APPROVED PATIENT INFORMATION LEAFLET

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

Phlexy 250 mg/5 ml (Injection)

COMPOSITION:

Each 5 ml vial contains:

Phenytoin sodium B.P.....250 mg

Contains Ethanol (96 %).....% v/v

The other ingredients are: propylene glycol and sodium hydroxide in water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION:

Phenytoin is an anticonvulsant. The primary site of action appears to be 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 seizures foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centres responsible for tonic phase of grand mal seizures.

Pharmacokinetics:

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 of phenytoin. Because this elimination route is readily saturable, small increases in dosage may produce substantial increase in plasma phenytoin concentration (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:

Phlexy 250 mg/5 ml is indicated for:

Prevention and treatment of seizures occurring during and after neurosurgery.

The control of status epilepticus of the grand mal type.

CONTRA-INDICATIONS:

Phlexy 250 mg/5 ml is contra-indicated in:

- those patients with a history of hypersensitivity to phenytoin or other hydantoin products, or to any of the other ingredients of **Phlexy 250 mg/5 ml**.
- porphyrics.

Because of its effects on ventricular automaticity, **Phlexy 250 mg/5 ml** is contra-indicated in:

- sinus bradycardia
- sino-atrial block
- second and third degree A-V bloc

- patients with Adams-Stokes syndrome

Fatalities due to:

- cardiac arrest
- ventricular fibrillation
- tonic seizures

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 **Phlexy 250 mg/5 ml** intravenously.

Concomitant use of lidocaine with **Phlexy 250 mg/5 ml.**

WARNINGS AND SPECIAL PRECAUTIONS:

Intravenous administration should not exceed 50 mg/minute in adults. **Phlexy 250 mg/5 ml** 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 **Phlexy 250 mg/5 ml** in the therapeutic range cannot be readily achieved by the intramuscular route.

The addition of **Phlexy 250 mg/5 ml** to intravenous infusion is not recommended due to lack of solubility and resultant precipitation. **Phlexy 250 mg/5 ml** 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 **Phlexy 250 mg/5 ml** should be followed by an injection of sterile saline through the same needle or intravenous catheter to reduce local venous irritation due to the alkalinity of the solution.

Continuous infusion should be avoided.

Hypotension usually occurs when **Phlexy 250 mg/5 ml** is administered rapidly by the intravenous route.

Phlexy 250 mg/5 ml should be used with caution in patients with hypotension and severe myocardial insufficiency.

Phlexy 250 mg/5 ml 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 phenytoin 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 **Phlexy 250 mg/5 ml** serum levels while chronic alcoholic use may decrease serum levels.

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.

Central Nervous System effect – Serum levels of **Phlexy 250 mg/5 ml** sustained above the optimal range may produce confusional states referred to as “delirium”, “psychosis” or “encephalopathy”, or irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, serum level determinations are recommended. Dose reduction is indicated if serum levels of **Phlexy 250 mg/5 ml** are excessive; if symptoms persist, termination of **Phlexy 250 mg/5 ml** therapy is recommended.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents such as **Phlexy 250 mg/5 ml.** Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Haemopoeitic effect – There have been a number of reports suggesting a relationship between **Phlexy 250 mg/5 ml** and the development of lymphadenopathy (local or generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkins 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 **Phlexy 250 mg/5 ml** therapy, a decrease in seizure control may occur.

Hepatic / Immunologic – The liver is the chief site of biotransformation of **Phlexy 250 mg/5 ml**. 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 **Phlexy 250 mg/5 ml**. 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, leukocytosis and eosinophilia. The clinical course of acute **Phlexy 250 mg/5 ml** hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, **Phlexy 250 mg/5 ml** 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.

Injection site effect – Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of IV **Phlexy 250 mg/5 ml**. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing, and in rare instances has led to amputation. Improper administration including subcutaneous or perivascular injection should be avoided.

Integumentary effect - **Phlexy 250 mg/5 ml** should be discontinued if skin rash appears. If the rash is exfoliative, purpuric, or bullous or of lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of **Phlexy 250 mg/5 ml** 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 **Phlexy 250 mg/5 ml** therapy is contraindicated. Literature reports suggest that the combination of **Phlexy 250 mg/5 ml**, 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 effect – Hyperglycaemia, resulting from **Phlexy 250 mg/5 ml's** inhibitory effects on insulin

release, has been reported. Phenytoin also may raise serum glucose levels in diabetics.

