1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

PHENYTOIN SODIUM 100 mg TABLETS

PHENYTOIN SODIUM CAPSULES

COMPOSITION

PHENYTOIN SODIUM 100 mg TABLETS: Each tablet contains phenytoin sodium 100 mg.

Excipients: Calcium stearate, hydrogenated vegetable oil, lactose monohydrate, macrogol, polyvinyl alcohol (partially hydrolysed), starch maize, talc, titanium dioxide.

Contains Sugar: Lactose monohydrate 26,00 mg

PHENYTOIN SODIUM CAPSULES: Each capsule contains 100 mg phenytoin sodium.

Excipients: Colloidal silicone dioxide, gelatin, magnesium stearate, pregelatinised starch, sodium lauryl sulphate, talc (purified), titanium dioxide.

Sugar Free.

PHARMACOLOGICAL CLASSIFICATION

A - 2.5 : Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Phenytoin exerts an anticonvulsant action without causing general depression of the CNS.

It is believed to stabilise rather than elevate the seizure threshold and to limit the spread of seizure activity.

Phenytoin limits the repetitive firing of action potentials evoked by a sustained depolarisation of mouse spinal cord neurons maintained *in vitro*. This effect is mediated by a slowing of the rate of recovery of voltage-activated Na^+ channels from inactivation.
These effects of phenytoin are evident at concentrations in the range of therapeutic medicine levels in cerebrospinal fluid (CSF) in human beings, concentrations that correlate with the free (or unbound) concentration of phenytoin in the serum. At these concentrations, the effects of Na^+ channels are selective, in that no changes of spontaneous activity or responses to iontophoretically - applied GABA or glutamate are detected. At concentrations 5- to 10-fold higher, multiple effects of phenytoin are evident, including reduction of spontaneous activity, enhancement of responses to GABA, and others; these effects may underlie some of the unwanted toxicity associated with high levels of phenytoin.

Pharmacokinetic properties

Distribution

The pharmacokinetic characteristics of phenytoin are influenced markedly by its binding to serum proteins, by the nonlinearity of its elimination kinetics, and by its metabolism by cytochrome P 450 isoenzymes (CYPs). Phenytoin is extensively (about 90 %) bound to plasma proteins, mainly albumin. Small variations in the percentage of phenytoin that is bound dramatically affect the absolute amount of free (active) phenytoin; increased proportions of free medicine are evident in the neonate, in patients with hypoalbuminaemia, and in uraemic patients.

Metabolism

The plasma half-life of phenytoin ranges between 6 and 24 hours at plasma concentrations below 10 µg/ml, but increases with higher concentrations.This results in the plasma medicine concentration increasing disproportionately as dosage is increased even with small adjustments for levels near the therapeutic range. The majority (95 %) of phenytoin is metaboli[≠]sed principally in the hepatic endoplasmic reticulum by CYP2C9/10 and to a lesser extent CYP2C19.

Elimination

The rate of elimination of phenytoin varies as a function of its concentration (i.e.the rate is nonlinear).

INDICATIONS

PHENYTOIN SODIUM is indicated for the control of generalised tonic-clonic (grand mal) and complex partial psychomotor, temporal lobe seizures.

CONTRAINDICATIONS

PHENYTOIN SODIUM is contraindicated in:

- Patients with hypersensitivity to the active ingredient or to any of the excipients in PHENYTOIN SODIUM (see COMPOSITION) and in those patients with a history of hypersensitivity to hydantoin products.
- Cardiac function impairment, such as Adams Stokes syndrome, sinoatrial block and sinus bradycardia.
- Co-administration with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.
- Porphyria

WARNINGS AND SPECIAL PRECAUTIONS

General

PHENYTOIN SODIUM tablets contain lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

PHENYTOIN SODIUM is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence seizures are present together, combined medicine therapy is needed.

PHENYTOIN SODIUM is not indicated for seizures due to hypoglycaemia or other

metabolic causes.

Abrupt withdrawal of phenytoin, as contained in PHENYTOIN SODIUM, 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 medicine not belonging to the hydantoin chemical class.

Phenytoin sodium may precipitate or aggravate absence seizures and myoclonic seizures.

Herbal preparations containing St. John's Wort (Hypericum perforatum) should not be used while taking PHENYTOIN SODIUM due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin, contained in PHENYTOIN SODIUM (see INTERACTIONS).

