SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

EPANUTIN® READY MIXED PARENTERAL (injection)

COMPOSITION:

Each 5 ml vial contains a ready mixed solution of 250 mg phenytoin sodium B.P. equivalent to 230 mg phenytoin, in a vehicle containing 40 % propylene glycol and 10 % alcohol in water for injection adjusted to pH 12 with sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 synapses. 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 *grand mal* seizures.

Pharmacokinetic properties:

The plasma elimination half-life of phenytoin in humans averages 22 hours, with the range varying from 6 to 42 hours.

Phenytoin is approximately 90 % plasma protein bound; substantially less binding may occur in patients with renal or hepatic disease and may give rise to significantly elevated concentrations of unbound phenytoin.

The liver is the major organ of elimination for phenytoin. Because this elimination route is readily saturable, small increases in dosage may produce substantial increases in plasma phenytoin

concentrations (as little as a 10 % increase in daily dose may double or triple the steady state plasma phenytoin concentration).

In therapeutic doses, approximately 2 % of phenytoin is excreted unchanged via the kidneys.

Wide variability in pharmacokinetic handling of phenytoin underscores the advisability of appropriate monitoring of plasma phenytoin levels to assist in establishing the optimal dose and dosing interval in individual patients.

INDICATIONS:

EPANUTIN READY MIXED PARENTERAL is indicated for:

(1) Prevention and treatment of seizures occurring during and after neurosurgery;

(2) The control of *status epilepticus* of the *grand mal* type;

(3) It is of use in the treatment of certain cardiac arrhythmias, especially when these are digitalis-induced.

CONTRAINDICATIONS:

EPANUTIN READY MIXED PARENTERAL is contraindicated in those patients with a history of hypersensitivity to phenytoin or its inactive ingredients or other hydantoin products. EPANUTIN is contraindicated in porphyrics.

Because of its effects on ventricular automaticity, EPANUTIN READY MIXED PARENTERAL is contraindicated in sinus bradycardia, sino-atrial block, second and third-degree A-V block, and patients with Adams-Stokes 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.

WARNINGS AND SPECIAL PRECAUTIONS:

Intravenous administration should not exceed 50 mg/minute in adults. EPANUTIN READY MIXED PARENTERAL should be administered to neonates at a rate not exceeding 1 – 3 mg/kg/minute.

The intramuscular 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 intramuscular route.

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

EPANUTIN READY MIXED PARENTERAL 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 antiepileptic 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 antiepileptic medicine not belonging to the hydantoin chemical class.

A small percentage of individuals who have been treated with EPANUTIN READY MIXED PARENTERAL 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.

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

The addition of EPANUTIN READY MIXED PARENTERAL to intravenous infusion is not recommended due to lack of solubility and resultant precipitation. EPANUTIN READY MIXED PARENTERAL should be injected slowly (not exceeding 50 mg per minute in adults), directly into a large vein through a large gauge needle or intravenous catheter. Each injection of intravenous EPANUTIN READY MIXED PARENTERAL should be followed by an injection of sterile saline through the same needle or intravenous catheter to reduce local nervous irritation due to the alkalinity of the solution. Continuous infusion should be avoided.

Suicide:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic agents 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:

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.

Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare medicine induced, multi-organ syndrome which is potentially fatal and occurs in patients taking EPANUTIN READY MIXED PARENTERAL. It is characterised by fever, rash, lymphadenopathy, and other multi-organ pathologies, often hepatic. The mechanism is unknown. The interval between first medicine exposure and symptoms is usually 2 – 4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. Although up to 1 in 5 patients on EPANUTIN may develop cutaneous eruptions, only a small proportion will progress to AHS. Drug rash with eosinophilia and systemic symptoms (DRESS) reflects a serious hypersensitivity reaction to medicines, characterised by skin rash, fever, lymph node enlargement, and internal organ involvement. Cases of DRESS have been noted in patients taking phenytoin.

Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients. The syndrome is more severe in previously sensitised individuals. If a patient is diagnosed with AHS, discontinue the EPANUTIN READY MIXED PARENTERAL and provide appropriate supportive measures.

