SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Phenytoin sodium Milpharm 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 100 mg of phenytoin sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White to off-white, oval shaped, film-coated tablets debossed with ‘C’ on one side and ‘70’ on the other side. The size is 11.6 mm X 6.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Phenytoin sodium 100 mg tablets are indicated for the following:

- Control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these
- The prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Phenytoin sodium has also been employed in the treatment of trigeminal neuralgia but it should only be used as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

Note: Phenytoin sodium is not effective in absence status epilepticus or in the prophylaxis and treatment of febrile convulsions.
4.2 **Posology and method of administration**

**Posology**

**Dosage:**
Dosage should be individualised as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. Phenytoin should be introduced in small dosages with gradual increments until control is achieved or until toxic effects appear. In some cases serum level determinations may be necessary for optimal dosage adjustments - the clinically effective level is usually 10-20mg/l (40-80 micromoles/l) although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin. With recommended dosage a period of seven to ten days may be required to achieve steady state serum levels with Phenytoin and changes in dosage should not be carried out at intervals shorter than seven to ten days. Maintenance of treatment should be the lowest dose of anticonvulsant consistent with control of seizures.

Phenytoin sodium tablets contain phenytoin sodium. Although 100 mg of phenytoin sodium is equivalent to 92 mg of phenytoin on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent. Physicians should therefore exercise care in those situations where it is necessary to change the dosage form and serum level monitoring is advised.

**Prevention and treatment of seizures**

a) **Slow titration**

*Adults and adolescents over 12 years of age* (i.e. with over 50 kg bodyweight) take up to 3 tablets (corresponding to 300 mg phenytoin) single or divided in up to three doses.

Dose is adjusted according to clinical requirements and according to controls of phenytoin plasma concentration (especially when higher doses are applied).

*Children up to 12 years* receive 2 mg phenytoin/kg bodyweight per day. The daily dose can be increased in 1 mg/day increments every 3 days according to phenytoin plasma concentration.

b) **Maintenance dose**

The maintenance dose is determined individually according to seizure control, undesirable effects and phenytoin plasma concentration.

c) **Rapid Saturation**

Rapid saturation should be performed only in in-patients using phenytoin plasma controls.

*Adults and adolescents over 12 years of age* (i.e. with over 50 kg bodyweight) take up to 10 tablets (corresponding to 1 g phenytoin) divided in three doses (4 tablets, 3
tablets, 3 tablets) every 2 hours. After the second day the dosing procedure is the same as with slow titration.

Children up to 12 years receive 5-8 mg phenytoin/kg bodyweight on the 1st day of treatment.

From the 2nd day on, children ≥ 6 years receive 2 tablets (corresponding to 200 mg phenytoin) per day.

In children below 6 years, dose from the 2nd day on is determined according to phenytoin plasma concentration.

**Trigeminal neuralgia:**

Adults take 3 tablets per day (corresponding to 300 mg phenytoin) as a single or up to 3 divided doses.

Dose is adjusted according to clinical requirements and according to controls of phenytoin plasma concentration (especially when higher doses are applied).

**Duration of administration**

The tablets should be swallowed with a sufficient quantity of liquid (e.g. water).

Duration of administration is dependent on the underlying disease and the course of the illness. If the medicinal product is well-tolerated, it can be used indefinitely.

**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.

**Method of administration**

For oral administration only.

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4.3 **Contraindications**

Phenytoin should not be administered:

- If the patient is hypersensitive to phenytoin, or to any of the excipients listed in section 6.1.
- If the patient is hypersensitive to other hydantoins.
- If the patient already has severe damage to the blood cells and bone marrow
- In grade II and grade III AV block or Stoke-Adams syndrome due to its effect on ventricular automaticity.
• If the patient suffers from sick sinus syndrome, sinus bradycardia, sino-atrial block
• Within the first three months after myocardial infarction and in case of cardiac output failure (left ventricular ejection fraction > 35%).

4.4. Special warnings and precautions for use

Phenytoin sodium should not be taken in the following conditions, unless the benefit clearly outweighs the risks:

• cardiac insufficiency
• impaired pulmonary function
• severe hypotension (systolic blood pressure below 90 mmHg)
• bradycardia (less than 50 beats per minute)
• sinuatrial block and grade I AV block
• atrial fibrillation/flutter

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 Sodium.

