SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

EPANUTIN® READY MIXED PARENTERAL Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL contains a ready mixed solution of 250 mg phenytoin sodium B.P. equivalent to 230 mg phenytoin.

Sugar free.

Excipients with known effect

Each 5 mL also contains 2,075 g propylene glycol, 446,7 mg ethanol 96 % and 20,95 mg sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless ready mixed solution containing 50 mg phenytoin sodium per mL in a 6 mL flint glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EPANUTIN READY MIXED PARENTERAL is indicated for:

- Prevention and treatment of seizures occurring during or following neurosurgery.
- The control of *status epilepticus* of the tonic-clonic *(grand mal)* type.

4.2 Posology and method of administration

Posology

General

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 level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and vice versa.

Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 µg/mL.

Because of the risk of local toxicity, IV EPANUTIN READY MIXED PARENTERAL should only be administered directly into a large peripheral or central vein through a large-gauge catheter. Prior to the administration, the patency of the IV catheter should be tested with a flush of sterile saline. Each injection of parenteral EPANUTIN READY MIXED PARENTERAL should then be followed by a flush of sterile saline through the same catheter to avoid local venous irritation due to the alkalinity of the solution [see section 4.4, Local toxicity (including purple glove syndrome)].

EPANUTIN READY MIXED PARENTERAL solution should not be added to intravenous infusions due to lack of solubility and resultant precipitation.

EPANUTIN READY MIXED PARENTERAL should be inspected visually for particulate matter and discolouration prior to administration. The solution is suitable for use as long as it remains free of haziness and precipitate. Upon refrigeration or freezing, a precipitate might form; this will dissolve again after the solution is allowed to stand at room temperature. The product is still suitable for use. Only a clear solution should be used. A faint yellow colouration may develop; however, this has no effect on the potency of the solution.

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/mL).

The rate of administration is very important. It should not exceed 50 mg/min in adults and should not exceed 1 to 3 mg/kg/min in neonates. At this rate toxicity should be minimised.

Use in neurosurgery

For initiating prophylaxis and for the treatment of seizures, an intravenous loading dose followed by maintenance doses (oral if possible) should be administered; see Use in *status epilepticus*.

Use in status epilepticus

Adults

An initial loading dose of 10 to 15 mg/kg body mass should be administered slowly intravenously, at a rate not exceeding 50 mg/min. This initial dose (usually administered over 20 minutes in a 70 kg patient) should be followed by the appropriate maintenance doses. For most adults, the satisfactory maintenance dose will be 300 – 400 mg daily with a maximum daily dose of 600 mg.

Use in cardiac dysrhythmias

3,5 to 5 mg/kg of body mass injected slowly intravenously and at a uniform rate which does not exceed 1 mL (50 mg) per minute have been used. This dose may be repeated once if necessary. If there is no beneficial reaction at plasma levels of 20 µg/mL, it is unlikely that higher levels will have any effect. Slow administration of 30 – 50 mg/min is preferred.

Paediatric population

Use in status epilepticus

A loading dose of 10 to 20 mg/kg body mass intravenously at a rate not exceeding 1 to 3 mg/kg/minute. Paediatric dosage may also be calculated on the basis of 250 mg/m^2 body surface. The appropriate maintenance dosing (oral if possible) should be administered in divided doses; the recommended daily maintenance dosage is usually in the range of 4 to 8 mg/kg.

Determination of phenytoin serum levels is advised, to monitor the adequacy of the dosage administered.

EPANUTIN READY MIXED PARENTERAL contains 2,075 g of propylene glycol per 5 mL solution, therefore a phenytoin loading dose of 20 mg/kg would result in an amount of 165,6 mg/kg of propylene glycol. In neonates and infants less than or equal to 1 year of age, this may result in potential adverse reactions (see section 4.4).

Method of administration

For parenteral administration.

4.3 Contraindications

- Hypersensitivity to phenytoin or to any of the excipients of EPANUTIN READY MIXED PARENTERAL (listed in section 6.1) or to other hydantoin medicines.
- Porphyria.

