
- Isopropyl Alcohol 99%

### 6.2 Incompatibilities:

None Known.

### 6.3 Shelf Life:

36 Months.

### 6.4 Special Precautions for Storage:

Store in a dry place below 30°C.
Protect from light.
Keep all medicines out of reach of children.

### 6.5 nature and contents of container:

White, circular, biconvex film coated tablets plain on both sides. Packed in blisters of 10 x 10's, 100 x 10's in a unit box with and in 1000's in HDPE containers with literature insert.

### 6.6 Special Precautions for Disposal and other Handling:

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

## 7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES:

**Marketing Authorization Holder:**

**Company Name:** LABORATORY & ALLIED LTD
**Address:** Plot No. 209/10349, Opposite Sameer Business Park, Next to Libra House, Mombasa Road, P.O. Box 42875 GPO 00100, Nairobi-Kenya.
**Country :** Kenya
**Telephone :** +254 20 8040306
**Telefax :** +254 20 8040309
**E-Mail :** info@laballied.com.

**Manufacturing Site Address:**

**Company Name:** LABORATORY & ALLIED LTD
**Address:** Plot No. 209/10349, Opposite Sameer Business Park, Next to Libra House, Mombasa Road, P.O. Box 42875 GPO 00100, Nairobi-Kenya.
**Country :** Kenya
**Telephone :** +254 20 8040306
**Telefax :** +254 20 8040309
**E-Mail :** info@laballied.com

**8. MARKETING AUTHORIZATION NUMBER:**
**Kenya Reg No.:** H2000/7058.

**9. DATE OF FIRST REGISTRATION/ RENEWAL OF THE REGISTRATION:**
**Registration Date:** 01/11/2000.
**Renewal Date:** To be retained annually.

**10. DATE OF REVISION OF THE TEXT:**
March, 2024.

**11. DOSIMETRY (IF APPLICABLE)**
Not Applicable.

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