Brand Name : TOPHEN-100 TABLETS **Generic Name :** Phenytoin Tablets BP 100 mg		2024
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

TOPHEN-100 TABLETS (Phenytoin Tablets BP 100 mg)

2. Qualitative and Quantitative Composition:

Each film coated tablet contains: Phenytoin Sodium BP 100 mg

3. Pharmaceutical form:

Off white colour, biconvex, film coated tablets.

4. Clinical particulars:

4.1 Therapeutic Indications:

Prophylaxis of partial epilepsy and of convulsive seizures of generalized epilepsy

Used prophylactically, for either indication, oral phenytion need not be taken more often than twice daily, and often once daily therapy suffices to keep steady state plasma and tissue concentrations of the drug within acceptable limits over each dosage interval. Unless a satisfactory clinical response occurs at lower plasma phenytion concentrations within the therapeutic range of 10-20 $mg.1^{-1}$ (40-80 $\mu mol.1^{-1}$). The average dose to achieve such levels in adults is 5 $mg.kg^{-1}$ per day, and in children 11 mg.kg-1 daily. A slightly lower initial dose may be advisable, with subsequent dose adjustments being made in the knowledge of the non linear relation in the individual between steady state plasma phenytion levels and dose increments. In adults, if plasma phenytion concentrations are below 10 mg.1-1 a 100 mg per dose increment will generally be tolerated, and with levels in the range 10-15 mg.1-1 a 50 mg per day increment. At levels above 15 mg.1-1 even a 30 mg per day dose increment may lead to toxicity after a few days. Dosage adjustments should be made, guided by plasma phenytion concentration measurements, only when steady state

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conditions apply (usually 1 week or longer after the most recent dose increment). If the patient's symptoms are not controlled with plasma phenytion concentrations in the therapeutic range, and if no significant adverse effects of therapy are present, the phenytion dose may still be increased cautiously in the hope of relieving the disorder being treated without causing unacceptable adverse effects of therapy.

Status epilepticus

In status epilepticus phenytion needs to be given parenterally. The drug is best given into the tubing of a running intravenous infusion (because the drug is irritant to veins) at a rate of up to 50 $mg.min^{-1}$ (in adults). The drug is so insoluble that it may precipitate out if injected into the contents of a fluid reservoir, resulting in unreliable intake of the drug.

The solvent in parenteral phenytion preparations tends to cause hypotension, a circumstance which contributes to the need for slow infusion of the drug. The adult phenytion dose to achieve therapeutic range plasma levels in a previously untreated patient may be of the order of 1000 mg, and this dose may have to be given intravenously in stages over several hours to avoid hypotension.

Intramuscular phenytion is absorbed too slowly and too unpredictably to provide reliable therapy.

Prophylaxis of cardiac arrhythmias and tic douloureux

If used for these purposes oral phenytoin is prescribed as for the prevention of epileptic seizures.

4.2 Posology and Method of Administration:

Doses may be expressed in terms of phenytoin or phenytoin sodium; although phenytoin 92 mg is approximately equivalent to 100 mg of phenytoin sodium these molecular equivalents are not necessarily biologically equivalent. In the UK an oral suspension of phenytoin 90 mg in 15 mL may be considered approximately equivalent in therapeutic effect to tablets containing phenytoin sodium 100 mg. In the USA a suspension containing phenytoin 125 mg in 5 mL is available.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; in many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some are controlled at concentrations outside this range. A suggested initial dose by mouth of phenytoin or phenytoin sodium given as a single dose or in divided doses is 3 to 4 mg/kg daily or 150 to 300 mg daily progressively increased with care to 600 mg daily if necessary; the suggested minimum interval between increments has ranged from about 7 to 10 days. Particular care is needed at higher doses, where saturation of

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metabolism may mean that a small increment produces a large rise in plasma concentrations. A usual maintenance dose is 200 to 500 mg daily.

A suggested initial dose for children is 5 mg/kg daily in 2 or 3 divided doses up to a maximum of 300 mg daily; a suggested maintenance dose is 4 to 8 mg/kg daily in divided doses. Young children may require a higher dose per kg body-weight than adults due to more rapid metabolism.

