APPROVED PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

EPANUTIN® FORTE SUSPENSION

COMPOSITION:

Each 5 ml medicine measure contains:

Phenytoin 125 mg

Alcohol 0,48 % v/v

Preservative: Sodium benzoate 0,5 % m/v

EPANUTIN FORTE SUSPENSION contains the following inactive ingredients: magnesium aluminium silicate, sodium benzoate, sodium carboxymethyl cellulose, glycerine, polysorbate 40, sucrose, alcohol, vanillin, banana flavour, orange oil, citric acid and yellow colourant.

PHARMACOLOGICAL CLASSIFICATION:

A2.5 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 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.

Pharmacokinetic properties:

Phenytoin is a weak acid and has limited hydrosolubility, even in the intestine. The compound undergoes a slow and somewhat variable absorption after oral administration. After oral absorption is complete, it is rapidly distributed into all tissues.

The plasma elimination half-life of phenytoin in man averages 22 hours, with the range varying from 7 to 42 hours. Steady state therapeutic levels are achieved at least 7 to 10 days after initiation of therapy with recommended doses of 300 mg/day. For phenytoin sodium, peak serum levels occur 1½ – 3 hours after administration. 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 cerebrospinal fluid (CSF), saliva, semen, gastrointestinal fluids, bile and breast milk. The concentration of phenytoin in CSF, brain, and saliva approximates the level of free phenytoin in plasma.

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 steady state level may be disproportionately increased with resultant intoxication from an increase in dosage of 10 % or more.

Most of the drug 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.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low serum levels may be noncompliant or hypermetabolisers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin serum levels, despite standard doses,

presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. When they are necessary, they should be obtained at least 7 – 10 days after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady state will have been achieved. Trough levels, obtained just prior to the patient's next scheduled dose, provide information about clinically effective serum level range and confirm patient compliance. Peak drug levels, obtained at the time of expected peak concentration, indicate an individual's threshold for emergence of dose-related side effects.

Pharmacokinetic interactions:

Co-administration of nelfinavir tablets (1 250 mg twice a day) with phenytoin capsules (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.

INDICATIONS:

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

CONTRAINDICATIONS:

EPANUTIN is contraindicated in those patients with a history of hypersensitivity to phenytoin or other hydantoin products, and to any inactive ingredients in the product. EPANUTIN is contraindicated in porphyrics.

WARNINGS AND SPECIAL PRECAUTIONS:

General:

EPANUTIN FORTE 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 FORTE is not indicated for seizures due to hypoglycaemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

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

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

Acute alcoholic intake may increase EPANUTIN FORTE serum levels while chronic alcoholic use may decrease serum levels.

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 anti-epileptic 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 phenytoin.

Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare medicine-induced, multi-organ syndrome which is potentially fatal and occurs in some patients taking anticonvulsant medication. 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 FORTE and provide appropriate supportive measures.

Central nervous system:

Serum levels of EPANUTIN FORTE 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, determination of serum medicine levels is recommended.

Dose reduction of EPANUTIN FORTE therapy is indicated if serum levels are excessive; if symptoms persist, termination of EPANUTIN FORTE therapy is recommended.

Haematopoietic:

There have been a number of reports suggesting a relationship between EPANUTIN FORTE 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 medicines.

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

Hepatic/ immunologic:

The liver is the chief site of biotransformation of EPANUTIN FORTE. 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 FORTE. 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 FORTE hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, EPANUTIN FORTE should be immediately discontinued 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.

Skin:

EPANUTIN FORTE 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 FORTE medication is contraindicated.

Published literature has suggested that 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 FORTE. Consideration should be given to avoiding use of medicines associated with SJS/TEN, including EPANUTIN FORTE, in HLA-B*1502 positive patients when alternative therapies are available.

Literature reports suggest that the combination of EPANUTIN FORTE, 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.

Metabolic:

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

Hyperglycaemia, resulting from the medicine's inhibitory effects on insulin release, has been reported. EPANUTIN FORTE may also raise serum glucose levels in diabetic patients.

Musculoskeletal:

EPANUTIN FORTE and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D_3. This

may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcaemia and hypophosphataemia in chronically treated epileptic patients.

Vitamin D supplements may be necessary with long-term therapy.

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 does not affect their ability to engage in these activities.

