SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pentran 100 mg Tablets
Phenytoin Sodium Teva 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of phenytoin sodium.

Excipient(s) with known effect:
Sucrose

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Coated tablets
White, sugar coated tablets, coded APS or plain on one side and 100/2302 on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and Method of Administration

Posology
The dosage should be adjusted to the individual patient's needs and should be determined by the clinical response and serum phenytoin levels. 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.

Therapeutic plasma levels usually range from 10 to 20 μg/ml (40 to 80 μmol/l), although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin.

With recommended dosages 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.

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.

Adults
Initially 3 to 4 mg/kg/day with subsequent dosage adjustment if necessary. An initial dose of 100 mg 2 to 4 times daily is suggested. This can be increased at intervals of 7 to 10 days to a maximum of 600 mg daily. The usual maintenance dose is 200 to 500 mg daily in divided doses. Exceptionally, a daily dose outside this range may be indicated. Dosage should normally be adjusted according to serum levels where assay facilities exist.

Special populations

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 4-8mg/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.

Elderly
As with adults the dosage of phenytoin should be titrated to the patient's individual requirements using the same guidelines unless serum albumin is low or hepatic or renal dysfunction is present. Polypharmacy is common in the elderly therefore the possibility of drug interactions should be borne in mind.

If it is necessary to transfer a patient from phenytoin to other anticonvulsant therapy, this is best effected over a period of one week with gradual withdrawal of phenytoin.

If the physician considers that the benefits of phenytoin out weigh the risks during pregnancy (see section 4.6 Pregnancy), measurement of phenytoin levels are valuable as its altered absorption and/or metabolism may require dose adjustments.

Dosage in hepatic and renal impairment
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. Reduced doses may also be necessary in patients with renal impairment.

Certain drugs may require the dose of phenytoin to be adjusted (see section 4.5).

Method of administration
For oral administration.

4.3. Contraindications

Hypersensitivity to the active substance or other hydantoins or to any of the excipients listed in section 6.1

4.4 Special Warnings and Precautions for Use

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for 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

Withdrawal: Phenytoin should be withdrawn slowly as sudden withdrawal 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 10-20μg/ml (40-80 μmol/l). Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity.

Ineffective in petit mal: 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.

Glucose metabolism: 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.

CNS toxicity: 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. Early signs of toxicity may be observed in patients with impaired liver function, elderly patients or those who are gravely ill.

Herbal preparations: 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. 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 Sodium.
- 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. (Adoption to individual drug if such data are available)
- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Phenytoin Sodium 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 Sodium, Phenytoin Sodium must not be re-started in this patient at any time.

Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. Phenytoin should be discontinued if a rash appears, and should not be resumed if the rash is exfoliative, purpuric or bullous, or if lupus erythematosus or Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. If the rash is of a milder type (measles like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. 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.

HLA-B*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 HLA-B*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 the HLA-B*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.

Case-control, genome-wide association studies in Taiwanese, Japanese, Malaysian and Thai patients have identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant.

CYP2C9 metabolism

Phenytoin is metabolised by the CYP450 CYP2C9 enzyme. Patients who are carriers of the decreased function CYP2C9*2 or CYP2C9*3 variants (intermediate or poor metabolisers of CYP2C9 substrates) may be at risk of increased phenytoin plasma concentrations and subsequent toxicity. In patients who are known to be carriers of the decreased function CYP2C9*2 or *3 alleles, close monitoring of clinical response is advised and monitoring of plasma phenytoin concentrations may be required.

Musculoskeletal Effect

Vitamin D metabolism: 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. In the absence of an adequate dietary intake of Vitamin D or exposure to sunlight may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcaemia or rickets, 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.

Women of childbearing potential
Phenytoin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for major congenital malformations and other adverse development outcomes (see Section 4.6).

Phenytoin should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

Before the initiation of treatment with phenytoin in a woman of childbearing potential, pregnancy testing should be considered.

Women of childbearing potential should be fully informed of the potential risk to the foetus if they take phenytoin during pregnancy.

