SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

EPANUTIN® 100 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains phenytoin sodium 100 mg equivalent to 92 mg phenytoin.

Contains sugar (lactose monohydrate and sucrose).

Excipients with known effect

Each capsule contains 57,50 mg lactose monohydrate and 57,20 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

Hard, filled No. 3, capsules containing a white powder. The medium orange cap having the “VLE” logo printed in black ink and the white, opaque, body having “DILANTIN” over “100 mg” printed in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EPANUTIN 100 mg is indicated for the control of generalised tonic-clonic (*grand mal*) and complex partial (psychomotor, temporal lobe) seizures.

4.2 Posology and method of administration

Posology

General

EPANUTIN 100 mg capsules and EPANUTIN READY MIXED PARENTERAL are formulated with the sodium salt of phenytoin. Because there is approximately an 8 % increase in medicine content with the free acid form over that of the sodium salt, dosage adjustments and serum concentration monitoring may be necessary when switching from a medicine formulated with the free acid to a medicine formulated with the sodium salt and vice versa.

Dosage should be individualised to provide maximum benefit. Serum phenytoin concentrations are needed to optimise dosage adjustments. Optimum control without clinical signs of toxicity occurs more often with serum concentrations between 10 and 20 µg/mL, although some mild cases of tonic-clonic (*grand mal*) epilepsy may be controlled with lower serum concentrations of EPANUTIN 100 mg. With recommended dosage, a period of 7 to 10 days may be required to achieve steady state serum concentrations with EPANUTIN 100 mg, and changes in dosage (increase or decrease) should not be carried out at intervals shorter than 7 to 10 days.

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

Adult dosage

Divided daily dosage

Patients who have received no previous treatment may be started on 300 mg daily, to be taken in three equally divided doses, and the dosage then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be 300 to 400 mg daily, to be taken in three to four equally divided doses, respectively. An increase up to 600 mg daily may be necessary.

Non-emergency oral loading dose in adult patients

An oral loading dose of EPANUTIN 100 mg may be used for non-emergency initiation of therapy in adults who require rapid steady state serum concentrations, and for whom intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinic or hospital setting where EPANUTIN 100 mg serum concentrations can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading dose regimen.

The recommended oral loading dose is 1 g of EPANUTIN 100 mg divided into three equal doses (400 mg, 300 mg, and 300 mg) and administered at 2-hour intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum concentration determinations.

Alternate dosage

Once-a-day dosage for adults may be considered if seizure control is established with divided doses. Studies comparing divided doses of 100 mg three times daily with a single, daily dose of 300 mg indicated that absorption, peak serum concentrations, biological half-life, difference between peak and minimum values, and urine recovery were equivalent. 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.

Paediatric population

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualised 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 of age and adolescents 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.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to phenytoin or to any of the excipients of EPANUTIN 100 mg (listed in section 6.1) or to other hydantoin medicines.
- Porphyria.
- Co-administration of EPANUTIN 100 mg with delavirdine is contraindicated due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

4.4 Special warnings and precautions for use

General

EPANUTIN 100 mg is not effective for absence (*petit mal*) seizures.

EPANUTIN 100 mg is not effective for seizures due to hypoglycaemic or other metabolic causes.

EPANUTIN 100 mg should not be abruptly discontinued because of the possibility of increased seizure frequency, including *status epilepticus*. When, in the judgment of the medical practitioner, the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medicine 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 anticonvulsant medicine which does not belong to the hydantoin chemical class.

Some individuals who have been treated with EPANUTIN 100 mg have been shown to metabolise the medicine slowly. Slow metabolism may be due to limited enzyme activity and appears to be genetically determined (polymorphism).

Acute alcoholic intake may increase EPANUTIN 100 mg serum concentrations, while chronic alcoholic use may decrease serum concentrations.

Women of childbearing potential

EPANUTIN 100 mg may cause foetal harm when administered to a pregnant woman. Prenatal exposure to EPANUTIN 100 mg may increase the risks for major congenital malformations and other adverse development outcomes (see section 4.6).

EPANUTIN 100 mg 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 EPANUTIN 100 mg 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 EPANUTIN 100 mg during pregnancy.

Women of childbearing potential should be counselled regarding the need to consult their medical practitioner 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 EPANUTIN 100 mg.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, EPANUTIN 100 mg 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).

Suicide

Suicidal ideation and behaviour have been reported in patients treated with anticonvulsant medicines, such as EPANUTIN 100 mg, in several indications. The mechanism of this risk is not known.

Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms

Hypersensitivity syndrome (HSS) or drug reaction with eosinophilia and systemic symptoms (DRESS), which may be life-threatening or fatal, has been reported in patients taking anticonvulsant medicines, including EPANUTIN 100 mg.

HSS/DRESS typically, although not exclusively, presents with fever, rash and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, haematological

abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between the first medicine exposure and symptoms is usually 2 to 4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. EPANUTIN 100 mg should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past (with EPANUTIN 100 mg or other anticonvulsant medicines), patients who have a family history of this syndrome and immunosuppressed patients. The syndrome is more severe in previously sensitised individuals.

Serious dermatologic reactions

EPANUTIN 100 mg can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of HSS/DRESS (see section 4.4, Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms) and should seek medical advice from their medical practitioner immediately when observing any indicative signs or symptoms. The medical practitioner should advise the patient to discontinue treatment if the rash appears. 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 EPANUTIN 100 mg medicine is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to EPANUTIN 100 mg may be higher 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 human leukocyte antigen HLA-B*1502, an inherited allelic variant of the HLA-B gene, in patients using carbamazepine. Limited evidence 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 EPANUTIN 100 mg. Consideration should be given to avoiding use of medicines associated with SJS/TEN, including EPANUTIN 100 mg, in HLA-B*1502 positive patients when alternative therapies are otherwise equally available.

Literature reports suggest that the combination of EPANUTIN 100 mg, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme, and/or

SJS, and/or TEN.

Hepatic injury

The liver is the chief site of metabolism of EPANUTIN 100 mg.

Toxic hepatitis and liver damage have been reported and may be fatal.

Cases of acute hepatotoxicity, including acute hepatic failure, have been reported with EPANUTIN 100 mg. These incidents usually occur within the first 2 months of treatment and may be associated with HSS/DRESS (see section 4.4, Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms).

Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

The clinical course of acute EPANUTIN 100 mg hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, EPANUTIN 100 mg should be immediately discontinued and not re-administered.

The risk of hepatotoxicity and other hypersensitivity reactions to EPANUTIN 100 mg may be higher in black patients.

Haematopoietic system

Haematopoietic complications, some fatal, have been reported in association with administration of EPANUTIN 100 mg. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports suggesting a relationship between EPANUTIN 100 mg and the development of lymphadenopathy (local or 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 signs and symptoms resembling HSS/DRESS (see section 4.4, Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms). 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 anticonvulsant medicines.

While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. If folic acid is added to EPANUTIN 100 mg therapy, a decrease in seizure control may

occur.

Central nervous system effect

Serum concentrations of EPANUTIN 100 mg above the therapeutic range may produce confusional states referred to as “delirium”, “psychosis”, or “encephalopathy”, or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, determination of serum concentrations is recommended. Dose reduction of EPANUTIN 100 mg therapy is indicated if serum concentrations exceed the therapeutic range; if symptoms persist, EPANUTIN 100 mg therapy should be stopped.

Metabolic effect

In view of reports associating EPANUTIN 100 mg with exacerbation of porphyria, EPANUTIN 100 mg should not be used in patients suffering from porphyria (see section 4.3).

Hyperglycaemia, resulting from EPANUTIN 100 mg’s inhibitory effects on insulin release, has been reported.

EPANUTIN 100 mg may also raise serum glucose concentrations in diabetic patients.

Musculoskeletal effect

EPANUTIN 100 mg induces the CYP450 enzyme system and may 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, hypocalcaemia and hypophosphataemia in epileptic patients. Vitamin D supplements may be necessary with long-term therapy.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sucrose

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

4.5 Interaction with other medicines and other forms of interaction

Medicine interactions

EPANUTIN 100 mg is extensively bound to plasma proteins and is prone to competitive displacement. EPANUTIN 100 mg is metabolised by hepatic cytochrome (CYP) P450 enzymes CYP2C9 and

CYP2C19 and is particularly susceptible to inhibitory medicine interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating EPANUTIN 100 mg concentrations and enhance the risk of toxicity.

EPANUTIN 100 mg is a potent inducer of hepatic drug-metabolising enzymes and may reduce the concentrations of medicines metabolised by these enzymes.

There are many medicines that may increase or decrease serum EPANUTIN 100 mg concentrations or that EPANUTIN 100 mg may affect. Serum concentration determinations for EPANUTIN 100 mg are especially helpful when possible medicine interactions are suspected.

The most commonly occurring medicine interactions are listed below.