INTERACTIONS:

There are many medicines which may increase or decrease serum EPANUTIN FORTE levels or which EPANUTIN FORTE may affect. Determinations of serum EPANUTIN FORTE concentrations are especially helpful when possible medicine interactions are suspected. The most commonly occurring medicine interactions are listed below.

Medicines which may increase EPANUTIN FORTE serum levels:

Various medicines may increase EPANUTIN FORTE 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 FORTE 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 FORTE plasma levels:

Table 2 summarises the medicine classes which may potentially decrease EPANUTIN FORTE 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 FORTE. Ingestion times of EPANUTIN FORTE 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, phenytoin concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration (see Pharmacokinetic properties – Pharmacokinetic interactions).

Medicines which may either increase or decrease EPANUTIN FORTE serum levels:

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

TABLE 3

MEDICINE CLASSES	MEDICINES IN EACH CLASS (SUCH AS)
Antibacterial agents	Ciprofloxacin
Anticonvulsants	Carbamazepine Phenobarbital Sodium valproate Valproic acid
Psychotropic agents	Chlordiazepoxide Diazepam

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

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

Table 4 summarises the medicine classes in which blood levels and/or effects may be altered by EPANUTIN FORTE:

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 FORTE dosage may need to be adjusted.

Medicine-enteral feeding/nutritional preparations interaction:

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

Medicine-laboratory test interactions:

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

PREGNANCY AND LACTATION:

Pregnancy:

EPANUTIN FORTE 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 FORTE during pregnancy should be informed of the risk and should be offered prenatal counselling.

An increased incidence of congenital malformations such as cleft lip/palate and heart malformations have been reported in children of women receiving EPANUTIN FORTE. 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. There is evidence of a genetic predisposition to congenital abnormalities induced by EPANUTIN FORTE.

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

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered EPANUTIN FORTE absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or EPANUTIN FORTE. 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.

Lactation:

Infant breastfeeding is not recommended for women taking EPANUTIN FORTE because EPANUTIN FORTE appears to be secreted in low concentrations in human milk. EPANUTIN FORTE

concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

DOSAGE AND DIRECTIONS FOR USE:

NOT FOR PARENTERAL USE

EPANUTIN capsules and solution for injection are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in EPANUTIN FORTE SUSPENSION (125 mg/5 ml) and in EPANUTIN tablets. Because there is approximately an 8 % increase in drug 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.

Dosage should be individualised to provide maximum benefit. In some cases serum medicine level determinations may be necessary for optimal dosage adjustments. Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 – 20 mcg/ml, although some mild cases of tonic-clonic (*grand mal*) epilepsy may be controlled with lower serum levels of EPANUTIN FORTE. With recommended dosage, a period of seven to ten days may be required to achieve steady state serum levels with EPANUTIN FORTE, and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten 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 level is reached.

Adult 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.

Non-emergency loading dose in adult patients:

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

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

Paediatric dosage:

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 old may require the minimal adult dosage (300 mg/day).

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 plasma levels, biologic 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. A major problem in motivating noncompliant patients may be lessened also when the patient can take all of the medication once a day. However, patients should be cautioned not to miss a dose.

Shake the suspension well before use.

SIDE EFFECTS:

The adverse event terms were 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; leucopenia; lymphadenopathy including benign lymph node

		hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease; macrocytosis and 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	Transient 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
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
Investigations	Rare	Immunoglobulin abnormalities

Post-marketing experience:

Musculoskeletal system: Bone fractures and osteomalacia have been associated with long-term (> 10 years) use of EPANUTIN FORTE by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcaemia, hypophosphataemia and decreased levels of Vitamin D metabolites have also been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The lethal dose in paediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, 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 serum levels where toxicity may occur. Nystagmus on lateral gaze usually appears at 20 mcg/ml and ataxia at 30 mcg/ml. Dysarthria and lethargy appear when the serum concentration is > 40 mcg/ml, but a concentration as high as 50 mcg/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 mcg/ml with complete recovery.

Treatment:

Treatment is non-specific 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 FORTE 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.

IDENTIFICATION:

A pleasant orange/vanilla/banana flavoured, opaque orange coloured suspension.

PRESENTATION:

Bottles of 237 ml.

STORAGE INSTRUCTIONS:

Store in a cool (below 25 ºC), dry place.

KEEP OUT OF REACH OF CHILDREN.

REFERENCE NUMBER:

B555 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

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