Women of childbearing potential should be counselled regarding the need to consult their physician as soon as they are planning a pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see Section 4.6).

Women of childbearing potential should be counselled to contact their doctor immediately if they become pregnant or might be pregnant and are taking phenytoin.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, phenytoin 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 Sections 4.5 and 4.6).

Pregnancy (see also section 4.6): Women who are likely to get pregnant, trying for a baby or who are pregnant should receive specialist advice because of the potential risk of neural tube defects and teratogenicity. If the physician considers that the benefits of phenytoin outweigh the risks during pregnancy; measurement of phenytoin levels are valuable as its altered absorption and/or metabolism may require dose adjustments (see section 4.6).

Frequent blood counts and urinalysis are recommended when treatment is begun and thereafter at monthly intervals for several months. Liver function tests and blood glucose should also be monitored.

It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary.

Phenytoin should be withdrawn if liver damage occurs (see section 4.2 and 4.8).

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5. Interactions with other medical products and other forms of Interaction

1. Drugs which may increase phenytoin serum levels include:

Amiodarone, antifungal agents (such as, but not limited to, amphotericin B, fluconazole, ketoconazole, miconazole and itraconazole), chloramphenicol, chlordiazepoxide, diazepam, dicoumarol, diltiazem (but also effect of diltiazem reduced),disulfiram, fluoxetine, fluvoxamine, sertraline, H2-antagonists e.g. cimetidine, halothane, isoniazid, methylphenidate, nifedipine, omeprazole, oestrogens, phenothiazines, phenylbutazone, salicylates, succinimides, sulphonamides, tolbutamide (possibility of toxicity), trazodone and viloxazine.

2. Drugs which may decrease phenytoin serum levels include:

Folic acid, 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, 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:

Antifungal agents (e.g. azoles), antineoplastic agents, calcium channel blockers (phenytoin reduces effects of felodipine, isradipine and verapamil; phenytoin probably reduces effects of dihydropyridines, nicardipine and nifedipine; phenytoin reduces plasma concentration of nisoldipine),clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, furosemide, lamotrigine, neuromuscular blockers, oestrogens (reduced contraceptive effect), oral contraceptives, paroxetine, sertraline, quinidine, rifampicin, theophylline and vitamin D, effects of phenytoin possibly enhanced by NSAID's, phenytoin accelerates metabolism of methadone (reduced effect and risk of withdrawal effects), effects of phenytoin enhanced by aspirin.

6. Drugs whose effect is altered 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.

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 (also plasma concentration of phenytoin possibly increased). 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.

Anti-arrhythmics: phenytoin reduces plasma concentration of disopyramide; phenytoin accelerates metabolism of mexiletine (reduced plasma concentration).

Antibacterials: Metabolism of phenytoin inhibited by clarithromycin, and metronidazole (increased plasma concentration); metabolism of phenytoin accelerated by rifamycins (reduced plasma concentration); phenytoin reduces plasma concentration of telithromycin (avoid during and for 2 weeks after phenytoin); plasma concentration of phenytoin increased by trimethoprim (also increased antifolate effect).

Anticoagulants: Phenytoin accelerates metabolism of coumarins (possibility of reduced anticoagulant effect, but enhancement also reported).
Phenytoin may also reduce the serum levels and/or effects of oral anticoagulants e.g. rivaroxaban, dabigatran, apixaban, edoxaban.

Antidepressants: Phenytoin reduces plasma concentration of mianserin and mirtazapine; anticonvulsant effect of antiepileptics possibly antagonised by MAOIs (convulsive threshold lowered); anticonvulsant effect of antiepileptic antagonised by SSRIs and tricyclics (convulsive threshold lowered); phenytoin possibly reduces plasma concentration of tricyclics.