Medicines that may increase EPANUTIN 100 mg serum concentrations

Table 1 summarises the medicine classes that may potentially increase EPANUTIN 100 mg serum concentrations:

Table 1

Medicine classes	Medicines in each class (such as*)
Alcohol (acute intake)	
Analgesic/ anti-inflammatory medicines	Azapropazone Phenylbutazone Salicylates
Anaesthetics	Halothane
Antibacterial medicines	Chloramphenicol Erythromycin and other macrolide antibiotics Isoniazid Sulphamethoxazole-trimethoprim Sulphonamides
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
Calcium channel blockers/ cardiovascular medicines	Amiodarone Dicumarol Diltiazem Nifedipine Ticlopidine
H_2-antagonists	Cimetidine
HMG-CoA reductase inhibitors	Fluvastatin
Hormones	Estrogens
Immunosuppressant medicines	Tacrolimus
Oral hypoglycaemic medicines	Tolbutamide
Proton pump inhibitors	Omeprazole
Serotonin re-uptake inhibitors	Fluoxetine Fluvoxamine Sertraline

*This list is not intended to be inclusive or comprehensive. Individual medicine labels should be

consulted.

Medicines that may decrease EPANUTIN 100 mg serum concentrations

Table 2 summarises the medicine classes that may potentially decrease EPANUTIN 100 mg serum concentrations:

Table 2

Medicine classes	Medicines 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
Hyperglycaemic medicines	Diazoxide
St John's Wort	St John's Wort

*This list is not intended to be inclusive or comprehensive. Individual medicine labels should be consulted.

Molindone hydrochloride contains calcium ions, which interfere with the absorption of EPANUTIN 100 mg. Ingestion times of EPANUTIN 100 mg and calcium preparations, including antacid preparations containing calcium, should be staggered to prevent absorption problems.

Concurrent use with zidovudine: There have been several reports of decreased phenytoin serum concentrations, and one case of increased phenytoin serum concentration. However, a pharmacokinetic interaction study showed no effect on phenytoin kinetics, but a 30 % decrease in zidovudine clearance was observed with concurrent use.

Concurrent use with ritonavir: In a medicine interaction study reported in the literature, phenytoin exhibits a two-way interaction with lopinavir/ritonavir. Co-administration of lopinavir/ritonavir decreased phenytoin trough concentration and AUC by 34 % and 31 %, respectively. Co-administration of phenytoin decreased lopinavir trough concentration and AUC by 46 % and 33 %, respectively, and decreased ritonavir trough concentration and AUC by 47 % and 28 %, respectively.

Pharmacokinetic interaction

Co-administration of nelfinavir tablets (1 250 mg twice daily) with phenytoin capsules (300 mg once a day) did not change the serum concentration of nelfinavir. However, co-administration of nelfinavir reduced the AUC values of phenytoin (total) and free phenytoin by 29 % and 28 %, respectively.

Medicines that may either increase or decrease EPANUTIN 100 mg serum concentrations

Table 3 summarises the medicine classes that may either increase or decrease EPANUTIN 100 mg serum concentrations:

Table 3

Medicine classes	Medicines in each class (such as*)
Antibacterial medicines	Ciprofloxacin
Anticonvulsants	Carbamazepine Phenobarbitone Sodium valproate Valproic acid
Antineoplastic medicines	
Psychotropic medicines	Chlordiazepoxide Diazepam Phenothiazines

*This list is not intended to be inclusive or comprehensive. Individual medicine labels should be consulted.

Medicines whose serum concentrations and/or effects may be altered by EPANUTIN 100 mg

Table 4 summarises the medicine classes whose serum concentrations and/or effects may be altered by EPANUTIN 100 mg:

Table 4

Medicine classes	Medicines in each class (such as*)
Antibacterial medicines	Doxycycline Rifampicin Tetracycline
Anticonvulsants	Carbamazepine Lamotrigine Phenobarbitone Sodium valproate Valproic acid
Antifungal medicines	Azoles Posaconazole Voriconazole
Anthelminthics	Albendazole Praziquantel
Antineoplastic medicines	Teniposide
Antiretrovirals	Delavirdine Efavirenz Fosamprenavir Indinavir Lopinavir/ritonavir Nelfinavir Ritonavir Saquinavir
Bronchodilators	Theophylline