Central nervous system:

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

Haematopoietic:

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 symptoms and signs resembling serum sickness, e.g. fever,

rash, and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative anticonvulsant medication. 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.

Hepatic/ immunologic:

The liver is the chief site of biotransformation of EPANUTIN READY MIXED PARENTERAL. Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

Toxic hepatitis and liver damage have been reported and may, in rare cases, be fatal.

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with EPANUTIN READY MIXED PARENTERAL. These incidents have been associated with a hypersensitivity syndrome characterised by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include arthralgias, rash, jaundice, hepatomegaly, elevated serum transaminase levels, leucocytosis, and eosinophilia. The clinical course of acute EPANUTIN READY MIXED PARENTERAL hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, EPANUTIN READY MIXED PARENTERAL should be discontinued immediately and not re-administered.

Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients.

Local toxicity (including Purple Glove Syndrome):

Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of intravenous EPANUTIN READY MIXED PARENTERAL. Oedema, discolouration and pain distal to the site of injection (described as “purple glove syndrome”) have been reported following peripheral intravenous EPANUTIN READY MIXED PARENTERAL. Soft tissue irritation may vary from slight tenderness to extensive necrosis and sloughing of skin. The syndrome may not develop for several days after injection. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischaemia have occurred and required such interventions as fasciotomies, skin grafting, and, in rare 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.

Skin:

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 signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should seek medical advice from their doctor immediately when observing any indicative signs or symptoms. The doctor 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 medication is contraindicated.

There may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, hepatotoxicity and Anticonvulsant Hypersensitivity Syndrome in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using another anticonvulsant medication. 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 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 Stevens-Johnson syndrome, and/or toxic epidermal necrolysis.

EPANUTIN READY MIXED PARENTERAL should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of EPANUTIN READY MIXED PARENTERAL should not be resumed and alternative therapy should be considered. 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 medication is

contraindicated.

Metabolic:

In view of isolated 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 also may raise serum glucose levels in diabetics.

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.

INTERACTIONS:

Medicines which may increase EPANUTIN serum levels:

Medicines which may increase EPANUTIN serum levels either by decreasing its rate of metabolism by the hepatic CYP450 2C9 and 2C19 enzymatic systems (e.g. dicumarol, disulfiram, omeprazole, ticlopidine), by competing for protein binding sites (e.g. salicylates, sulfisoxazole, tolbutamide), or by a combination of both processes (e.g. phenylbutazone, valproate sodium).

Table 1 summarises the medicine classes which may potentially increase EPANUTIN serum levels.

TABLE 1	
MEDICINE CLASSES	**MEDICINES IN EACH CLASS (SUCH AS)**
Alcohol (acute intake)	
Analgesic/ anti-inflammatory agents	Azapropazone Phenylbutazone Salicylates
Anaesthetics	Halothane
Antibacterial agents	Chloramphenicol Erythromycin Isoniazid

	Sulphonamides
Anticonvulsants	Felbamate Succinimides
Antifungal agents	Amphotericin B Fluconazole Ketoconazole Miconazole Itraconazole
Antineoplastic agents	Fluorouracil
Benzodiazepines/ psychotropic agents	Chlordiazepoxide Diazepam Disulfiram Methylphenidate Trazodone Viloxazine
Calcium channel blockers/ cardiovascular agents	Amiodarone Dicumarol Diltiazem Nifedipine Ticlopidine
H_2-antagonists	Cimetidine
Hormones	Oestrogens
Oral hypoglycaemic agents	Tolbutamide
Proton pump inhibitors	Omeprazole
Serotonin re-uptake inhibitors	Fluoxetine Fluvoxamine Sertraline

Medicines which may decrease EPANUTIN plasma levels:

Table 2 summarises the medicine classes which may potentially decrease EPANUTIN plasma levels.

