1.3 SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND INSTRUCTIONS FOR MEDICAL USE:

1.3.1. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1.3.1.1 NAME OF MEDICIANAL PRODUCT

Product Name: Phenytoin Injection BP

Strength: 250mg/5ml

Pharmaceutical dosage from: Injection

1.3.1.2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The quantitative composition and function of each component in the drug product is listed below in **Table P.1.T01**

Label claim:

Each ml contains:

Phenytoin Sodium BP	50mg
Propylene glycol BP	40% v/v
Ethanol BP	10% v/v
Water for Injection BP	qs

Batch Size:

100 Ltr (18,868 Ampoules)

Table P.1.T01:

Sr. No.	Ingredients	Specification	Mg/ml	Std. Qty.	Unit	Uses
1	Phenytoin Sodium* (with 3% overages)	BP	51.5	5.150	Kg	Active ingredient

2	Propylene Glycol	BP	0.4	40.00 = 42.00	Ltr. Kg	Drug solublizer
3	Absolute alcohol	BP	0.1	10.00	Ltr.	Solvent
4	Sodium Hydroxide	BP	q.s. pH 11.8	0.050	Kg	pH adjuster
5	Water for Injection	BP	q.s. 1.0	q.s. 100.0	Ltr	Vehicle
6	Amp., Flint, Type-I 2ml, S/O yellow	IH	----	19,800	Nos.	-----

Note:

Target fill volume 5.3 ml (21.2 ml for 4 dose in 25 ml graduated cylinder, (limit 20.8 to 21.6 ml))

pH of Injection 11.5 to 12.1

Actual quantity of Phenytoin Sodium to be issued = $\frac{5.150 \times 100 \times 100}{X \times (100 - Y)}$ = A kg

[Where X = Assay of Phenytoin Sodium on anhydrous basis…….and Y = Water]

Sodium hydroxide to be dissolved in 200 ml of WFI and to be used for pH adjustment.

1.3.1.3 PHARMACEUTICAL FORM:

Injection

1.3.1.4 CLINICAL PARTICULATE

a) **INDICATIONS:** Phenytoin injection is an anticonvulsant medication that is used to treat a prolonged seizure (status epilepticus). Phenytoin injection is also used to prevent seizures during a surgery.

b) POSOLOGY AND METHOD OF ADMINISTRATION:

Method of administration

Phenytoin Injection BP should be injected slowly and directly into a large vein through a large-gauge needle or intravenous catheter. It must be administered slowly. Intravenous administration should not exceed 50 mg/minute in adults. In neonates the drug should be administered at a rate

not exceeding 1 to 3 mg/kg/min. Each injection should be followed by an injection of 0.9% sodium chloride through the same needle or catheter to avoid local venous irritation due to the alkalinity of the solution.

Continuous monitoring of the electrocardiogram and blood pressure is essential. Cardiac resuscitative equipment should be available. The patient should be observed for signs of respiratory depression. If administration of intravenous Phenytoin Injection BP does not terminate seizures, the use of other measures, including general anaesthesia, should be considered.

Status epilepticus: In a patient having continuous seizure activity, as compared to the more common rapidly recurring seizures, i.e. serial epilepsy, injection of intravenous diazepam or a short acting barbiturate is recommended because of their rapid onset of action, prior to administration of Phenytoin Injection BP. Following the use of diazepam in patients having continuous seizures and in the initial management of serial epilepsy, a loading dose of 10-15 mg/kg should be given by slow intravenous injection at a rate not exceeding 50 mg/minute in adults to avoid hypotension (this will require approximately 20 minutes in a 70kg patient). The loading dose is then followed by a maintenance dose of 100 mg given orally or intravenously every 6-8 hours. In geriatric patients with heart disease, it has been recommended that the drug be given at a rate of 50 mg over 2-3 minutes.

Paediatric Population

As for adults, however it has been shown that children tend to metabolise phenytoin more rapidly than adults. This should be borne in mind when determining dosage regimens; the use of serum level monitoring being particularly beneficial in such cases.

Determination of phenytoin serum levels is advised when using Phenytoin Injection BP in the management of status epilepticus and in the subsequent establishing of maintenance dosage. The clinically effective level is usually 10-20 mg/l although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin.

In a patient who has not previously received the drug, Phenytoin Injection BP, 100 mg-200 mg (2-4 ml), may be given intramuscularly at approximately 4 hourly intervals prophylactically during neurosurgery and continued during the postoperative period for 48-72 hours. The dosage should then be reduced to a maintenance dose of 300 mg and adjusted according to serum level estimations.

When given by intramuscular injection, phenytoin precipitates out at the injection site and is absorbed slowly and erratically. This route is not, therefore, recommended for treating status epilepticus. If phenytoin is administered by intramuscular injection to patients unable to take the drug orally, the dose should be increased by 50% over the previously established oral dose. To avoid drug accumulation resulting from eventual absorption from intramuscular injection sites, it is recommended that for the first week back on oral therapy the dose is reduced to one-half the original dose. Monitoring of serum concentrations is also recommended. Intramuscular therapy should generally be limited to 1 week.