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

Hyperglycaemia may be potentialted in patients with diabetes mellitus.

PHENYTOIN SODIUM should be administered with caution to patients receiving thyroid replacement therapy. It is suggested that caution be exercised in its use during early pregnancy, and during breastfeeding (see PREGNANCY AND LACTATION).

PHENYTOIN SODIUM should be prescribed with caution where ulcers or lesions of the gastrointestinal tract exist.

Alcohol

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

Suicide

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines.

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.

Anticonvulsant Hypersensitivity Syndrome (AHS)

Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare medicine-induced, multiorgan syndrome which is potentially fatal and occurs in some patients taking anticonvulsant medication such as PHENYTOIN SODIUM. It is characterized by fever, rash, lymphadenopathy, and other multi-organ pathologies, often hepatic. The mechanism is unknown. The interval between first medicine exposure and symtoms is usually 2 to 4 weeks but has been reported in individuals receiving anticonvulsants for three or more months. Although up to 1 in 5 patients may develop cutaneous eruptions, only a small proportion will progress to AHS.

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 sensitised individuals. If a patient is diagnosed with AHS, discontinue the PHENYTOIN SODIUM and provide appropriate supportive measures.

Hypersensitivity Syndrome (HSS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past (with phenytoin, as contained in PHENYTOIN SODIUM or other anticonvulsant medicines), patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitised individuals.

Serious skin reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of phenytoin, as contained in PHENYTOIN SODIUM. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of HSS/DRESS i.e. occurrence of rash and should be monitored closely for skin reactions. Patients should seek medical advice from their medical practitioner immediately when observing any indicative signs or symptoms. 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 SODIUM treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any

suspect medicines. 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.

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. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin, as contained in PHENYTOIN SODIUM, may be higher in black patients.

Data suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking medicines associated with SJS/TEN, including phenytoin, as contained in PHENYTOIN SODIUM. Consideration should be given to avoiding use of medicines 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, as contained in PHENYTOIN SODIUM. If these patients are known to be positive for HLA-B*1502, the use of PHENYTOIN SODIUM should only be considered if the benefits are thought to exceed risks.

Hepatic Injury

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 medicine 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 to 20 mg/l (40 to 80 micromoles/l).

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin, as contained in PHENYTOIN SODIUM. These incidents usually occur within the first 2 months of treatment and may be associated with HSS/DRESS . Patients with impaired liver function, older patients or those who are gravely ill may show early signs of toxicity.

The risk of hepatotoxicity and other hypersensitivity reactions to phenytoin, as contained in PHENYTOIN SODIUM may be higher in black patients.

Haematopoietic system

Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin, as contained in PHENYTOIN SODIUM. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

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, pseudo lymphoma, 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 HSS/DRESS. 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 medicines.

Central Nervous System Effect

Serum levels of phenytoin, as contained in PHENYTOIN SODIUM, sustained above the optimal range may produce confusional states referred to as “delirium”, “psychosis”, or “encephalopathy”, or rarely irreversible cerebellar dysfunction (see SIDE EFFECTS). Accordingly, at the first sign of acute toxicity, serum medicine level determinations are recommended. Dose reduction of PHENYTOIN SODIUM therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with PHENYTOIN SODIUM is recommended.

Musculoskeletal Effect

Phenytoin, as contained in PHENYTOIN SODIUM, 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 D_3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

It is suggested that patients on long-term treatment receive not less than 100 µg of vitamin D as calciferol per week.

Metabolic Effect

In view of reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using PHENYTOIN SODIUM in patients suffering from this disease (see CONTRAINDICATIONS).

Phenytoin, as contained in PHENYTOIN SODIUM, may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported in association with toxic levels

Effects on the endocrine system and metabolism

Although it may be difficult to separate from the effects of the disease itself, there is some evidence that antiepileptics, like PHENYTOIN SODIUM, can diminish sexual potency and fertility in male epileptics. Phenytoin is excreted in human semen in small quantities and might affect sperm morphology and motility. Reduced plasma concentrations of free testosterone have been detected in male epileptic patients receiving phenytoin as contained in PHENYTOIN SODIUM.

AIDS associations

Renal abnormalities or hypalbuminaemia associated with AIDS may increase the risk of elevated free phenytoin concentrations and subsequent toxicity.