TABLE 2	
MEDICINE CLASSES	**MEDICINES IN EACH CLASS (SUCH AS)**
Alcohol (chronic intake)	
Antibacterial agents	Rifampin Ciprofloxacin
Anticonvulsants	Vigabatrin
Antiulcer agents	Sucralfate
Bronchodilators	Theophylline
Cardiovascular agents	Reserpine
Hyperglycaemic agents	Diazoxide

Molindone hydrochloride contains calcium ions which interfere with the absorption of EPANUTIN. Ingestion times of EPANUTIN 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.

A pharmacokinetic interaction study between nelfinavir and phenytoin both administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29 % and 28 %, respectively. Therefore, EPANUTIN concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce EPANUTIN plasma concentration.

Medicines which may either increase or decrease EPANUTIN serum levels:

Table 3 summarises the medicine classes which may either increase or decrease EPANUTIN serum levels.

TABLE 3	
MEDICINE CLASSES	**MEDICINES IN EACH CLASS (SUCH AS)**
Antibacterial agents	Ciprofloxacin
Anticonvulsants	Carbamazepine Phenobarbital

	Sodium valproate Valproic acid
Antineoplastic agents	
Psychotropic agents	Chlordiazepoxide Diazepam

Similarly, the effect of EPANUTIN on carbamazepine, phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

Medicines where blood levels and/or effects may be altered by EPANUTIN:

Table 4 summarises the medicine classes where blood levels and/or effects may be altered by EPANUTIN.

TABLE 4	
MEDICINE CLASSES	**MEDICINES IN EACH CLASS (SUCH AS)**
Antibacterial agents	Doxycycline Praziquantel Rifampin Tetracycline
Anticonvulsants	Lamotrigine
Antifungal agents	Azoles
Antineoplastic agents	Teniposide
Bronchodilators	Theophylline
Calcium channel blockers/ cardiovascular agents	Digitoxin Nicardipine Nimodipine Quinidine Verapamil
Corticosteroids	
Coumarin anticoagulants	
Cyclosporine	
Diuretics	Furosemide

Hormones	Oestrogens Oral contraceptives
Hyperglycaemic agents	Diazoxide
Neuromuscular blocking agents	Alcuronium Pancuronium Vecuronium
Opioid analgesics	Methadone
Oral hypoglycaemic agents	Chlorpropamide Glyburide Tolbutamide
Psychotropic agents/ antidepressants	Clozapine Paroxetine Sertraline
Vitamin D	

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.

Enteral feeding/nutritional preparations interaction:

Literature reports suggest that patients who receive enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels. It is therefore suggested that EPANUTIN READY MIXED PARENTERAL not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin monitoring may be necessary in these patients.

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 raised serum levels of glucose, alkaline phosphatase and gamma glutamyl transpeptidase (GGT). EPANUTIN READY MIXED PARENTERAL may affect blood calcium and blood sugar metabolism tests.

PREGNANCY AND LACTATION:

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

Safe usage during pregnancy has not been established.

Reports indicate a higher incidence of congenital abnormalities in children whose mothers used anticonvulsant medication during pregnancy. Reported abnormalities include cleft lip/palate, heart malformations, and the foetal hydantoin syndrome (consisting of craniofacial abnormalities, nail and digital hypoplasia, prenatal growth deficiency, microcephaly and mental deficiency associated with intrauterine development during therapy). There is good evidence of a genetic predisposition to congenital abnormalities induced by EPANUTIN.

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

Usage should not be discontinued if the medicine is administered to prevent major seizures because of the possibility of precipitating *status epilepticus* with attendant hypoxia and threat to life.

Exposure to EPANUTIN prior to delivery may lead to an increased risk of life-threatening haemorrhage in the neonate, usually within 24 hours of birth. EPANUTIN may also produce a deficiency of vitamin K in the mother, causing increased maternal bleeding during delivery. The risk of maternal and infant bleeding may be reduced by administering water-soluble vitamin K to the mother during delivery and to the neonate, intramuscularly or subcutaneously, immediately after birth.

Because of altered absorption, increased protein binding, and/or increased metabolic clearance of EPANUTIN during pregnancy, pregnant women receiving EPANUTIN may experience an increased incidence of seizures. Serum hydantoin concentrations must be monitored and doses increased accordingly. A gradual resumption of the patient's usual dosage may be necessary after delivery.