The practice of starting phenytoin therapy with initial small doses means that more than a week may be required before therapeutic plasma concentrations are attained; it has been reported that it may even be several weeks before a steady-state concentration is established. An initial loading dose may therefore be given, with the usual maintenance dosage being instituted 24 hours after the loading dose. Once the patient is stabilised the long half-life of phenytoin may permit the total daily dose to be given in two daily divisions or as a single dose, usually at night.
Although clinical evidence is lacking, different brands of phenytoin, as well as different formulations from the same manufacturer, may vary in their bioavailability and patients may need to be restabilised in the event of a change.

In order to lessen gastric irritation, phenytoin should be taken with or after food. The time and manner of taking phenytoin should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

Method of administration : Oral.

4.3 Contraindications:

1. Known hypersensitivity to phenytoin
2. Acute intermittent porphyria.

4.4 Special Warnings and Precautions for Use :

The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared.

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If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar compounds (e.g., barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients.
Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended.

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g., fever, rash, and liver involvement.
In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels, while chronic alcohol use may decrease serum levels.

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In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

4.5 Interaction with other medicinal products, and other forms of interaction:

Several detailed accounts of the interactions of phenytoin are available.

Potentially hazardous interactions

There do not appear to be any consistently dangerous interactions between phenytoin and other substances. Phenytoin shortens the half lives of dicumarol and dexamethasone. If phenytoin intake is ceased and dicumarol dose is not reduced there is risk of subsequent hemorrhage as dicumarol accumulates. If phenytoin intake is ceased and dicumarol dose is not reduced there is risk of subsequent hemorrhage as dicumarol accumulates. If phenytoin is added to therapy when a patient is receiving dexamethasone or other glucocorticoids to control raised intracranial pressure the intracranial pressure may subsequently rise if the steroid dose is not increased. The dose increase is necessary to compensate for the greater glucocorticoid clearance which results from induction of the liver mono-oxygenase system due to exposure to the anticonvulsant.

A large number of interactions involving phenytoin are known. The following co-administered substances have been reported to raise plasma phenytoin levels, and to thereby expose patients to the risk of phenytoin intoxication: carbamazepine (inconsistently), sulthiame, clonazepam (inconsistently), diazepam, ethosuximide, valproate (in early stages of therapy), trimethadione, mephenytoin, phenylacetylurea, pheneturide, dicumarol (inconsistently), warfarin (inconsistently), various sulfonamides, isoniazid, methylphenidate (inconsistently), tricyclic antidepressants, disulfiram, calcium carbamide, chloramphenicol, chlordiazepoxide, chlorphentermine, chlorpromazine, clofibrate, furosemide, halothane, propoxyphene, and propranolol. The following substances have been reported to interact with phenytoin to lower its plasma levels, and possibly to thus compromise the control of epilepsy: Phenobarbital (inconsistently), primidone (inconsistently), carbamazepine (inconsistently), clonazepam (inconsistently), valproate (late in therapy), folate, calcium sulfate, antacids, diazoxide, oxacillin, pyridoxine, tolbutamide, cimetidine, and the dietary supplement isocal.

Phenytoin, probably by virtue of inducing liver mono-oxygenase activity, increases the biotransformation of primidone to Phenobarbital, and shortens the half lives and / or decreases the plasma levels of Phenobarbital (inconsistently), carbamazepine, clonazepam, digitoxin, dicumarol, doxycycline, nortriptyline, phenazone, pyridoxine, cortisol, prednisolone, and dexamethasone. Thus concurrent therapy with phenytoin may diminish the efficacy of these drugs if their doses are not increased. Women taking combined oral contraceptive steroids with usually need to take a high dose preparation if they are also taking phenytoin.

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Other significant interactions

Tobacco smoking and mild to moderate alcohol intake do not alter the relationship between steady state plasma phenytoin level and phenytoin dose in adults. Chronic alcoholism may be associated with faster phenytoin elimination.