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.

Important information regarding treatment:
Patients who suffer from genetically determined slow hydroxylation may develop signs of overdose even at moderate doses. The dose should be reduced and phenytoin-plasma samples checked.

Switching preparations
Phenytoin has a narrow therapeutic index and its absorption can be quite variable. Therefore if there is reason to change to another product or formulation containing the active substance phenytoin, monitoring of phenytoin plasma concentrations may be helpful. If the dose is kept the same, steady state can be expected after 5 to 14 days.

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anti-epileptic 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 anti-epileptic drug not belonging to the hydantoin chemical class.

Phenytoin is highly protein bound and extensively metabolised by the liver. Reduced dosage to prevent accumulation and toxicity may therefore be required in patients with impaired liver function. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, the pharmacologically active free drug concentration is unlikely to be altered. Therefore, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range of 10-20mg/l (40-80 micromoles/l). Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity.

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

Phenytoin may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported in association with toxic levels. Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes.

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, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with phenytoin is recommended.

Herbal preparations containing St John's wort (Hypericum perforatum) should not be used while taking phenytoin due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin (see Section 4.5).

Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare drug induced, multiorgan syndrome which is potentially fatal and occurs in some patients taking anticonvulsant medication. It is characterized by fever, rash, lymphadenopathy, and other multiorgan pathologies, often hepatic. The mechanism is unknown. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals. Patients should be alert for the symptoms of AHS and be instructed to seek medical advice immediately in case respective symptoms occur. If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.

Serious skin reactions
Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Phenytoin Tablets.

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, Phenytoin Tablets 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 Phenytoin Tablets, Phenytoin Tablets must not be re-started in this patient at any time.

If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. Published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, and hepatotoxicity in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLAB* 1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of drugs associated with SJS/TEN, including phenytoin, in HLA-B*1502 positive patients when alternative therapies are otherwise equally available.

HLAB* 1502 may be associated with an increased risk of developing Stevens Johnson Syndrome (SJS) in individuals of Thai and Han Chinese Origin when treated with phenytoin. If these patients are known to be positive for HLAB*1502, the use of phenytoin should only be considered if the benefits are thought to exceed risks.

In the Caucasian and Japanese population, the frequency of HLAB*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not available.

**Musculoskeletal Effect**

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

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

Treatment should be monitored monthly during the first three months and then six-monthly including controls of Phenytoin plasma concentration, blood count, liver enzymes (AST, ALT, gamma-GT) , alkaline phosphatase and additionally in children thyroid function.

A blood count showing moderate, stable leukopenia and an isolated increase in gamma-GT should not normally necessitate withdrawal of treatment.
4.5 Interaction with other medicinal products and other forms of interaction

1. Drugs which may increase phenytoin serum levels include:

- Amiodarone, antiepileptics (felbamate, succinimides, sulthiamine, valproic acid)
- Antifungal agents (such as, but not limited to, amphotericin B, fluconazole, ketoconazole, miconazole anditraconazole), antibiotics (e.g. chloramphenicol, erythromycin, isoniazid, sulphonamides), benzodiazepines (e.g. chlor Diazepam, diazepam), calcium channel inhibitors (diltiazem, nifedipine), cycloserine, cytostatic drugs (fluoropyrimidine, fluorouracil), disulfiram, H2-antagonists (e.g. cimetidine, ranitidine), halothane, methylphenidate, non-steroidal antirheumatics (e.g. azapropazone, phenylbutazone, salicylates), omeprazole, oestrogens, oral anticoagulants (e.g. dicoumarol), phenothiazines, phenylbutazone, salicylates, SSRI (fluoxetine, fluvoxamine, sertraline), ticlopidine, tolbutamide, trazodone, tricyclic psychotropic drugs and viloxazine.

Additional administration of valproic acid or increasing the dose of valproic acid can increase the amount of free phenytoin (concentration of non protein-bound portion) without increasing the serum level of total phenytoin. This can increase the risk of undesirable effects, especially brain damage (see section 4.8).