Calcium channel blockers/ cardiovascular medicines	Digoxin Mexiletine Nicardipine Nimodipine Nisoldipine Quinidine Verapamil
Corticosteroids	
Coumarin anticoagulants	Warfarin
Diuretics	Furosemide
HMG-CoA reductase inhibitors	Atorvastatin Fluvastatin Simvastatin
Hormones	Estrogens Oral contraceptives
Hyperglycaemic medicines	Diazoxide
Immunosuppressant medicines	Ciclosporin
Neuromuscular blocking medicines	Alcuronium Cisatracurium Pancuronium Rocuronium Vecuronium
Opioid analgesics	Methadone
Oral hypoglycaemic medicines	Chlorpropamide Glyburide Tolbutamide

Psychotropic medicines/ antidepressants	Clozapine Paroxetine Quetiapine Sertraline
Vitamin D	Vitamin D

*This list is not intended to be inclusive or comprehensive. Individual medicine labels should be consulted.

Although not a true medicine interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and EPANUTIN 100 mg dosage may need to be adjusted.

Medicine-enteral feeding/nutritional preparations interaction

Patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected EPANUTIN 100 mg plasma concentrations. Therefore, EPANUTIN 100 mg should not be administered concomitantly with an enteral feeding preparation. More frequent serum EPANUTIN 100 mg concentration monitoring may be necessary in these patients.

Medicine-laboratory test interactions

EPANUTIN 100 mg may cause decreased serum concentrations of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. EPANUTIN 100 mg may cause increased serum concentrations of glucose, alkaline phosphatase and gamma-glutamyl transpeptidase (GGT). EPANUTIN 100 mg may affect blood calcium and blood sugar metabolism rates.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

EPANUTIN 100 mg 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 EPANUTIN 100 mg.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, EPANUTIN 100 mg 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

EPANUTIN 100 mg has been associated with teratogenicity when given to women in the first trimester of pregnancy. Its use should be avoided in pregnant women and women likely to become pregnant unless its continued use is considered essential by the medical practitioner. Women who have been exposed to EPANUTIN 100 mg in the first trimester of pregnancy should be informed of the risk and should be offered prenatal counselling.

A number of reports suggest an association between the use of anticonvulsant medicines by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to EPANUTIN 100 mg and phenobarbital, but these are also the most commonly prescribed anticonvulsant medicines. Less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant medicines.

It is important to note that anticonvulsant medicines should not be discontinued in patients in whom the medicine is administered to prevent major seizures because of the strong possibility of precipitating *status epilepticus* with attendant hypoxia and threat to life.

An increased incidence of congenital malformations such as cleft lip/palate and heart malformations have been reported in children of women receiving EPANUTIN 100 mg. There have been reports of a foetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly, craniofacial abnormalities, nail and digital hypoplasia, and mental deficiency in children born to mothers who have received EPANUTIN 100 mg. There is evidence of a genetic predisposition to congenital abnormalities induced by EPANUTIN 100 mg.

There have been reports of malignancies, including neuroblastoma, in children whose mothers received EPANUTIN 100 mg during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered EPANUTIN 100 mg absorption or metabolism. Periodic measurement of serum phenytoin

concentrations 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 EPANUTIN 100 mg. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

EPANUTIN 100 mg is teratogenic in rats, mice and rabbits.

Breastfeeding

Breastfeeding is not recommended for women taking EPANUTIN 100 mg because EPANUTIN 100 mg is secreted in human milk. EPANUTIN 100 mg concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

Fertility

In animal studies, EPANUTIN 100 mg had no direct effect on fertility.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that EPANUTIN 100 mg does not affect their ability to engage in these activities.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The adverse event terms are categorised utilising the incidence rate as follows: 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).

If a listed adverse event term was not reported in the above documentation, it was categorised as rare, based on reporting rates versus estimated medicine use worldwide.

Post-marketing experience

MedDRA system organ class	Frequency	Adverse event

Blood and lymphatic system disorders	Rare	Thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, macrocytosis, megaloblastic anaemia, lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, Hodgkin's disease
Immune system disorders	Rare	Anaphylactoid reaction, anaphylaxis, periarteritis nodosa
Psychiatric disorders	Common	Mental confusion, insomnia, transient nervousness
Nervous system disorders	Very common	Dizziness, nystagmus, paraesthesia
	Common	Ataxia, slurred speech, decreased coordination, headache, somnolence. Cerebellar atrophy has been reported and appears more likely in settings of elevated phenytoin concentrations and/or long-term phenytoin use.
	Rare	Phenytoin-induced dyskinesias, including chorea, dystonia, tremor and asterixis, sensory peripheral polyneuropathy, taste perversion
Ear and labyrinth disorders	Rare	Vertigo
Gastrointestinal disorders	Common	Nausea, vomiting
	Rare	Constipation, gingival hyperplasia, enlargement of lips
Hepatobiliary disorders	Rare	Acute hepatic failure which may be fatal, toxic hepatitis, liver damage