Effects on ability to drive and use machines

Since adverse reactions such as headache, dizziness and visual disturbances have been reported in patients taking PHENYTOIN SODIUM, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that PHENYTOIN SODIUM does not adversely affect their ability to do so (see SIDE EFFECTS).

Excipients

Lactose warning

PHENYTOIN SODIUM tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not PHENYTOIN SODIUM.

PHENYTOIN SODIUM tablets contain lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS

Medicines [~~which~~] that may increase PHENYTOIN SODIUM serum levels include but are not limited to:

MEDICINE CLASSES	**Medicine in each class (such as)**
Alcohol (acute intake)	
Analgesic/Anti-inflammatory medicines	azapropazone phenylbutazone salicylates
Anaesthetics	halothane
Antibacterial medicines	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole

	sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides topiramate
Antifungal medicines	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastic medicines	capecitabine fluorouracil
Benzodiazepines/psychotropic medicines	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine phenothiazine
Calcium channel blockers/Cardiovascular medicines	amiodarone

	diltiazem nifedipine ticlopidine
H_2-antagonists	cimetidine ranitidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	oestrogens
Immunosuppressant medicines	tacrolimus
Oral hypoglycemic medicines	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline imipramine
others	Phenyramidol Sulthiame Clofibrate Thyroid preparations

Medicines that may decrease PHENYTOIN SODIUM serum levels include:

- Ingestion times of PHENYTOIN SODIUM and antacid preparations containing calcium

should be staggered to prevent absorption problems.

MEDICINE CLASSES	**MEDICINE in each class (such as)**
Alcohol (chronic intake)	
Antibacterial medicines	ciprofloxacin rifampicin
Anticonvulsants	vigabatrin
Antineoplastic medicines	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiulcer medicines	sucralfate
Antiretrovirals	fosamprenavir nelfinavir ritonavir
Bronchodilators	theophylline
Cardiovascular medicines	reserpine
Folic acid	folic acid
Hyperglycemic medicines	diazoxide
St. John's Wort	St. John's Wort

Serum levels of phenytoin, as contained in PHENYTOIN SODIUM, can be reduced by concomitant use of the herbal preparations containing St. John's Wort (*Hypericum perforatum*). This is due to induction of medicines metabolising enzymes by St. John's Wort. Herbal preparations containing St. John's Wort should therefore not be combined with PHENYTOIN SODIUM. 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 PHENYTOIN SODIUM may need adjusting.

Medicines that may either increase or decrease PHENYTOIN SODIUM serum levels include:

The effect of PHENYTOIN SODIUM on phenobarbitone, valproic acid and sodium valproate serum levels is unpredictable. Serum level determinations may be helpful when such interactions are suspected.

Medicine Classes	**Medicines in each Class (such as)**
Antibacterial medicines	ciprofloxacin
Anticonvulsants	carbamazepine phenobarbital sodium valproate valproic acid
Antineoplastic medicines	Antineoplastic medicines
Psychotropic medicines	chlordiazepoxide diazepam phenothiazines

Medicines of which the efficacy may be enhanced by PHENYTOIN SODIUM include:

Warfarin, dicoumarol, alcohol and other central nervous system depressants.

PHENYTOIN SODIUM may increase lithium levels and may produce toxicity.

PHENYTOIN SODIUM may destabilise thyroxine therapy due to displacement from its protein binding sites.

Medicines of which the efficacy is impaired by PHENYTOIN SODIUM include:

Antifungal medicines, antineoplastic medicines, clozapine, corticosteroids, coumarin anticoagulants, oral contraceptives, quinidine, vitamin D, doxycycline, theophylline, oestrogens, furosemide, tricyclic antidepressants, rifampicin, paroxetine.

Tricyclic antidepressants may precipitate seizures in susceptible patients and PHENYTOIN SODIUM dosage may need to be adjusted.

Medicines whose serum levels and/or effects may be altered by PHENYTOIN SODIUM include:

Antibacterial medicines	doxycycline rifampicin tetracycline
Anticonvulsants	carbamazepine lamotrigine phenobarbital sodium valproate valproic acid
Antifungal medicines	azoles posaconazole voriconazole
Antihelmintics	albendazole

	praziquantel
Antineoplastic medicines	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular medicines	digitoxin digoxin mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	oestrogens

	oral contraceptives
Hyperglycemic medicines	diazoxide
Immunosuppressant medicines	
Neuromuscular blocking medicines	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic medicines	chlorpropamide glyburide tolbutamide
Psychotropic medicines/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamin D	vitamin D

Laboratory test Interactions:

Phenytoin, as contained in PHENYTOIN SODIUM, 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

SODIUM. Phenytoin, as contained in PHENYTOIN SODIUM 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 SODIUM 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 SODIUM may affect blood sugar metabolism tests.