*Topiramate*: The addition of topiramate to other antiepileptic drugs such as phenytoin has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

*Oxcarbazepine*: Oxcarbazepine and nonhydroxy metabolite [MHD] inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses of oxcarbazepine with medicinal products that are mainly metabolised by CYP2C19 (e.g. phenytoin). Phenytoin plasma levels increased by up to 40% when oxcarbazepine was given at doses above 1,200 mg/day. In this case, a reduction of co-administered phenytoin may be required.

2. Drugs which may decrease phenytoin serum levels include:

- Diazoxide, folic acid, primidone, reserpine, rifampicin, sucralfate, theophylline and vigabatrin.

Serum levels of phenytoin can be reduced by concomitant use of the herbal preparations containing St John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising 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. If a patient is already taking St John's wort check the anticonvulsant levels and stop St John's wort. Anticonvulsant levels may increase on stopping St John's wort. The dose of anticonvulsant may need adjusting.
A pharmacokinetic interaction study between nelfinavir and phenytoin both administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively. Therefore, phenytoin concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

3. Drugs which may either increase or decrease phenytoin serum levels include:

Carbamazepine, phenobarbital, valproic acid, sodium valproate, benzodiazepines (e.g. chlordiazepoxide, diazepam), antineoplastic agents, certain antacids and ciprofloxacin. Similarly, the effect of phenytoin on carbamazepine, phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

Acute alcohol intake may increase phenytoin serum levels while chronic alcoholism may decrease serum levels.

4. Although not a true pharmacokinetic interaction, tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose effect is impaired by phenytoin include:

Antiepileptics (felbamate, lamotrigine, valproic acid,) Antifungal agents (e.g. azoles), antineoplastic agents, calcium channel blockers (e.g. nicardipine, nimodipine, verapamil), clozapine, corticosteroids, ciclosporin, diazoxide, digitoxin, furosemide, methadone, neuromuscular blockers (alcuronium, pancuronium, vecuronium), oestrogens, oral contraceptives (the contraceptive effect can be unreliable), oral anticoagulants (e.g. dicoumarol), praziquantel, SSRI (paroxetine, sertraline), tetracyclines (e.g. doxycycline), tacrolimus, quinidine, rifampicin, theophylline, tricyclic psychotropic drugs and vitamin D.

**Eslicarbazepine:** In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1.200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite, eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of Zebinix may need to be increased and the dose of phenytoin may need to be decreased”.

**Zonisamide:** Enzyme induction: Exposure to zonisamide is lower in epileptic patients receiving CYP3A4-inducing agents such as phenytoin. These effects are unlikely to be of clinical significance when zonisamide is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the zonisamide dose may be required.
Topiramate: Phenytoin and carbamazepine decrease the plasma concentration of topimarate. The addition or withdrawal of phenytoin or carbamazepine to Topamax therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect.

Tigabine: Anti-epileptic agents which induce hepatic enzymes (CYP 450) such as phenytoin, enhance the metabolism of tiagabine. In case of combination with one or several of these drugs (anti-epileptic agents, rifampicine), the dose of tiagabine could be adapted: increase of daily dose and/or more frequent administration in order to achieve the clinical response.

6. Drugs whose effect is altered by phenytoin include:

Warfarin. The effect of phenytoin on warfarin is variable and international normalized ratio (INR) should be determined when these agents are combined.

Phenytoin may increase the toxicity of methotrexate.

Serum level determinations are especially helpful when possible drug interactions are suspected.

Drug/Laboratory Test Interactions:

Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result of enhanced peripheral metabolism. These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hypothyroidism. It may, however, produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

4.6 Pregnancy and lactation

Pregnancy

Based on human experience, phenytoin is suggested to cause congenital malformations like craniofacial dysmorphia, anomalies of the distal phalanges, pre- and postnatal growth retardation and cardiac defects when administered during pregnancy. For this reason, phenytoin sodium tablet should not be used during pregnancy unless the clinical condition of the woman requires treatment with
phenytoin. Women of childbearing potential should be advised that the efficacy of oral contraceptives can be reduced (see section 4.5).