Phenytoin sodium can be useful in cardiac arrhythmias, particularly those due to digitalis. The recommended dosage is one intravenous injection of Phenytoin Injection BP of 3.5 to 5 mg/kg bodyweight initially, repeated once if necessary. The solution should be injected slowly, intravenously and at a uniform rate which should not exceed 1ml (50mg) per minute

c) CONTRAINDICATIONS:

- Hypersensitivity to phenytoin or to any of the excipients.
- Patients with sinus bradycardia, sino-atrial block, second and third degree AV block or Adams-Stokes syndrome.
- Intra-arterial administration must be avoided in view of the high pH of the preparation.

d) 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 Phenytoin. 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.

Hypotension may occur. Severe cardiotoxic reactions and fatalities have been reported with arrhythmias including bradycardia, atrial and ventricular depression, and ventricular fibrillation. In some cases cardiac arrhythmias have resulted in asystole/ cardiac arrest and death. Severe

complications are most commonly encountered in elderly or gravely ill patients. Cardiac adverse events have also been reported in adults and children without underlying cardiac disease or comorbidities and at recommended doses and infusion rates. Therefore, careful cardiac (including respiratory) monitoring is needed when administering IV loading doses of phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed. Phenytoin should be used with caution in patients with hypotension and/or severe myocardial insufficiency.

In these patients, the drug should be administered at a rate not exceeding 25 mg/minute, and if necessary, at a slow rate of 5 to 10 mg/minute.

Phenytoin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes

Patients with renal function impairment should also be carefully observed when prescribing phenytoin, as excretion and protein binding may be altered.

Phenytoin may affect glucose metabolism and inhibit insulin release.

Hyperglycaemia has been reported. Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes. Phenytoin should be used with caution in diabetic patients as hyperglycaemia may be potentiated.

e) INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Drugs which may increase serum levels of phenytoin include: amiodarone, antifungal agents (such as, but not limited to, amphotericin B fluconazole, ketoconazole, miconazole and itraconazole), chloramphenicol, coumarin anticoagulants, chlordiazepoxide, dicoumarol, diltiazem, fluoxetine, fluvoxamine, sertraline, nifedipine, omeprazole, H2-antagonists e.g. cimetidine, ranitidine, disulfiram, phenylbutazone, isoniazid, salicylates, chlordiazepoxide, phenothiazines, diazepam, oestrogens, ethosuximide, sulthiame, halothane, methylphenidate, trimethadione, mephenytoin, sulphonamides, trazodone, succinimides, tolbutamide, fluorouracil, oxcarbazepine and viloxazine.

Drugs which may decrease serum levels of phenytoin include: carbamazepine, reserpine, bleomycin, carboplatin, carmustine, cisplatin, methotrexate, vinblastine, folic acid, calcium folinate, rifampicin, sucralfate, theophylline and vigabatrin.

The serum levels of phenytoin can also be reduced by concomitant use of the herbal remedy St. John's wort (Hypericum perforatum). This is due to induction of drug metabolizing enzymes by St John's wort. Herbal preparations containing St John's wort should therefore not be combined with phenytoin. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort. The patient's physician should be consulted for adjustments in either therapy.

Drugs which may either increase or decrease serum levels of phenytoin and vice versa include: barbiturates, valproic acid and sodium valproate, ciprofloxacin, primidone, carbamazepine, phenobarbital, antineoplastic agents, certain antacids.

Acute alcohol intake may increase serum levels of phenytoin while chronic alcohol use may decrease them.

Tricyclic antidepressants, haloperidol, monoamine oxidase inhibitors and thioxanthenes may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

Phenytoin impairs the efficacy of several drugs, including: anticonvulsants (succinimide and lamotrigine), corticosteroids, coumarin anticoagulants (dicoumarol), cyclosporine, vitamin D, digoxin, disopyramide, doxycycline, frusemide, L-dopa, mexiletine, oestrogens, oral contraceptives (see sections 4.4 and 4.6), quinidine, and xanthines. Antifungal agents e.g. azoles, antineoplastic agents (dacarbazine), calcium channel blockers, clozapine, methadone, neuromuscular blockers, paroxetine, sertraline, rifampicin, ticagrelor and theophylline.

Drugs whose effect is enhanced by phenytoin include: warfarin. The effect of phenytoin on warfarin is variable and prothrombin times should be determined when these agents are combined. Serum level determinations are especially helpful when possible drug interactions are suspected.

f) PEGNANCY AND LACTATION:

Pregnant Women: 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. Phenytoin crosses the placenta in humans. Similar concentrations of phenytoin have been reported in the umbilical cord and maternal blood. Prenatal exposure to phenytoin may increase the risks for congenital malformation and other adverse developmental outcomes..