- Because of its effects on ventricular automaticity, EPANUTIN READY MIXED PARENTERAL is contraindicated in patients with sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular (AV) block, and in patients with Stokes-Adams syndrome. Fatalities due to cardiac arrest, ventricular fibrillation, tonic seizures and respiratory arrest have been reported following intravenous administration of phenytoin in cases with cardiac dysrhythmias. Alterations of cardiac and respiratory function can be produced by too rapid administration of EPANUTIN READY MIXED PARENTERAL intravenously.
- Co-administration of EPANUTIN READY MIXED PARENTERAL with antiretroviral nucleoside reverse transcriptase inhibitors (NRTI's), non-nucleoside reverse transcriptase inhibitors (NNRTI's) and ritonavir (including nelfinavir and delavirdine) is contraindicated due to the potential for loss of virologic response and possible resistance of NNRTI's.

4.4 Special warnings and precautions for use

General

EPANUTIN READY MIXED PARENTERAL is for intravenous use only.

EPANUTIN READY MIXED PARENTERAL should not be used by IM injection.

EPANUTIN READY MIXED PARENTERAL is not effective for absence (*petit mal*) seizures. If tonic-clonic (*grand mal*) and absence (*petit mal*) seizures are present, combined medicine therapy is needed.

EPANUTIN READY MIXED PARENTERAL is not indicated for seizures due to hypoglycaemia or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

The most notable signs of toxicity associated with the IV use of this medicine are cardiovascular collapse and/or central nervous system depression. Hypotension does occur when the medicine is administered rapidly by the IV route. The rate of administration is very important; it should not exceed 50 mg/minute in adults, and 1 to 3 mg/kg/minute in neonates and children. At this rate, toxicity should be minimised.

As hypotension occurs usually when EPANUTIN READY MIXED PARENTERAL is administered by the IV route, EPANUTIN READY MIXED PARENTERAL should be used with caution in patients with hypotension and severe myocardial insufficiency.

The IM route is not recommended for the treatment of *status epilepticus*, since serum levels of

EPANUTIN READY MIXED PARENTERAL in the therapeutic range cannot be readily achieved by the IM route.

Phenytoin should not be abruptly discontinued because of the possibility of increased seizure frequency, including *status epilepticus*. When, in the judgement of the medical practitioner, 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.

A small percentage of individuals have been shown to metabolise phenytoin slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined (polymorphism).

Acute alcoholic intake may increase EPANUTIN READY MIXED PARENTERAL serum levels, while chronic alcoholic use may decrease serum levels.

Case reports have reported an increased incidence of hypersensitivity reactions, including skin rash and hepatotoxicity in black patients.

Women of childbearing potential

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

EPANUTIN READY MIXED PARENTERAL 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 READY MIXED PARENTERAL 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 READY MIXED PARENTERAL 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 READY MIXED PARENTERAL.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, EPANUTIN READY MIXED PARENTERAL 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 anti-epileptic medicines in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for EPANUTIN READY MIXED PARENTERAL.

Cardiovascular effect

Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients.

Local toxicity (including purple glove syndrome)

Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of IV EPANUTIN READY MIXED PARENTERAL.

Oedema, discolouration and pain distal to the site of injection (described as purple glove syndrome) have been reported following peripheral IV EPANUTIN READY MIXED PARENTERAL. Soft tissue irritation may vary from slight tenderness to extensive necrosis and sloughing of the skin. The syndrome may not develop for several days after injection. Skin necrosis and limb ischaemia have occurred and required such interventions as fasciotomies, skin grafting, and, in cases, amputation.

Improper administration including subcutaneous or perivascular injection should be avoided.

Intramuscular EPANUTIN READY MIXED PARENTERAL administration may cause pain, necrosis and abscess formation at the injection site (see section 4.2).

Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms

Hypersensitivity syndrome (HSS) or drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking anticonvulsant medicines, including EPANUTIN READY MIXED PARENTERAL. Some of these events have been fatal or life-threatening.