If treatment is considered essential, phenytoin should preferably be prescribed as monotherapy and at the lowest effective dose, because the incidence of birth defects rises with increasing dosage.

The plasma concentration of phenytoin may decline during pregnancy, while reaching original levels postpartum. Therefore, periodic measurements of phenytoin plasma concentrations should be performed to guide appropriate dose adjustments for maintaining adequate seizure control.

There have been also isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K$_1$ has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth.

**Breast-feeding**

Infant breast-feeding is not recommended for women taking phenytoin because phenytoin appears to be secreted in low concentrations in human milk.

### 4.7 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 (see Section 4.8).

#### 4.8. Undesirable effects

**Immune system disorders:** Anaphylactoid reaction, and anaphylaxis.

**Nervous System disorders:**
The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, diplopia, ataxia, slurred speech, decreased co-ordination, mental confusion,
memory disorder, cognitive disorder, paraesthesia, somnolence, drowsiness and vertigo. Dizziness, insomnia, transient nervousness, increasing irritability, motor twitchings, taste perversion and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, high-frequent resting tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdose or long-term plasma concentrations of phenytoin above 25 µg/ml. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Long-term treatment with phenytoin concomitant with other anticonvulsive drugs, especially valproic acid, may lead to signs of encephalopathy: increased seizure frequency, listlessness, stupor, muscular hypotonia, choreiform dyskinesias and severe general changes on the EEG.

_Gastrointestinal disorders:_
Nausea, vomiting and constipation, toxic hepatitis, and liver damage.

_Skin and subcutaneous tissue disorders:_
Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash is the most common; dermatitis is seen more rarely. Other more serious and rare forms have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Hyperpigmentation (chloasma), severe cutaneous adverse reactions (SCARs) like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

_Musculoskeletal and connective tissue disorders:_
Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely.

_Blood and lymphatic tissue disorders:_
Haemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local and generalised) 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.

Frequent blood counts should be carried out during treatment with phenytoin.

**Immune System disorders:**
Hypersensitivity syndrome has been reported and may in rare cases be fatal (the syndrome may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, polyarteritis nodosa, and immunoglobulin abnormalities may occur. Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients (see section 4.4).

**Other:**
Polyarthropathy, interstitial nephritis, pneumonitis.

**Musculoskeletal System disorders:** Bone fractures and osteomalacia have been associated with longterm (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported.

Reversible muscular weakness (myasthenic syndrome).

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenytoin. The mechanism by which phenytoin affects bone metabolism has not been identified.

**Endocrine disorders**
Disturbance of thyroid function may occur, especially in children

**Metabolism and nutrition disorders**
There is evidence in the literature that phenytoin may trigger attacks of porphyria.

**Cardiac disorders:**
Rare – asystole due to inhibition of the sinus node, conduction blockade and suppression of the ventricular escape rhythm in patients with total AV block, especially when phenytoin is administered intravenously. Proarhythmic effects in the form of changes or increases in cardiac arrhythmias can occur which can lead to severe impairment of cardiac activity or even cardiac arrest. With intravenous administration in particular, decreased blood pressure, deterioration in existing heart and respiratory failure can occur. In isolated cases ventricular fibrillation has been triggered. Atrial fibrillation and flutter is not cured by phenytoin. However, as AV node refractory time can be shortened, acceleration in ventricular rate is possible.
General disorders and administration site conditions

Exhaustion

In case dose dependent undesirable effects occur, treatment should be reassessed and the dose reduced, to prevent intoxication.

Paediatric population

The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

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.

4.9 Overdose

Symptoms of overdose:

The lethal dose in children is not known. The mean lethal dose for adults is estimated to be 2 to 5g. The initial symptoms are nystagmus, diplopia, tremor, vertigo, nausea, stomach trouble, cerebellar ataxia and dysarthria. Longer lasting overdose may present with stare gaze, loss of appetite, vomiting, weight loss, apathia, sedation, disturbance of perception and/or consciousness, seizures. Irreversible cerebellar impairment may occur. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus on lateral gaze usually appears at 20mg/l, and ataxia at 30mg/l, dysarthria and lethargy appear when the serum concentration is greater than 40mg/l, but a concentration as high as 50mg/l has been reported without evidence of toxicity.