Information relating to the excipients

Phlexy 250 mg/5 ml contains ethanol (alcohol). This may be harmful for those suffering from alcoholism. This should also be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease.

Effects on ability to drive and use machines

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as treatment with **Phlexy 250 mg/5 ml** may cause central nervous system side effects such as dizziness and drowsiness (see SIDE EFFECTS).

INTERACTIONS:

Medicines which may increase Phlexy 250 mg/5 ml serum levels – Medicines which may increase **Phlexy 250 mg/5 ml** serum levels either by decreasing its rate of metabolism by the hepatic CYP450 2C9 and 2C19 enzymatic systems (e.g. warfarin, disulfiram, omeprazole, toclopidine), 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 Phlexy 250 mg/5 ml 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	Amphoterecin B Fluconazole Ketoconazole Miconazole Itraconazole
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 Phlexy 250 mg/5 ml plasma levels.

Table 2 summarises the medicine classes which may potentially decrease Phlexy 250 mg/5 ml plasma levels.

Table 2

Medicine Classes	Medicines in Each Class (Such as)
Alcohol (chronic intake)	
Antibacterial agents	Rifampicin Ciprofloxacin
Anticonvulsants	Vigabatrin
Antiulcer agents	Sucralfate
Bronchodilators	Theophylline
Cardiovascular agents	Reserpine
Hyperglycaemic agents	Diazoxide

Medicines which may either increase or decrease Phlexy 250 mg/5 ml serum levels.

Table 3 summarises the medicine classes which may either increase or decrease Phlexy 250 mg/5 ml serum levels.

Table 3

Medicine Classes	Medicines in Each Class (Such as)
Anticonvulsants	Carbamazepine Phenobarbital Sodium valproate Valproic acid
Antineoplastic agents	
Psychotropic agents	Chlordiazepoxide Diazepam

Medicines which blood levels and/or effects may be altered by Phlexy 250 mg/5 ml.

Table 4 summarise the medicine classes which blood levels and/or effects may be altered by Phlexy 250 mg/5 ml.

Table 4

Medicine Classes	Medicines in Each Class (Such as)
Antibacterial agents	Doxycycline Praziquantel Rifampicin Tetracycline
Anticonvulsants	Lamotrigine
Antifungal agents	Azoles
Antineoplastic agents	Teniposide
Bronchodilators	Theophylline
Calcium channel blockers / Cardiovascular agents	Digoxin Nicardipine Nimodipine Quinidine Verapamil
Corticosteroids	
Coumarin anticoagulants	Warfarin
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 interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and **Phlexy 250 mg/5 ml** dosage may need to be adjusted.

Laboratory Test Interactions - **Phlexy 250 mg/5 ml** may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metapyrone tests. **Phlexy 250 mg/5 ml** may cause raised serum levels of glucose, alkaline phosphatase and gamma glutamyl transpeptidase (GGT). **Phlexy 250 mg/5 ml** may affect blood calcium and blood sugar metabolism tests.

PREGNANCY AND LACTATION:

Pregnancy:

Phenytoin sodium, as in **Phlexy 250 mg/5 ml**, has been associated with teratogenicity when given to women in the first trimester of pregnancy. Its use should be avoided in pregnant women and women likely to become pregnant unless its continued use is considered essential by the doctor. Women who have been exposed to **Phlexy 250 mg/5 ml** in the first trimester of pregnancy should be informed of the risk and should be offered prenatal counselling.

During pregnancy, safe use of **Phlexy 250 mg/5 ml** has not been established. Higher incidence of

congenital abnormalities were reported in children whose mothers received anticonvulsant medication such **as Phlexy 250 mg/5 ml** 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 phenytoin, as in **Phlexy 250 mg/5 ml**.

There have been reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin 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 **Phlexy 250 mg/5 ml** prior to delivery may lead to an increased risk of life threatening haemorrhage in the neonate, usually within 24 hours of birth. **Phlexy 250 mg/5 ml** may also produce a deficiency of vitamin K in the mother causing increased maternal bleeding during delivery.

Because of increased protein binding, and/or increased metabolic clearance of phenytoin during pregnancy, pregnant women receiving **Phlexy 250 mg/5 ml** may experience an increased incidence of seizures. Serum phenytoin 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:

Since phenytoin is excreted in breast milk, thus allowing the infant to ingest significant amounts, **Phlexy 250 mg/5 ml** is not recommended during lactation.