PREGNANCY AND LACTACTION

Safety and efficacy in pregnancy and lactation has not been established.

Pregnancy

PHENYTOIN SODIUM should not be taken by pregnant women.

There are intrinsic methodologic problems in obtaining adequate data on medicine teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than medicine therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant medicines should not be discontinued in patients in whom the medicines 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 medicine 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 SODIUM may produce congenital abnormalities in the offspring of a small number of epileptic patients. The exact role of medicine therapy in these abnormalities is unclear and genetic factors have also been shown to be important. PHENYTOIN SODIUM should only be used during pregnancy, especially early pregnancy, if in the judgement of the physician the potential benefits clearly outweigh the risk.

In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin, as contained in PHENYTOIN SODIUM, 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. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

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, as contained in PHENYTOIN SODIUM, 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, as contained in PHENYTOIN SODIUM. 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

Lactation

Infant breastfeeding is not recommended for women taking phenytoin because phenytoin appears to be secreted in low concentrations in human milk (see SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS).

Women of childbearing potential

Fertility

Decrease or diminish sexual potency and fertility in male epileptics (see SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS).

DOSAGE AND DIRECTIONS FOR USE

To be taken with half a glassful of water after meals.

Dosage should be individualised to provide maximum benefit. In some cases, serum level determinations may be necessary for optimal dosage adjustments, the clinically effective serum level is usually 40 to 80 µmol/l (10 to 20 µg/mi). With recommended dosage, a period of 7 to 10 days may be required to achieve therapeutic blood levels with PHENYTOIN SODIUM.

The dosages below are approximate guides only. Individual requirements vary in different patients, and the dosage should be increased gradually until a therapeutic blood level is reached.

Adult dosage:

Divided daily dose:

Patients who have received no previous treatment may be started on 100 mg three times daily, and the dosage is then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be 300 to 400 mg daily, with a maximum daily dose of 600 mg.

Loading dose:

Non-emergency oral loading dose in adult patients:

An oral loading dose of PHENYTOIN SODIUM may be used for non-emergency initiation of therapy in adults who require rapid steady state serum levels, and for whom intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinical or hospital; setting where PHENYTOIN SODIUM can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading regimen.

The recommended oral loading dose is one gram divided into three equal doses (400 mg, 300 mg, 300 mg) administered at two-hour intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum levels determinations.

Paediatric and children dosage:

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually in the range of 4 to 8 mg/kg

Children over 6 years old may require the minimal adult dosage (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

Alternate dosage:

Once-a-day dosage for adults may be considered if seizure control is established with divided doses. Once-a-day dosage offers a convenience to the patient and is intended to be used only for patients who demonstrate adequate control on a once-a-day dosage. Patients should be cautioned not to miss a dose.

SIDE EFFECTS

Neoplasms benign and malignant (including cysts and polyps)

Frequency unknown: Pseudolymphoma mimicking cutaneous T-cell lymphoma.

Blood and the lymphatic system disorders

Less frequent: Lymphadenopathy, polyarteritis nodosa, *Frequency unknown:* Leucopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, aplastic anaemia, macrocytosis and megaloblastic anaemia, development of lymphadenopathy (local and generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease, polyarthropathy, eosinophilia, thrombocytopenia.

Immune system disorders

Frequency unknown: Hypersensitivity syndrome/Drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) \ 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 incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients) and lymphocytosis with interstitial nephritis, interstitial pulmonary infiltrates, myopathy, diffuse intravascular coagulation,

Metabolism and nutrition disorders

Frequency unknown: Hyperglycaemia, interferes with vitamin D and folate metabolism, hypocalcaemia and elevated alkaline phosphatase

Psychiatric disorders

Frequent: Hallucinations

Nervous system disorders

Less frequent: Irreversible cerebellar dysfunction associated with severe phenytoin overdosage

Frequency unknown: exacerbations of seizure frequency, ataxia, slurred speech, decreased coordination, mental confusion, paraesthesia, somnolence, drowsiness vertigo, dizziness, insomnia, transient nervousness, motor twitchings, taste perversion, headaches, phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, sensory peripheral polyneuropathy

Eye disorders

Less frequent: Nystagmus, blurred vision or diplopia.