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.

Lactation:

EPANUTIN READY MIXED PARENTERAL is not recommended for use in breastfeeding women as

EPANUTIN READY MIXED PARENTERAL is excreted in breast milk; significant amounts may be ingested by the infant.

DOSAGE AND DIRECTIONS FOR USE:

EPANUTIN solution for injection is 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 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 mcg/ml.

Because of the risk of local toxicity, intravenous EPANUTIN READY MIXED PARENTERAL should 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 WARNINGS AND SPECIAL PRECAUTIONS).

The addition of EPANUTIN READY MIXED PARENTERAL solution to intravenous infusions is not recommended due to lack of solubility and resultant precipitation. Parenteral medicine products 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.

Children – 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.

Use in cardiac dysrhythmias:

3,5 to 5 mg per kg of body mass injected slowly intravenously and at a uniform rate which does not exceed 1 ml (50 mg) per minute. 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.

SIDE EFFECTS:

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.

The intramuscular route is not recommended because blood levels of EPANUTIN READY MIXED PARENTERAL in the therapeutic range cannot be readily nor predictably achieved.

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

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

Very common: ≥ 1/10 (≥ 10 %); Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %); Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %); Very rare < 1/10 000 (< 0,01 %).

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.

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Rare	Agranulocytosis; granulocytopenia; leukopenia; lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, and Hodgkin's disease; macrocytosis; megaloblastic anaemia; pancytopenia with or without bone marrow suppression; thrombocytopenia
Immune system disorders	Rare	Anaphylactoid reaction; anaphylaxis; hypersensitivity syndrome; periarteritis nodosa. Drug rash with eosinophilia and systemic symptoms (DRESS).
Psychiatric disorders	Common	Nervousness
	Rare	Insomnia; mental confusion
Nervous system disorders	Very common	Dizziness; nystagmus; paraesthesia
	Common	Ataxia; decreased coordination; headache; somnolence
	Rare	Phenytoin-induced dyskinesias, including chorea, dystonia, tremor, and asterixis; sensory peripheral

		neuropathy; slurred speech, taste perversion
Vascular disorders	Common	Hypotension
Gastrointestinal disorders	Common	Nausea, vomiting
	Rare	Constipation, gingival hyperplasia
Hepatobiliary disorders	Rare	Liver damage; toxic hepatitis
Skin and subcutaneous tissue disorders	Rare	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 which may be fatal have included bullous, exfoliative, or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis; enlargement of lips; 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
General disorders and administration site conditions	Common	Local irritation, inflammation, tenderness, necrosis, and sloughing of skin have been reported with or without extravasation of intravenous EPANUTIN READY MIXED PARENTERAL. Oedema, discolouration and pain distal to the site of injection (described as "purple glove syndrome") have also been reported.
	Rare	Injection site necrosis and sloughing with or without extravasation
Investigations	Rare	Immunoglobulin abnormalities

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The mean lethal dose in adults is estimated to be 2 to 5 grams. The cardinal initial symptoms are nystagmus, ataxia, dysarthria. Other signs include tremor, hyperreflexia, lethargy, slurred speech, nausea and vomiting. The patient then becomes comatose, the pupils are unresponsive, and hypotension occurs. This may be followed by respiratory depression and apnoea.

There are marked variations among individuals with respect to serum phenytoin 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.

Treatment:

There is no known antidote. Treatment is supportive and symptomatic. Ventilatory and cardiovascular support may be necessary. Peritoneal dialysis and haemodialysis reduce phenytoin plasma levels rapidly. Total exchange transfusion has been utilised in the treatment of severe intoxication in children.

IDENTIFICATION:

Clear, colourless ready mixed solution containing 50 mg phenytoin sodium per ml in a 5 ml flint glass vial.

PRESENTATION:

5 ml vial containing 250 mg (50 mg/ml) phenytoin sodium B.P.

STORAGE INSTRUCTIONS:

Store at room temperature (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.

KEEP OUT OF REACH OF CHILDREN.

REFERENCE NUMBER:

B1624 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

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