4.6 Pregnancy and Lactation:

Pregnancy

Phenytoin clearance increases during pregnancy, and returns to pre-pregnant values between 2 weeks and 6 months after parturition. The oral bioavailability of the drug is not decreased in pregnancy. Phenytoin doses must be increased during pregnancy to maintain plasma phenytoin levels at pre-pregnancy values. If this is not done seizures may increase in frequency. Phenytoin intake in pregnancy may cause hypoprothrombinemia and hemorrhage in the newborn. Vitamin K given in labor will protect against these latter complications.

In humans, several studies have shown that phenytoin intake during pregnancy is associated with an approximately doubled or trebled risk of malformation (cleft palate and / or lip, diaphragmatic hernia, congenital heart disease). Minor reversible terminal phalangeal abnormalities also occur in neonates exposed to phenytoin in utero. Despite the possibility of such teratogenesis, it is generally thought wise for pregnant women to continue to take the drug throughout pregnancy, if the therapy is indicated clinically. Preferably, the situation should have been discussed with the patient before pregnancy is undertaken.

Lactation

Phenytoin concentrations in breast milk are 20-50% of simultaneous plasma phenytoin levels. If a mother has plasma phenytoin levels in the therapeutic range it may be calculated that the usual daily volume of milk taken by her infant is unlikely to produce clinically significant plasma phenytoin concentrations in the infant. This is particularly so if there has been in utero exposure to the drug so that the infant's mono-oxygenase system is already induced.

4.7 Effects on ability to drive and use machines:

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Phenytoin Tablets refrain from driving or using machines.

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4.8 Undesirable effects:

Several reviews of the adverse effects of phenytoin are available.

Potentially life threatening effects

Very rarely phenytoin associated hepatitis or dermatitis may assume life threatening proportions. In humans, phenytoin very occasionally causes a reversible pseudo-lymphoma syndrome in which the enlarged lymph nodes have a histological appearance resembling that of Hodgkin's disease. There have been suggestions that the drug may occasionally be responsible for the development of malignant lymphomas and leukemia. However, one study found no association between phenytoin intake and neoplasia in humans.

Severe or irreversible adverse effects

There is some controversy as to whether chronic phenytoin overdosage in experimental animals and humans causes cerebellar purkinje cell degeneration.

Other serious adverse effects include exfoliative dermatitis, osteomalacia, hepatitis, thyroiditis, and subclinical peripheral neuropathy.

Symptomatic adverse effects

Chronic overdosage manifestations include intellectual dulling, depression of mood, gum hypertrophy, and hyperglycemia (from suppression of insulin release), as well as the features of acute toxicity described above.

Phenytoin may cause various types of dyskinesia, overgrowth of body hair, altered collagen growth in the lips, heel pads and pulmonary alveoli, hypocalcemia, manifestations of folate depletion (e.g. macrocytic anemia), and various skin rashes.

Other effects

Chronic phenytoin intake causes decreased serum and red blood cell folate levels, hypocalcemia, reduced serum 25-hydroxycholecalciferol levels, raised serum alkaline phosphatase and raised γ-glutamyl transpeptidase levels, decreased serum protein bound iodine and total thyroxine levels with increased unbound thyroxine concentrations, a shortened plasma cortisol half life, hypercholesterolemia, raised serum ceruloplasmin and copper levels, raised serum sex hormone binding globulin levels (in women), and reduced concentrations of IgA in serum and saliva, with some tendency to reduced serum IgC and IgM levels.

4.9 Overdose:

Death from acute phenytoin overdosage in humans is very uncommon. Adults have survived doses up to 21 g, but a 4-year-old child has died after ingesting 2 g. Clinical features of poisoning are nystagmus, blurred vision, diplopia and ataxia of gait,

nausea, vomiting, drowsiness, stupor, and finally coma with hypotension. Gastric lavage or activated charcoal are expected to reduce absorption if given within 1 or 2 h of overdose and repeated doses of activated charcoal should be given to hasten elimination. In very severe cases, charcoal hemoperfusion may be used.