Cardiac disorders

Frequency unknown: Cardiac dysrhythmias, impaired cardiac conduction

Vascular disorders

Frequency unknown: Hypotension

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Respiratory depression

Less frequent: Pneumonitis,

Gastrointestinal disorders

Frequent: Lack of appetite, tenderness of the gums

Frequency unknown: Nausea, vomiting , constipation, gingival hyperplasia of the gums

Hepato-biliary disorders

Frequency unknown: Acute hepatic failure, toxic hepatitis, liver damage

Skin and subcutaneous tissue disorders

Frequent: Acne, skin rashes, morbilliform skin rashes,

Less frequent: Hirsutism, bullous, exfoliative, dermatitis or purpuric rashes may be symptoms of lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome (SJS) or toxic

epidermal necrolysis(TEN)

Musculoskeletal, connective tissue and bone disorders

Less frequent: Rickets, osteomalacia, coarsening of the facial features, enlargement of the lips, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur

Frequency unknown: Bone mineral density, osteopenia, osteoporosis, fractures, bone mineral metabolism may be affected 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.

Pregnancy, puerperium and perinatal conditions

Frequent: Increased risk of neural tube defects, syndromes (foetal hydantoin syndrome) such as craniofacial and digital abnormalities (see PREGNANCY AND LACTATION).

Less frequent: Cleft lip and palate, neonatal bleeding (see PREGNANY AND LACTATION).

Reproductive system and breast disorders

Frequency unknown: Decrease in sexual potency and fertility in male epileptics, gynaecomastia

Investigations

Frequent: Decreased serum levels of protein bound iodine (PBI), lower than normal values for dexamethasone or metyrapone tests, raised serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT) (see INTERACTIONS).

Less frequent: Immunoglobulin abnormalities

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088 / +27 (0)11 239-6200

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

The lethal dose in children is not known.The mean lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia and dysarthria. Other signs include tremor, hypereflexia, lethargy, slurred speech, nausea and vomiting. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs. This may be 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 20 mg/l, and ataxia at 30 mg/l, dysarthria and lethargy appear when the serum concentration is greater than 40 mg/l, but a concentration as high as 50 mg/l 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/l (400 micromoles/l) with complete recovery.

Treatment

Treatment is non-specific 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. 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.

IDENTIFICATION

PHENYTOIN SODIUM 100 mg Tablets: A white, round, shallow biconvex film-coated tablet, free from cracking, peeling and chipping.

PHENYTOIN SODIUM CAPSULES: A white No 3 opaque gelatin capsule containing a white powder.

PRESENTATION

PHENYTOIN SODIUM 100 mg Tablets:

90, 500 or 1 000 tablets are packed in a white polypropylene container with a white linear low density polyethylene snap-on cap, together with a foam or rayon insert and a leaflet.

5 000 tablets are packed in a high density polyethylene bucket lined with a polyethylene bag or, alternatively, into a 2,5 l metal tin lined with a polyethylene bag, together with a leaflet.

84 tablets are packed in a patient ready pack in Ziploc lay-flat bags or metalised lay-flat bags. These packed bank bags are grouped, packed and sealed into polyethylene bags together with a leaflet.

PHENYTOIN SODIUM CAPSULES:

100 capsules are packed in a white polypropylene securitainer with a white, low density polyethylene snap-on cap, together with a dessicant disc and leaflet.

1 000 capsules are packed in an amber polyvinyl chloride xactic container with a high density polyethylene screw cap, together with a silica gel sachet and a leaflet.

84 capsules are packed into pre-printed low density polyethylene Ziploc lay-flat or metallocene lay-flat bags.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Store in airtight containers.

Keep in original packaging until required for use.

REGISTRATION NUMBER

PHENYTOIN SODIUM 100 mg Tablets: B884 (ACT 101/1965)

PHENYTOIN SODIUM CAPSULES: B0885 (ACT 101/1965)

NAME AND BUSINESS ADDRESS HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of registration: Old medicines

Date of the most recent amendment to the professional information as approved by the Authority: 03 February 2020

Botswana: 100 mg tablet: B9321350 S2

Namibia: NS2 100 mg tablet: 14/2.6/0217

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