Antiepileptics: Plasma concentration of phenytoin possibly increased by ethosuximide, also plasma concentration of ethosuximide possibly reduced; tiagabine and zonisamide; plasma concentration of phenytoin increased by oxcarbazepine, also plasma concentration of an active metabolite of oxcarbazepine reduced; phenytoin possibly reduces plasma concentration of primidone (but concentration of an active metabolite increased), plasma concentration of phenytoin often reduced but may be increased; plasma concentration of phenytoin increased by topiramate (also plasma concentration of topiramate reduced);

Concomitant administration of phenytoin and valproate has been associated with an increased risk of valproate-associated hyperammonaemia. Patients treated concomitantly with these two drugs should be monitored for signs and symptoms of hyperammonaemia.

Antifungals: Phenytoin reduces plasma concentration of ketoconazole, anticonvulsant effect of phenytoin enhanced by miconazole (plasma concentration of phenytoin increased), plasma concentration increased by fluconazole (consider reducing dose of phenytoin), phenytoin reduces plasma concentration of itraconazole- avoid concomitant use, plasma concentration of phenytoin increased by voriconazole, also phenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for phenytoin toxicity); phenytoin possibly reduces plasma concentration of caspofungin – consider increasing dose of caspofungin.

Antimalarials: Possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptic antagonised by mefloquine; anticonvulsant effect of phenytoin antagonised by pyrimethamine, also increased antifolate effect.

Antipsychotics: Anticonvulsant effect of phenytoin antagonised by antipsychotics (convulsive threshold lowered); phenytoin possibly reduces plasma concentration of aripiprazole – increase dose of aripiprazole; phenytoin accelerates metabolism of quetiapine and sertindole reduced plasma concentration).

Antivirals: Phenytoin possibly reduces plasma concentration of abacavir, amprenavir, indinavir, lopinavir and saquinavir; plasma concentration of phenytoin increased or decreased by zidovudine.

Anxiolytics and Hypnotics: Phenytoin often reduces plasma concentration of clonazepam; plasma concentration of phenytoin possibly increased or decreased by benzodiazepines such as diazepam.

Aprepitant: Phenytoin possibly reduces plasma concentration of aprepitant.

Barbiturates: Phenytoin often increases plasma concentration of phenobarbital

Bupropion: Phenytoin reduces plasma concentration of bupropion.

Cardiac Glycosides: Phenytoin possibly reduces plasma concentration of digoxin.

Cytotoxics: Metabolism of phenytoin possibly inhibited by fluorouracil (increased risk of toxicity); phenytoin increases antifolate effect of methotrexate; absorption of phenytoin possibly reduced by cytotoxics; phenytoin possibly reduces plasma concentration of etoposide; phenytoin reduces plasma concentration of imatinib – avoid concomitant use.

Diazoxide: Plasma concentration of phenytoin reduced by diazoxide, also effect of diazoxide may be reduced.

Disulfram: Metabolism of phenytoin inhibited by Disulfram (increased risk of toxicity).

Diuretics: Phenytoin reduces plasma concentration of eplerenone – avoid concomitant use; increased risk of osteomalacia when phenytoin given with carbonic anhydrase inhibitors.

Dopaminergics: Phenytoin possibly reduces effects of levodopa.

Enteral Foods: Absorption of phenytoin possibly reduced by enteral foods.

Hormone Antagonists: Phenytoin accelerates metabolism of gestrinone (reduced plasma concentration); phenytoin possibly accelerates metabolism of toremifene.

$5HT_3$ Antagonists: Phenytoin accelerates metabolism of ondansetron (reduced effect).

Leflunomide: Plasma concentration of phenytoin possibly increased by leflunomide.

Levamisole: Plasma concentration of phenytoin possibly increased by levamisole.

Lipid-regulating Drugs: Combination of phenytoin with fluvastatin may increase plasma concentration of either drug (or both).

Lithium: Neurotoxicity may occur when phenytoin given with lithium without increased plasma concentration of lithium.

Modafinil: Plasma concentration of phenytoin possibly increased by modafinil.

Muscle Relaxants: Phenytoin antagonises muscle relaxant effect of non-depolarising muscle relaxants (accelerated recovery from neuromuscular blockade).