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

Literature reports suggest that the combination of EPANUTIN READY MIXED PARENTERAL, 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 biotransformation of EPANUTIN READY MIXED PARENTERAL.

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

Cases of acute hepatotoxicity, including cases of acute hepatic failure, have been reported with EPANUTIN READY MIXED PARENTERAL. 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 READY MIXED PARENTERAL hepatotoxicity ranges from spontaneous recovery to fatal outcomes. In patients with acute hepatotoxicity, EPANUTIN READY MIXED PARENTERAL should be immediately discontinued and not be re-administered.

The risk of hepatotoxicity and other hypersensitivity reactions to EPANUTIN READY MIXED PARENTERAL may be higher in black patients.

Haematopoietic system

Haematopoietic complications, some fatal, have been reported in association with administration of EPANUTIN READY MIXED PARENTERAL. 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 READY MIXED PARENTERAL 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 medicine.

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

Central nervous system effect

Serum levels of EPANUTIN READY MIXED PARENTERAL sustained above the optimal range may produce confusional states manifesting as delirium, psychosis or encephalopathy, or irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum level determinations are recommended. Dose reduction of EPANUTIN READY MIXED PARENTERAL therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with EPANUTIN READY MIXED PARENTERAL is recommended.

Metabolic effect

In view of reports associating EPANUTIN READY MIXED PARENTERAL with exacerbation of porphyria, caution should be exercised in using EPANUTIN READY MIXED PARENTERAL in patients suffering from this disease.

Hyperglycaemia, resulting from EPANUTIN READY MIXED PARENTERAL's inhibitory effects on insulin release, has been reported. Phenytoin may also raise serum glucose levels in diabetic patients.

Patients should be cautioned on the use of other medicines or alcoholic beverages without first seeking their medical practitioner's advice.

Patients should be instructed to call their medical practitioner if skin rash develops.

Information on excipients

EPANUTIN READY MIXED PARENTERAL contains a number of excipients known to have a recognised action or effect. These are:

Ethanol

EPANUTIN READY MIXED PARENTERAL contains 446,7 mg ethanol, 96 % per 5 mL solution.

Harmful for those suffering from alcoholism.

Blood alcohol concentration (BAC) can vary based on indication and population; the following are only two examples in case EPANUTIN READY MIXED PARENTERAL is administered for *status epilepticus* in an emergency setting:

- A loading dose of 15 mg/kg for an adult weighing 70 kg would result in exposure to 27 mg/kg of ethanol which may cause a rise in BAC of about 4,0 mg/100 mL.
- A loading dose of 20 mg/kg for a child weighing 25 kg would result in exposure to 36 mg/kg of ethanol which may cause a rise in BAC of about 5,3 mg/100 mL.

For comparison, for an adult drinking a glass of wine or 500 mL of beer, the BAC is likely to be about 50 mg/100 mL.

Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

Propylene glycol

EPANUTIN READY MIXED PARENTERAL contains 2,075 g propylene glycol per 5 mL solution.

In case of propylene glycol content of 1 mg/kg/day in babies less than 4 weeks and 50 mg/kg/day in children less than 5 years, co-administration of any substrate for alcohol dehydrogenase such as ethanol including other medicines that contain propylene glycol, may induce serious adverse effects in neonates and adverse events children less than 5 years respectively and thus the benefit-risk balance needs to be assessed on an individual patient basis.

Based on the amount of propylene glycol contained in each 5 mL of EPANUTIN READY MIXED PARENTERAL, the paediatric population would receive 165,6 mg/kg of propylene glycol when phenytoin loading dose of 20 mg/kg is administered for the treatment of *status epilepticus* (see section 4.2). Due to the specificity of paediatric population, in neonates and infants less than or equal to 1 year, the adverse reactions listed under Description of selected adverse reactions for the threshold of 500 mg/kg/day (see section 4.8) may occur in this population also for lower threshold. The benefit-risk balance needs to be assessed on an individual patient basis.