Skin and subcutaneous tissue disorders	Rare	Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS). Dermatological manifestations, sometimes accompanied by fever, have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms that may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson Syndrome and toxic epidermal necrolysis, hypertrichosis
Musculoskeletal and connective tissue disorders	Common	Motor twitching
	Rare	Coarsening of facial features, systemic lupus erythematosus
Reproductive system and breast disorders	Rare	Peyronie's disease
Investigations	Rare	Immunoglobulin abnormalities

Musculoskeletal system

Bone fractures and osteomalacia have been associated with long-term (> 10 years) use of EPANUTIN 100 mg by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcaemia, hypophosphataemia and decreased concentrations of vitamin D metabolites have also been reported.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The lethal dose in paediatric patients is not known. The lethal dose in adults is estimated to be 2 g to 5

g. The initial symptoms are nystagmus, ataxia and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea and vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to EPANUTIN 100 mg serum concentrations where toxicity may occur. Nystagmus on lateral gaze usually appears at 20 µg/mL and ataxia at 30 µg/mL. Dysarthria and lethargy appear when the serum concentration is > 40 µg/mL, but a concentration as high as 50 µg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration > 100 µg/mL with complete recovery.

Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment

Treatment is symptomatic and supportive since there is no antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed, and appropriate supportive measures employed. Haemodialysis can be considered since EPANUTIN 100 mg is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in paediatric patients.

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

Category and class: A 2.5 Anticonvulsants, including anti-epileptics

Phenytoin is an anticonvulsant. The primary site of action appears to be the motor cortex where the spread of seizure activity is inhibited, possibly by promoting sodium efflux from neurons. Phenytoin tends to stabilise the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at the synaptic levels. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centres responsible for the tonic phase of tonic-clonic (*grand mal*) seizures.

5.2 Pharmacokinetic properties

Absorption

Phenytoin is a weak acid and is highly lipophilic (limited water solubility). It exhibits a slow and somewhat variable absorption after oral administration, but after absorption is complete, peak serum concentrations occur 1½ to 3 hours after administration.

Distribution

Phenytoin is rapidly distributed into all tissues, with an apparent volume of distribution of 0,6 L/kg. It is highly bound (90 %) to plasma proteins, mainly albumin.

Free phenytoin concentrations may be altered in patients whose protein-binding characteristics differ from normal. Phenytoin is distributed into the cerebrospinal fluid (CSF), saliva, semen, gastrointestinal fluids, bile and breast milk. The concentration of phenytoin in the CSF, brain and saliva approximates the concentration of free phenytoin in plasma.

Biotransformation

Phenytoin is metabolised in the liver by oxidative metabolism by cytochrome P450 enzymes. The major pathway involves 4-hydroxylation, which accounts for 80 % of all metabolites. CYP2C9 accounts for 90 % of the 4-hydroxylation while CYP2C19 has a minor (10 %) involvement.

Because the cytochrome system involved in phenytoin hydroxylation is easily saturable, small increments in doses of phenytoin (even by 10 %) may increase the half-life and produce substantial increases in serum concentrations when the levels are in the therapeutic range.

Elimination

The plasma half-life of phenytoin is about 22 hours, ranging from 7 to 42 hours and steady state concentrations are achieved in 7 to 10 days after initiation of therapy. The therapeutic range is 10 to 20 µg/mL.

Most of phenytoin is excreted in the bile as inactive metabolites, and less than 5 % is excreted as the parent compound.

Although most patients will attain stable therapeutic phenytoin serum concentrations (10 to 20 µg/mL) when maintained at steady state dosages, there may be wide interpatient variability in phenytoin serum concentrations with equivalent dosages. This may be due to enzyme polymorphs and formulation. Therefore, therapeutic drug monitoring is recommended in all patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Sucrose

Talc

Capsule shell

Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool place at or below 25 °C.

Protect from light and moisture.

6.5 Nature and contents of container

A white, opaque HDPE bottle with a white, polypropylene, child-resistant closure containing 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Kempton Park

Gauteng, 1601

Tel. no.: +27 11 451 1300

Manufacturer: Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico

8. REFERENCE NUMBER

B554 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Not applicable – Old Medicine.

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