Progestogens: Phenytoin accelerates metabolism of progestogens (reduced contraceptive effect).

Sulfinpyrazone: Plasma concentration of phenytoin increased by sulfinpyrazone.

Tibolone: Phenytoin accelerates metabolism of tibolone.

Ulcer-healing Drugs: Effects of phenytoin enhanced by esomeprazole;

Vaccines: Effects of phenytoin enhanced by influenza vaccine.

Lacosamide
Phenytoin may reduce the serum levels and/or effects of lacosamide.

Ticagrelor
Phenytoin may reduce the serum levels and/or effects of ticagrelor.

4.6. Fertility, pregnancy and lactation

Woman 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 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.

Pregnancy
There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or foetus.

Anticonvulsants including phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients. The exact role of drug therapy in these abnormalities is unclear and genetic factors, in some studies, have also been shown to be important.
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 that the frequency 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 used phenytoin alone or in combination with other AEDs during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded. A small number of studies found an increase of serious adverse outcomes compared to control subjects including foetal hydantoin syndrome and below average IQ.

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.

If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with phenytoin 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.

- There is an increased risk of neural tube defects in infants exposed to phenytoin *in utero*. Women should be warned of the possible consequences – see section 4.4.

- .In children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a foetal hydantoin syndrome. This consists of prenatal growth deficiency, micro-encephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or rimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

- There is a risk of neonatal bleeding/coagulation disorders

- Withdrawal symptoms may develop in the neonate

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

- An increase in seizure frequency during pregnancy occurs in a proportion of patients, and this may be due to altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

- 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.

However the exact role of drug therapy in these abnormalities is unclear and genetic factors or the epileptic condition itself may lead to birth defects.

In order to minimise risks to both the mother and the baby:

- women who are likely to get pregnant, trying for a baby or who are pregnant should receive specialist advice because of the potential risks of anticonvulsants and/or inadequately controlled epilepsy during pregnancy

- anticonvulsant drugs used to prevent major seizures should not be discontinued because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life

- folate administration has been recommended in those on phenytoin planning a pregnancy and during the 1st trimester, but folic acid can reduce serum phenytoin levels

- in cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy although it is not clear that if seizures occur, they do not pose some hazard to the developing embryo or foetus

- the absorption and metabolism of phenytoin may be altered during pregnancy, so phenytoin concentration should be monitored and dosage adjusted, upwardly, if necessary, in order to maintain therapeutic levels

- Vitamin K_1 has been shown to prevent or correct this neonatal coagulation 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

Phenytoin has minor or moderate influence on the 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

List of adverse reactions

The following side effects due to phenytoin have been reported. It is essential that the phenytoin induced aetiology of some of these side effects is carefully differentiated from their other aetiologies. The frequency of adverse events according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Immune System reactions

Not known: polyarteritis nodosa

Anaphylactoid reaction and anaphylaxis. 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.

Nervous system disorders:

The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased co-ordination, mental confusion, paraesthesia, somnolence, drowsiness, and vertigo. Dizziness, insomnia, transient nervousness, motor twitchings, taste perversion and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, 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 overdosage. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy. Aggression, cerebellar degeneration, cognitive impairment, depression, encephalopathy, fatigue, numbness, paradoxical seizures.

Skin and subcutaneous tissue disorders

Very rare: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4)

Not known: Hirsutism, hypertrichosis, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

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 Stevens-Johnson syndrome and bullous, exfoliative, purpuric dermatitis, lupus erythematosus or toxic epidermal necrolysis. (See section 4.4).

Blood and lymphatic system disorders

Haemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included liver damage, megaloblastic, thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and aplastic anaemia.

Not known: pure red cell aplasia

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, reduced serum IgA levels, polyarteritis nodosa, 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.