Propylene glycol at a threshold of 50 mg/kg/day may confer additional risks in pregnant and lactating

women and EPANUTIN READY MIXED PARENTERAL should not be used in this population unless other treatments are ineffective or not tolerated (see section 4.6).

Prolonged use of > 24 hours could result in propylene glycol toxicity (including haemolysis, CNS depression, hyperosmolality, lactic acidosis and renal insufficiency), especially in patients with pre-existing renal and/or hepatic dysfunction, or when co-administered with any other propylene glycol-containing product or substrate of alcohol dehydrogenase. Patients should be monitored for propylene glycol toxicity, including measurement of both osmolar and anion-gap, and/or lactic acid.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction, for propylene glycol threshold of 50 mg/kg/day.

Various adverse events (see section 4.8) have been reported with high doses or prolonged use of propylene glycol at a threshold of 500 mg/kg/day.

Sodium

EPANUTIN READY MIXED PARENTERAL contains 20,95 mg (0,96 mmol) sodium per 5 mL solution.

4.5 Interaction with other medicines and other forms of interaction

Medicine interactions

EPANUTIN READY MIXED PARENTERAL is extensively bound to serum plasma proteins and is prone to competitive displacement. EPANUTIN READY MIXED PARENTERAL 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 READY MIXED PARENTERAL concentrations and enhance the risk of medicine toxicity.

EPANUTIN READY MIXED PARENTERAL is a potent inducer of hepatic medicine-metabolising enzymes such as CYP3A4 and reduces the levels of medicines metabolised by these enzymes.

There are many medicines that may increase or decrease serum EPANUTIN READY MIXED PARENTERAL levels or that EPANUTIN READY MIXED PARENTERAL may affect. Serum level determinations for EPANUTIN READY MIXED PARENTERAL are especially helpful when possible

medicine interactions are suspected.

The most commonly occurring medicine interactions are listed below.

Medicines that may increase EPANUTIN READY MIXED PARENTERAL serum levels

Table 1 summarises the medicine classes that may potentially increase EPANUTIN READY MIXED PARENTERAL serum levels.

Table 1

Medicine classes	Medicines in each class (such as*)
Alcohol (acute intake)	
Analgesic/anti-inflammatory medicines	Salicylates
Anaesthetics	Halogenated anaesthetics
Antibacterial medicines	Chloramphenicol Erythromycin and other macrolide antibiotics Isoniazid Sulfamethoxazole-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 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 READY MIXED PARENTERAL serum levels

Table 2 summarises the medicine classes that may potentially decrease EPANUTIN READY MIXED PARENTERAL plasma levels.

Table 2	
Medicine classes	**Medicines in each class (such as*)**
Alcohol (chronic intake)	
Antibacterial medicines	Rifampicin Ciprofloxacin

Anticonvulsants	Vigabatrin
Antineoplastic medicines	Bleomycin Carboplatin Cisplatin Doxorubicin Methotrexate
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 READY MIXED PARENTERAL. Ingestion times of EPANUTIN READY MIXED PARENTERAL 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 plasma concentrations, and one case of increased phenytoin plasma concentration. However, a pharmacokinetic interaction study showed no effect on phenytoin kinetics, but a 30 % decrease in zidovudine clearance was observed with concurrent use.

Pharmacokinetic interaction

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

section 4.3).

Medicines that may increase or decrease EPANUTIN READY MIXED PARENTERAL serum levels

Table 3 summarises the medicine classes that may either increase or decrease EPANUTIN READY MIXED PARENTERAL serum levels.

Table 3

Medicine classes	Medicines in each class (such as*)
Antibacterial medicines	Ciprofloxacin
Anticonvulsants	Carbamazepine Phenobarbital 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 levels and/or effects may be altered by EPANUTIN READY MIXED PARENTERAL

Table 4 summarises the medicine classes whose serum levels and/or effects may be altered by EPANUTIN READY MIXED PARENTERAL.