Nursing Mothers: 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 Injection BP.

g) EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as treatment with phenytoin may cause central nervous system adverse effects such as dizziness and drowsiness. Phenytoin in appropriate doses may as such impair driving skills but epilepsy itself dictates the practice of driving. Patients affected by drowsiness should not drive or operate machinery.

h) UNDESIRABLE EFFECTS:

The most notable signs of toxicity are cardiovascular collapse and/or depression of the central nervous system. Hypotension can occur when the drug is administered rapidly by intravenous injection.

Cardiac disorders

Immune system disorders

Nervous System disorder

Gastrointestinal disorders

Skin and subcutaneous tissue disorders

Blood and lymphatic system disorders

Reproductive system and breast disorders

Musculoskeletal and connective tissue disorders

Hepatobiliary disorders

Respiratory, thoracic and mediastinal disorders

Renal and urinary disorders

i) OVERDOSE:

The lethal dose in adults is considered to be 2 to 5 grams. The lethal dose in children is not known. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea and vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

Attempts to relate serum levels of the drug to toxic effects have shown wide interpatient variation. Nystagmus on lateral gaze usually appears at 20 mg/l, and ataxia at 30 mg/l, dysarthria and lethargy appear when the serum concentration is >40 mg/l, but a concentration as high as 50 mg/l has been reported without evidence of toxicity.

As much as 25 times the therapeutic dose, which resulted in a serum concentration of 100 mg/l, was taken with complete recovery

Treatment: Treatment is nonspecific since there is no known antidote. The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. (If ingestion has taken place, the stomach should be emptied). If the gag reflex is absent, the airway should be supported. Oxygen and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular depression. Haemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been utilised in the treatment of severe intoxication in children. In acute overdosage the possibility of the presence of other CNS depressants, including alcohol, should be borne in mind.

1.3.1.5 PHARMACOLOGICAL PROPERTIE

a. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antiepileptics, ATC code: N03AB02

Phenytoin sodium inhibits the spread of seizure activity in the motor cortex. It appears that by promoting sodium efflux from neurons, phenytoin sodium tends to stabilise the threshold against hyperexcitability caused by environmental changes or excessive stimulation capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation of synapses.

Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin thereby reduces the over-activity of brain stem centres responsible for the tonic phase of grand mal seizures.

Phenytoin sodium's antiarrhythmic action may be attributed to the normalization of influx of sodium and calcium to cardiac Purkinje fibres. Abnormal ventricular automaticity and membrane responsiveness are decreased. It also shortens the refractory period, and therefore shortens the QT interval and the duration of the action potential.

Hydantoins induce production of liver microsomal enzymes, thereby accelerating the metabolism of concomitantly administered drugs.

b. PHARMACOKINETIC PROPERTIES:

Absorption

The onset of action after an intravenous dose is 30 to 60 minutes and the effect persists up to 24 hours. Phenytoin is about 90% protein bound. Protein binding may be lower in neonates and hyperbilirubinemic infants; also altered in patients with hypalbuminaemia, uraemia or acute trauma, and in pregnancy. Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 microgram/ml. In renal failure or hypalbuminaemia, 5 to 12 microgram/ml or even less may be therapeutic.

Elimination

Phenytoin is metabolised in the liver, the major inactive metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH). The rate of metabolism is increased in younger children, pregnant women, in women during menses and in patients with acute trauma. The rate decreases with advancing age. Phenytoin may be metabolised slowly in a small number of individuals due to genetic factors, which may cause limited enzyme availability and lack of induction.

Pharmacokinetic/pharmacodynamic relationship(s)

The plasma half-life is normally from 10 to 15 hours. Because phenytoin exhibits saturable or dose-dependent pharmacokinetics, the apparent half-life of phenytoin changes with dose and serum concentration. At therapeutic concentrations of the drug, the enzyme system responsible for metabolising phenytoin becomes saturated. Thus a constant amount of drug is metabolised, and small increases in dose may cause disproportionately large increases in serum concentrations and apparent half-life, possibly causing unexpected toxicity.

c. PRECLINICAL SAFETY DATA

There are no preclinical data of relevance to the prescriber additional to the data presented in other sections of this summary.

1.3.1.6. PHARMACEUTICAL PARTICULARS

a) LIST OF EXCIPIENTS

Propylene glycol BP

Absolute alcohol BP

Sodium hydroxide BP

Water for Injections BP

b) INCOMPATIBILITIES

Incompatible with amikacin sulphate, cephapirin sodium, clindamycin phosphate, and many other drugs.

It is recommended that phenytoin sodium not be mixed with other drugs or with any infusion solution other than sodium chloride 0.9%.

c) SHELF LIFE

24 months from date of manufacturing

d) SPECIAL PRECAUTIONS FOR STORAGE

Store at a temperature below 30°C. Protect from light.

e) NATURE AND CONTENTS OF CONTAINER

Five ml amber coloured glass ampoule with snap off, labeled and packed in a plastic tray with five ampoules and such one tray along with packing insert is packed in a carton.

1.3.1.7. MARKETING AUTHORISATION HOLDER

Samarth Life Sciences Pvt. Ltd.

1.3.1.8. MARKETING AUTHORISATION NUMBER(S)

B4-2796

1.3.1.9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 July, 2014