Eye disorders
Not known: Diplopia

Respiratory, thoracic and mediastinal disorders
Not known: Pneumonitis

Gastrointestinal disorders
Not known: Nausea, vomiting and constipation, gingival hyperplasia

Hepatobiliary disorders
Not known: Liver damage, hepatitis toxic

Renal and urinary disorders
Not known: Nephritis interstitial

General disorders and administration site conditions
Not known: Fatigue

Musculoskeletal and connective tissue disorders:

Not known: Systemic lupus erythematosus, polyarthropathy, rickets and osteomalacia, coarsening of the facial features, enlargement of the lips, and Dupuytren's contracture.

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.

Vitamin D supplements should be given to patients on long term phenytoin therapy.

Reproductive system and breast disorders
Not known: Peyronie's disease

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/yellowcardor search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

The lethal dose in children is not known.

Symptoms:

The mean lethal dose in adults is estimated to be 2 to 5 g. Initial signs of overdose are nystagmus, ataxia and dysarthria. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea. Respiratory and circulatory depression may be fatal.. Hyperglycaemia has also been reported in association with toxic levels.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus on lateral gaze usually appears at 20 mg/1, and ataxia at 30 mg/1, dysarthria and lethargy appear when the serum concentration is greater than 40 mg/1, but a concentration as high as 50 mg/1 has been reported without evidence of toxicity.

As much as 25 times therapeutic dose has been taken to result in serum concentration over 100 mg/1 (400 micromoles/1) with complete recovery.

Treatment

There is no specific antidote. The stomach should be emptied by gastric lavage if ingested within the previous 4 hours. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ATC Code: N03A B02 (antiepileptics, hydantoin derivatives)

Phenytoin is an antiepileptic agent. It limits the development of maximal seizure activity and prevents the spread of excitation from seizure foci. Phenytoin is effective in various animal models of generalised convulsive disorders, reasonably effective in models of partial seizures but relatively ineffective in models of myoclonic seizures.

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. 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)

The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours. Steady state therapeutic drug levels are achieved at least 7 to 10 days after initiation of therapy.

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 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.

5.3. Preclinical Safety Data

<u>Reproductive and developmental toxicity:</u>
Phenytoin causes embryofoetal death and growth retardation in rats, mice, and rabbits. Phenytoin is teratogenic in rats (craniofacial defects including cleft palate, cardiovascular malformations, neural and renal defects, and limb abnormalities), mice (cleft lip, cleft

palate, neural and renal defects, limb abnormalities, and digital and ocular abnormalities) and rabbits (cleft palate, limb abnormalities, and digital and ocular abnormalities). The defects produced are similar to major malformations observed in humans and abnormalities described for foetal hydantoin syndrome. The teratogenic effects of phenytoin in animals occur at therapeutic exposures, and therefore a risk to the patients cannot be ruled out.

Published data report adverse neurodevelopmental effects in the offspring of animals exposed to clinically relevant exposures of phenytoin during pregnancy.

Carcinogenesis:
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 clinical significance of these rodent tumours is unknown.

Genetic toxicity studies showed that phenytoin was not mutagenic in bacteria or in mammalian cells in vitro. It is clastogenic *in vitro* but not *in vivo*.

6 PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Tablet core:
Calcium hydrogen phosphate
Sucrose
Purified water
Magnesium stearate (E572)

Coating:
Gelatin
Titanium dioxide (E171)
Sucrose
Talc

Polish:
Shellac (E904)
Beeswax, white (E901)
Carnauba wax (E903)

Printing ink:
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

24 months – Polypropylene containers, HDPE containers and glass bottles
24 months – Blister packs

6.4. Special Precautions for Storage

Do not store above 25°C. Store in the original package

6.5. Nature and Contents of Container

Polypropylene containers with polyethylene security closures in packs of 500 tablets.

HDPE containers with LDPE lids or child resistant caps in packs of 50 or 500 tablets.

Amber glass bottles with black plastic caps in packs of 50 tablets.

PVdC coated PVC film with hard temper aluminium foil blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

Not all packs sizes may be marketed

6.6. Instruction for Use/Handling

Not applicable

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 00289/5236R

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

28.02.1996 / 15.05.2006

10 DATE OF REVISION OF THE TEXT

26/06/2023