Table 4

Medicine classes	Medicines in each class (such as*)
Antibacterial medicines	Doxycycline Rifampicin Tetracycline

Anticonvulsants	Carbamazepine Lamotrigine Phenobarbital Sodium valproate Valproic acid
Antifungal medicines	Azoles, including ketoconazole, itraconazole Posaconazole Voriconazole
Anthelmintics	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	
Anticoagulants	Warfarin (see below, Other oral anticoagulants)

Ciclosporin	
Diuretics	Furosemide
HMG-CoA reductase inhibitors	Atorvastatin Fluvastatin Simvastatin
Hormones	Estrogens Oral contraceptives
Hyperglycaemic medicines	Diazoxide
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 READY MIXED PARENTERAL dosage may need to be adjusted.

Other oral anticoagulants

No interaction studies have been done with rivaroxaban, dabigatran, apixaban and edoxaban. These medicines are substrates for P-glycoprotein (Pgp), while apixaban and rivaroxaban are metabolised by

CYP3A. Co-administration of EPANUTIN READY MIXED PARENTERAL with these medicines may reduce the anticoagulant effect.

Medicine-laboratory test interactions

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

EPANUTIN READY MIXED PARENTERAL 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 READY MIXED PARENTERAL.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, EPANUTIN READY MIXED PARENTERAL 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 READY MIXED PARENTERAL has been associated with teratogenicity when given to pregnant women. 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. Pregnant women who have

been exposed to EPANUTIN READY MIXED PARENTERAL should be informed of the risk and should be offered prenatal counselling.

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 possibility of precipitating *status epilepticus* with attendant hypoxia and threat to life.

The reported congenital malformations include cleft lip/palate and heart malformations. 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. There is some evidence of a genetic predisposition to congenital abnormalities induced by EPANUTIN READY MIXED PARENTERAL.

There have been reports of malignancies, including neuroblastoma, in children whose mothers received EPANUTIN READY MIXED PARENTERAL during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered EPANUTIN READY MIXED PARENTERAL absorption or metabolism. Periodic measurement of serum EPANUTIN READY MIXED PARENTERAL 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 EPANUTIN READY MIXED PARENTERAL. 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.

Some patients may experience a rapid reduction in maternal hepatic phenytoin metabolism at the time of delivery, requiring the dosage to be reduced within 12 hours postpartum.

Risks due to excipient propylene glycol

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. EPANUTIN READY MIXED PARENTERAL should not be used in this population unless other treatments are ineffective or not tolerated (see section 4.4).

Breastfeeding

Breastfeeding is not recommended for women taking EPANUTIN READY MIXED PARENTERAL because phenytoin is secreted in human milk.

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 READY MIXED PARENTERAL does not affect their ability to engage in these activities.

4.8 Undesirable effects

Summary of the safety profile

The most notable signs of toxicity associated with the intravenous use of EPANUTIN READY MIXED PARENTERAL are cardiovascular collapse and/or central nervous system depression. Hypotension is likely when EPANUTIN READY MIXED PARENTERAL is administered rapidly by the intravenous route. Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression, ventricular fibrillation and reduced cardiac output. Severe complications are most commonly encountered in elderly or gravely ill patients.

EPANUTIN READY MIXED PARENTERAL should not be given intramuscularly, as blood levels in the therapeutic range cannot be readily nor predictably achieved, and EPANUTIN READY MIXED PARENTERAL is extremely irritating.

There have been a number of reports of rickets, reduced bone density, and osteomalacia in patients treated with EPANUTIN READY MIXED PARENTERAL, probably due to the induction of phenytoin by liver enzymes involved in the metabolism of vitamin D.

Tabulated list 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 post-marketing reported adverse events.