Overdosage in humans has been reported to cause computerized tomographic appearances of cerebellar atrophy.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Phenytoin is reasonably effective in controlling the tonic clonic seizures of generalized epilepsy, and in both decreasing the frequency of partial seizures and diminishing the risk of their becoming secondarily generalized, with the occurrence of bilateral convulsions. The drug also helps prevent attacks of certain forms of supraventricular cardiac arrhythmia, possibly by a CNS effect. Phenytoin inhibits the conduction of trigeminal pain impulses in tic douloureux and in certain other forms of neuralgia. The drug prevents certain varieties of migraine through mechanisms of action which are not understood, and it acts on skeletal muscle to relieve myotonia, perhaps by altering C1 transport through sarcolemmal membrances.

The drug's effects correlate more closely with its plasma concentrations than with its dose.

5.2 Pharmacokinetic Properties:

Many assay methods have been described for phenytoin. However, plasma and serum Phenytoin levels are now preferably measured by one of a number of different forms of immunoassay, or by gas liquid or high performance liquid chromatography with UV detection. This last method may have a sensitivity as low as 100 mg.

Following oral administration, phenytoin is absorbed slowly but almost completely, although there have been some marketed formulations from which absorption was incomplete. The rate of absorption is prolonged as the dose increases. Peak plasma concentrations of phenytoin usually occur 2-4h after an oral dose, with a second peak at 10-12 h. There is no significant presystemic metabolism, hence bioavailability is usually >0.90, but will be less than this with formulations exhibiting poor absorption characteristics. Food does not appear to have any appreciable effect on the absorption of phenytoin. Although intramuscularly administered phenytoin is eventually absorbed completely, the drug first crystallizes out at its injection site, and then slowly redissolves in tissue fluids, before entering the circulation. As a consequence, absorption of phenytoin following intramuscular administration is too slow to produce a reliable therapeutic effect.

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The apparent volume of distribution of phenytoin is approximately 0.50-0.70 1.kg. Some 90 to 93% of the phenytoin in plasma is normally bound to plasma proteins, mainly albumin, though the degree of binding is decreased in renal insufficiency, severe liver disease, and in the very young and the elderly. CSF and salivary phenytoin concentrations are approximately 10% of those in plasma. Phenytoin is excreted in breast milk at concentrations 25-50% of those in plasma. Brain concentrations of phenytoin are generally similar to plasma concentrations of the drug. Phenytoin readily crosses the placenta and has been associated with teratogenicity.

Phenytoin is eliminated from the body almost entirely by metabolism in the liver. Only about 5% of the dose is excreted unchanged in urine. Up to about 15% of the dose is eliminated in the feces, the majority of the dose being excreted in the urine as metabolites. The rate of elimination of phenytoin is dose dependent, the terminal half life increasing with dose. The half life also varies considerably among individuals, with a range from 7-60 h, averaging 22 ± 9 h. Thus the elimination of phenytoin can be described by michaelis menten kinetics. The apparent K_m value is in the range 4-6 mg.1 (16-24 μmol.1^{-1}) and the V_{max} in the range 6 to 8 mg.kg per day for adults, and around 12 mg.kg per day for children. The total body clearance of phenytoin is in the range 0.016-0.0421.kg^{-1}.h^{-1}. As a consequence of the saturable elimination of phenytoin at clinically relevant doses, consecutive dose increments of equal size produce progressively increasing increments in steady state plasma phenytoin levels in a given subject. This non-linearity becomes quite marked while plasma phenytoin concentrations are within the normal therapeutic range for the treatment of epilepsy, 10-20 mg.1. Failure to appreciate this can lead to overdosage of patients by what would otherwise seem a reasonable and proportionate dose increment of the drug.

Severe liver disease may reduce the elimination of phenytoin, and occasional instances of inherited or sporadic slow elimination resulting from impaired hydroxylation of the drug have been reported. Plasma protein binding for phenytoin is reduced in the presence of renal insufficiency, but this is compensated for by increased elimination. The renal clearance of phenytoin is not affected by changes in urinary pH.