As much as 25 times therapeutic dose has been taken to result in serum concentration over 100mg/l (400 micromoles/l) with complete recovery.

Treatment of overdose:

Treatment is non-specific and includes monitoring on intensive care since there is no known antidote. If ingested within the previous 4 hours the stomach should be emptied. If the gag reflex is absent, the airway should be supported. Activated charcoal should be administered. Oxygen, and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular depression. Haemodialysis, forced diuresis and peritoneal dialysis are less effective, however, haemodialysis can be considered since phenytoin is not completely bound to plasma proteins.
Experience on the efficacy of haematogenic charcoal perfusion, complete plasma substitution and transfusion is inadequate. Total exchange transfusion has been utilised in the treatment of severe intoxication in children. Phenytoin plasma levels may initially still increase and should be monitored.

In acute overdosage the possibility of the presence of other CNS depressants, including alcohol, should be borne in mind.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiepileptic, hydantoin derivative
ATC-Code: N03AB02

Through hyperpolarisation it stabilizes the membranes of the central and peripheral nerves and thereby prevents spread of seizure activity rather than abolish the primary focus of seizure discharge. An increase in inhibitory impulses contributes to the anticonvulsive effect.

It appears to stabilise rather than raise the seizure threshold and prevents spread of seizure activity rather than abolish the primary focus of seizure discharge.

The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated however, possible contributory effects include:

1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation

2. Post-synaptic action to enhance gaba-mediated inhibition and reduce excitatory synaptic transmission

3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter.

5.2 Pharmacokinetic properties
Phenytoin is absorbed from the small intestine after oral administration. Various formulation factors may affect the bioavailability of phenytoin, however, non-linear techniques have estimated absorption to be essentially complete. Bioavailability is subject to large inter-and intra-individual fluctuations.
Following a single dose, the maximum plasma level is generally achieved after 4 to 6 hours (range 3 to 12 hours).

After absorption it is distributed into body fluid including CSF. Its volume of distribution has been estimated to be between 0.52 and 1.19 litres/kg, and it is highly protein bound (usually 90% in adults). In neonates plasma protein-binding is reduced.

Since phenytoin obeys saturation kinetics, the half-life is dependent on the plasma level. Plasma half life is between 20 and 60 hours; it is normally shorter in children; a prolonged half life can be expected in premature and newborn babies as well as with toxic dosages. The therapeutic range for plasma concentration is generally between 10 and 20 μg/ml. Steady state therapeutic drug levels are achieved at least 7 to 10 days after initiation of therapy.

95% of phenytoin is biotransformed. Phenytoin is hydroxylated in the liver by an enzyme system which is saturable. Small incremental doses may produce very substantial increases in serum levels when these are in the upper range of therapeutic concentrations. The main metabolite is the glucuronide of the p-hydroxy-diphenyl-hydantoin, which circulates in the entero-hepatic circulation.

The parameters controlling elimination are also subject to wide interpatient variation. The serum level achieved by a given dose is therefore also subject to wide variation.

Phenytoin passes through the placenta and reaches similar concentration in the fetal and maternal plasma. Phenytoin accumulates in the liver of the fetus.

5.3 Preclinical safety data
Non-clinical safety data do not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients

*Tablet core:*
- Mannitol
- Crospovidone
- Magnesium stearate
- Croscarmellose sodium

*Tablet coat:*
- Hypromellose
- Macrogol 400
- Titanium dioxide
- Sodium lauryl sulfate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Store in the original package in order to protect from moisture.
Keep the HDPE bottle tightly closed.

6.5 Nature and contents of container
Polyamide/Aluminium/PVC//Aluminium blister pack:
- 10, 14, 20, 28, 30, 50, 60, 84, 100, 112, 200 and 250 film-coated tablets.

HDPE container with a polypropylene closure and silica gel desiccant:
- 30 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Milpharm Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 16363/0279

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
19/06/2012

10 DATE OF REVISION OF THE TEXT
06/03/2017