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
	Rare	Phenytoin-induced dyskinesias, including chorea, dystonia, tremor and asterixis, sensory peripheral polyneuropathy, taste perversion
Ear and labyrinth disorders	Common	Vertigo
Vascular disorders	Common	Hypotension
Gastrointestinal disorders	Common	Nausea, vomiting
	Rare	Constipation, gingival hyperplasia, enlargement of lips
Hepatobiliary disorders	Rare	Acute hepatic failure, 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	Muscle twitching
	Rare	Coarsening of facial features, systemic lupus erythematosus
Reproductive system and breast disorders	Rare	Peyronie's disease
General disorders and administration site conditions	Common	Local irritation, inflammation, tenderness, necrosis and sloughing of skin have been reported with or without extravasation of IV EPANUTIN READY MIXED PARENTERAL. Oedema, discolouration and pain distal to the site of injection (described as purple glove syndrome) have also been reported.
Investigations	Rare	Immunoglobulin abnormalities

Description of selected adverse reactions

EPANUTIN READY MIXED PARENTERAL contains propylene glycol (see section 4.4) for use and at a threshold of 500 mg/kg/day, various adverse events, such as hyperosmolality, lactic acidosis, renal

dysfunction (acute tubular necrosis), acute renal failure, cardiotoxicity (arrhythmia, hypotension), central nervous system disorders (depression, coma, seizures), respiratory depression, dyspnoea, liver dysfunction, haemolytic reaction (intravascular haemolysis) and haemoglobinuria, or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol.

Therefore, doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case.

Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following haemodialysis. Medical monitoring is required.

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 requested to report any suspected drug reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 READY MIXED PARENTERAL serum levels 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 known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed, and appropriate supportive measures employed. Haemodialysis can be considered since EPANUTIN READY MIXED

PARENTERAL 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 central nervous system (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 medicine. 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 sites. 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

Distribution

The plasma half-life of phenytoin in man averages 22 hours, with a range of 7 to 42 hours. Phenytoin has an apparent volume of distribution of 0,6 l/kg and is highly bound (90 %) to plasma proteins, mainly albumin. Free phenytoin levels 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, breast milk and across the placenta. The concentration of phenytoin in the CSF, brain and saliva approximates the level of free phenytoin in plasma.

Biotransformation

Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80 % of all metabolites. CYP2C9 plays the major role in the metabolism of phenytoin (90 % of net intrinsic clearance), while CYP2C19 has a minor involvement in this process (10 % of net intrinsic clearance). This relative contribution of CYP2C19 to phenytoin

metabolism may, however, increase at higher phenytoin concentrations.

Because the cytochrome systems involved in phenytoin hydroxylation in the liver are saturable at high serum concentrations, small incremental doses of phenytoin may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The clearance of phenytoin has been shown to be impaired by CYP2C9 inhibitors such as phenylbutazone and sulfaphenazole. Impaired clearance has also been shown to occur in patients administered CYP2C19 inhibitors such as ticlopidine.

Elimination

Most of the medicine is excreted in the bile as inactive metabolites, which are then reabsorbed from the intestinal tract and eliminated in the urine partly through glomerular filtration, but more importantly via tubular secretion. Less than 5 % of phenytoin is excreted as the parent compound.

A fall in phenytoin serum levels may occur when patients are switched from oral to intramuscular (IM) administration. The drop is caused by slower absorption, as compared to oral administration, due to the poor hydrosolubility of phenytoin and the possibility of its precipitation at the site of injection. Intravenous administration is the preferred route for producing rapid therapeutic serum levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 5 mL contains 2,075 g propylene glycol, 446,7 mg ethanol 96 %, 20,95 mg sodium (as sodium hydroxide) and water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and excessive heat.

Solutions of EPANUTIN READY MIXED PARENTERAL should not be added to intravenous solutions because of precipitation of the acid.

6.5 Nature and contents of container

6 mL vial containing 250 mg (50 mg/mL) phenytoin sodium B.P.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

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Isando

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Tel. no.: +27 11 451 1300

Manufacturer: Pfizer Manufacturing Belgium N.V., Puurs, Belgium

8. REFERENCE NUMBER

B1624 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Not applicable – Old Medicine

10. DATE OF REVISION OF THE TEXT

14 October 2025

BOTSWANA: S2

Reg. No: BOT2303998

NAMIBIA: NS2

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