Phenytoin is a potent inducer of hepatic mono-oxygenase activity, increasing the elimination of dicumarol, primidone, carbamazepine, lamotrigine, valproic acid, prednisolone, dexamethasone, and othe rglucocorticoids. A large number of compounds inhibit the oxidation of phenytoin, thereby increasing plasma levels of the drug, through competition for the capacity-limited system. Such drugs include isoniazid, tricyclic antidepressants, phenylbutazone, and propozyphene.

Phenytoin oxidation can be induced by other anticonvulsants such as Phenobarbital, primidone, and carbamazepine, resulting in decreased concentrations of the drug.

The combination of a narrow therapeutic window and readily saturable metabolism means that even relatively modest changes in the kinetics of phenytion can result in profound changes in the efficacy and toxicity of the drug.

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Oral absorption	reasonably complete: > 90%
Presystemic metabolism	nil
Plasma half life	
range	7-60 h (dose dependent)
mean	22 ± 9 h
Volume of distribution	0.5-0.7 $I.kg^{-1}$
Plasma protein binding	90-93%

Concentration-effect relationship

It is generally accepted that plasma phenytion concentrations in the range 10-20 mg.1-1 (40-80 µmol.1^{-1}) offer the best chance of controlling epilepsy in most patients without producing an unacceptable incidence of adverse effects. Occasinally authors set the lower limit of the therapeutic range to as low as 5 mg.1^{-1} (20 µmol.$^{-1}$) and many patients tolerate plasma phenytion levels up to 25 mg.1^{-1} (100 µmol.1^{-1}). Occasional patients develop overdosage manifestations with plasma phenytion levels as low as 5-6 mg.1^{-1} (20-24 µmol.1^{-1}). Kutt and McDowell generalized that nystagmus tended to appear when plasma phenytion levels exceeded 20 mg.1^{-1} (80 µmol.1^{-1}), diplopia and ataxia of gait when levels exceeded 30 mg.1^{-1} (120 µmol.1^{-1}) and drowsiness at levels above 40 mg.1^{-1} (160 µmol.1^{-1})

The therapeutic range of plasma phenytion levels which correlates with control of susceptible cardiac arrhythmias is similar to that which applies for epilepsy. However, lower plasma phenytion levels usually suffice to control responsive forms of migraine.

Metabolism

Phenytion is extensively biotransformed by oxidation in the liver, with less than 5% of the dose excreted unchanged in the urine. The majority of the dose is excreted in the urine as metabolites, with up to 15% of the dose eliminated in the feces. The major route of metabolism of phenytion is aromatic hydroxylation of one of the benzene rings on C5 of the hydantoin ring. The major metabolite is 5-P-hydroxyphenyl-5-phenylhydantoin (HPPH), which is subsequently glucuronidated. Between them, free and conjugated HPPH in urine account for 60-80% of the dose. P-Hydroxylation is capacity limited, so that at higher doses a smaller proportion of the dose is excreted as HPPH. A number of minor phenolic and catechol metabolites of phenytion have been identified. Scission of the hydantoin ring and N-glucuronides of the drug have also been reported. Inherited and sporadic instances of a decreased capacity to form the p-hydroxyphenyl metabolite, associated with abnormally reduced tolerance to normal doses of phenytion, have been reported. None of the metabolites of phenytion appears to be active.

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6. Pharmaceutical particulars:

6.1 List of Excipients:

Microcrystalline cellulose Powder	BP
Lactose	BP
Sodium lauryl sulphate	BP
Sodium starch glycolate	BP
Isopropyl alcohol	BP
Polyvinyl pyrrolidone K-30 (Povidone)	BP
Purified talc	BP
Magnesium stearate	BP
Croscarmellose Sodium	BP
Colloidal anhydrous silica	BP

COATING

Colour Wincoat WT-MP-02005 White	In-house
Isopropyl alcohol	BP
Dichloromethane	BP

6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Do not store above 30ºC, Protect from light.

6.5 Nature and Contents of Container:
10 tablets packed in one blister. Such 10 blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

6.6 Special precautions for disposal:
None reported.

7. Registrant:
AGOG PHARMA LTD.
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The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane,
India.

8. Manufacturer:
AGOG PHARMA LTD.

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9. Date of revision of the text :