DOSAGE AND DIRECTIONS FOR USE:

Phlexy 250 mg/5 ml does not contain a preservative. Use immediately after opening and discard any remaining solution after administering the correct dosage as specified below. For single use only.

Use in Status Epilepticus

Adults: An initial loading dose of 10 to 15 mg/kg body mass. This initial dose (usually administered intravenously over 20 minutes) should be followed by the appropriate maintenance doses. For most adults, the satisfactory maintenance dose will be 300 – 400 mg daily with 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 dose 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 Neurosurgery

For initiating prophylaxis and for treatment of seizures, an intravenous loading dose followed by maintenance doses (oral if possible) should be administered; see “Use in Status Epilepticus”.

Addition of **Phlexy 250 mg/5 ml** ready mixed parenteral solution to intravenous infusions is not recommended due to lack of solubility and resultant precipitation. **Phlexy 250 mg/5 ml** should be inspected visually for particulate matter & 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 levels 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/minute in adults, and should not exceed 1 to 3 mg/kg/minute in neonates. At this rate toxicity should be minimized.

Incompatibilities:

- **Phlexy 250 mg/5 ml** has a pH in the range of 10 – 12.3. It will only stay in solution when the pH is considerably alkaline (about 10 – 12).
- **Phlexy 250 mg/5 ml** 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. Only a clear solution should be used.

- **Phlexy 250 mg/5 ml** should not be mixed with other medicines because of precipitation of phenytoin acid.

SIDE EFFECTS:

The most notable signs of toxicity associated with the intravenous use of **Phlexy 250 mg/5 ml** are cardiovascular collapse and/or central nervous system depression. Hypotension is likely when **Phlexy 250 mg/5 ml** 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.

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.

Blood and the lymphatic system disorders

Less frequent: Hodgkin disease, lymphoma. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g. fever, rash and liver involvement. Leukopenia, thrombocytopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, macrocytosis, megaloblastic anaemia.

Immune system disorders

Less frequent: Anaphylactoid reaction, anaphylaxis, hypersensitivity syndrome, periarteritis nodosa.

Psychiatric disorders

Frequent: Nervousness.

Less frequent: Insomnia, mental confusion.

Nervous system disorders

Frequent: Drowsiness, vertigo, headaches, ataxia, decreased coordination, dizziness, nystagmus, paraesthesia, somnolence.

Less frequent: Tonic seizures, slurred speech dyskinesias including chorea, dystonia, tremor and asterixis, sensory peripheral neuropathy, taste perversion.

Vascular disorders

Frequent: Hypotension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Alterations in respiratory function including respiratory arrest, pneumonitis.

Gastrointestinal disorders

Frequent: Nausea, vomiting.

Less frequent: Constipation, gingival hyperplasia.

Hepato-biliary disorders

Less frequent: Liver damage, toxic hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: 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 rash, lupus erythematosus, Stevens-Johnson syndrome, toxic epidermal necrolysis, enlargement of lips, hypertrichosis.

Musculoskeletal, connective tissue and bone disorders

Frequent: Motor twitching.

Less frequent: Dupuytren's contracture, coarsening of facial features, systemic lupus erythematosus.

Reproductive system and breast disorders

Less frequent: Peyronie's disease.

General disorders and administrative site conditions

Frequent: Polyarthropathy, interstitial nephritis, phlebitis.

Less frequent: Injection site necrosis and sloughing with or without extravasation.

Investigations

Less frequent: Immunoglobulin abnormalities.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The cardinal initial symptoms are nystagmus, ataxia and dysarthria. Other signs include tremor, hypereflexia, 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. Mean lethal dose in adults is estimated to be 2 to 5 g. 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.

Treatment:

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

IDENTIFICATION:

Phlexy 250 mg/5 ml: Clear colourless solution free from any particulate matter.

PRESENTATION:

Phlexy 250 mg/5 ml is available in a 5 ml Ph. Eur. type I clear transparent flint glass vial with a dark grey bromobutyl rubber stopper and a dark blue aluminium flip off seal. Vials are supplied in cartons of 5,10 or 20.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC. Keep the vials in the carton until required for use. Protect from light. The injection cannot be added to other medicines due to the possible precipitation of phenytoin acid. If only a part of the vial is used, discard the remaining solution.

Keep out of reach of children.

REGISTRATION NUMBER:

45/2.5/0493

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