SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

EPANUTIN® FORTE SUSPENSION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL contains phenytoin 125 mg.

Contains sugar (sucrose).

Excipients with known effect

Each 5 mL contains 1,044 g sucrose.

Alcohol 0,48 % v/v

Preservative: Sodium benzoate 0,5 % m/v

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

An opaque orange suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EPANUTIN FORTE SUSPENSION 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

EPANUTIN FORTE SUSPENSION IS NOT FOR PARENTERAL USE.

Posology

General

EPANUTIN 100 mg capsules and EPANUTIN READY MIXED PARENTERAL are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in EPANUTIN FORTE SUSPENSION. 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 FORTE SUSPENSION. With recommended dosage, a period of 7 to 10 days may be required to achieve steady state serum concentrations with EPANUTIN FORTE SUSPENSION, 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 125 mg (5 mL) of the 125 mg/5 mL suspension three times daily, and the dosage then adjusted to suit individual requirements. An increase to 625 mg (25 mL) daily may be made if necessary.

Non-emergency oral loading dose in adult patients

An oral loading dose of EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION divided into three 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.

Shake the suspension well before use.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to phenytoin or to any of the excipients of EPANUTIN FORTE SUSPENSION (listed in section 6.1) or to other hydantoin medicines.
- Porphyria.
- Co-administration of EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION is not effective for absence (*petit mal*) seizures.

EPANUTIN FORTE SUSPENSION is not effective for seizures due to hypoglycaemic or other metabolic causes.

EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION serum concentrations, while chronic alcoholic use may decrease serum concentrations.

Women of childbearing potential

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

EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION.

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

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 FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION medicine is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION. Consideration should be given to avoiding use of medicines associated with SJS/TEN, including EPANUTIN FORTE SUSPENSION, in HLA-B*1502 positive patients when alternative therapies are otherwise equally available.

Literature reports suggest that the combination of EPANUTIN FORTE SUSPENSION, 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 FORTE SUSPENSION.

Toxic hepatitis and liver damage have been reported and maybe fatal.

Cases of acute hepatotoxicity, including acute hepatic failure, have been reported with EPANUTIN FORTE SUSPENSION. 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 FORTE SUSPENSION hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, EPANUTIN FORTE SUSPENSION should be immediately discontinued and not re-administered.

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

Haematopoietic system

Haematopoietic complications, some fatal, have been reported in association with administration of EPANUTIN FORTE SUSPENSION. 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 FORTE SUSPENSION 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 FORTE SUSPENSION therapy, a decrease in seizure control may occur.

Central nervous system effect

Serum concentrations of EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION therapy is indicated if serum concentrations exceed the therapeutic range; if symptoms persist, EPANUTIN FORTE SUSPENSION therapy should be stopped.

Metabolic effect

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

Hyperglycaemia, resulting from the EPANUTIN FORTE SUSPENSION's inhibitory effects on insulin release, has been reported.

EPANUTIN FORTE SUSPENSION may also raise serum glucose concentrations in diabetic patients.

Musculoskeletal effect

EPANUTIN FORTE SUSPENSION 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.

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 FORTE SUSPENSION is extensively bound to plasma proteins and is prone to competitive displacement. EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION concentrations and enhance the risk of toxicity.

EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION concentrations or that EPANUTIN FORTE SUSPENSION may affect. Serum concentration determinations for EPANUTIN FORTE SUSPENSION are especially helpful when possible medicine interactions are suspected.

The most commonly occurring medicine interactions are listed below.

Medicines that may increase EPANUTIN FORTE SUSPENSION serum concentrations

Table 1 summarises the medicine classes that may potentially increase EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION serum concentrations

Table 2 summarises the medicine classes that may potentially decrease EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION. Ingestion times of EPANUTIN FORTE SUSPENSION 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) 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 FORTE SUSPENSION serum concentrations

Table 3 summarises the medicine classes that may either increase or decrease EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION

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

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 FORTE SUSPENSION 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 FORTE SUSPENSION plasma concentrations. Therefore, EPANUTIN FORTE SUSPENSION should not be administered concomitantly with an enteral feeding preparation. More frequent serum EPANUTIN FORTE SUSPENSION concentration monitoring may be necessary in these patients.

Medicine-laboratory test interactions

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION. 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 FORTE SUSPENSION. There is evidence of a genetic predisposition to congenital abnormalities induced by EPANUTIN FORTE SUSPENSION.

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

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION. 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 FORTE SUSPENSION is teratogenic in rats, mice and rabbits.

Breastfeeding

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

Fertility

In animal studies, EPANUTIN FORTE SUSPENSION 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 FORTE SUSPENSION 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 product 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 FORTE SUSPENSION 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 FORTE SUSPENSION 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 FORTE SUSPENSION 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 the 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

Alcohol

Banana flavour

Carboxymethyl cellulose sodium

Citric acid

Glycerine

Magnesium aluminium silicate

Orange oil

Polysorbate 40

Purified water

Sodium benzoate

Sucrose granulated

Vanillin

Yellow colourant

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool (at or below 25 °C), dry place.

6.5 Nature and contents of container

Round amber glass or polyethylene terephthalate (PET) bottles of 237 mL with a white polypropylene closure.

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: Pharmacia and Upjohn Company LLC, Kalamazoo, USA

8. REFERENCE NUMBER

B555 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Not applicable – Old Medicine.

10. DATE OF REVISION OF THE TEXT

05 June 2026

BOTSWANA: S2

Reg. No.: B9321760

NAMIBIA: NS2

Reg. No.: 14/2.6/0333