

1 NAME OF THE MEDICINAL PRODUCT

Phenytoin Injection B.P. 250mg/5ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains Phenytoin Sodium B.P. 250mg.

3 PHARMACEUTICAL FORM

Clear, colourless, particle free solution intended for parenteral administration to human beings.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Phenytoin Injection B.P. is indicated for the control of status epilepticus of the tonic clonic (grand mal) type and prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

4.2 Posology and method of administration

Method of administration: Intravenous. Intramuscular.

Solutions for parenteral administration should be inspected visually for particulate matter and discoloration prior to use.

Only a clear solution should be used and the product should be discarded if a precipitate or haziness develops in the solution. On refrigeration or freezing, a precipitate might form, but this will dissolve when 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 discoloration may develop, but this does not affect the potency of the solution.

There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug. Optimum control without clinical signs of toxicity can most often be achieved with serum levels in the range 10 - 20mg/l (40 - 80 micromoles/l).

Phenytoin Injection B.P. should be injected slowly directly into a large vein through a large-gauge needle or intravenous catheter. Because of the alkalinity of the solution, each injection or infusion of phenytoin should be preceded and followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation.

For administration by intravenous infusion phenytoin injection should be diluted in 50 - 100 ml of normal saline, and the final concentration of phenytoin in the solution should not exceed 10 mg/ml. Administration should commence immediately after the mixture

has been prepared and must be completed within one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22 - 0.50 microns) should be used. The diluted form is suitable for use as long as it remains free of haziness and precipitate.

Continuous monitoring of the electrocardiogram and blood pressure is essential and the patient should be observed for signs of respiratory depression. Cardiac resuscitative equipment should be available. If administration of intravenous phenytoin does not terminate seizures, the use of other measures, including general anaesthesia should be considered.

Adults :

Status epilepticus : In a patient having continuous seizure activity, as compared to the more common rapidly recurring seizures, i.e. serial epilepsy, intravenous diazepam or a short-acting barbiturate is recommended prior to administration of phenytoin because of the more rapid onset of action of the former.

Following the use of diazepam in patients having continuous seizures and in the initial management of serial epilepsy a loading dose of phenytoin 10 - 15mg/kg should be injected slowly intravenously, at a rate not exceeding 50mg per minute (this will require approximately 20 minutes in a 70kg patient). The loading dose should be followed by maintenance doses of 100mg orally or intravenously every 6 to 8 hours.

Studies in neonates have shown that absorption of phenytoin is unreliable after oral administration, but a loading dose of 15 - 20mg/kg of phenytoin intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10 - 20mg/l). The drug should be injected slowly intravenously at a rate of 1 - 3mg/kg/min.

Determination of phenytoin serum levels is advised during use in the management of status epilepticus and subsequently whilst establishing maintenance dosage. The clinically effective range is usually 10- 20mg/l although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin.

Intramuscular administration should not be used in the treatment of status epilepticus because peak plasma levels may not be reached for up to 24 hours.

Other clinical conditions: It is not possible to provide a universally applicable dosage schedule. The intravenous route of administration is preferred. Dosage and dosing interval will be determined by the needs of the individual patient and factors such as previous anti-epileptic therapy, seizure control, age and general medical condition must be considered. Although absorption of phenytoin is slow following i.m. injection, such use may be appropriate in certain conditions.

When short term intramuscular administration is necessary for a patient previously stabilised orally, compensating dosage adjustments are essential to maintain therapeutic serum levels. An intramuscular dose 50% greater than the oral dose is required to maintain these levels. When returned to oral administration, the dose of phenytoin should be reduced by 50% of the original oral dose for the same period of time the patient received phenytoin intramuscularly, to prevent excessive serum levels due to continued release from intramuscular injection sites.

Neurosurgery: In a patient who has not previously received the drug, Phenytoin Injection B.P. 100 - 200mg (2 - 4ml) may be given intramuscularly at approximately 4-hour intervals prophylactically during neurosurgery and continued during the postoperative period for 48 - 72 hours. The dosage should then be reduced to a maintenance dose of 300mg and adjusted according to serum level estimations.

If possible, intramuscular injections of phenytoin should not be continued for more than one week; after this, alternative routes such as naso-gastric intubation should be considered. For time periods less than one week, the patient switched from intramuscular administration should receive one half the original oral dose for the same period of time the patient received phenytoin intramuscularly. Serum levels are valuable as a guide to an appropriate adjustment of dosage.

Elderly: Elderly (over 65 years): As for adults. It should be noted that complications may occur more readily in elderly patients.

Neonates: Studies in neonates have shown that absorption of phenytoin is unreliable after oral administration, but a loading dose of 15 - 20mg/kg of phenytoin intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10 - 20mg/l). The drug should be injected slowly intravenously at a rate of 1 - 3mg/kg/min.

Infants and children: As for adults. Children tend to metabolise phenytoin more rapidly than adults and this should be borne in mind when determining dosage regimens. Monitoring of phenytoin serum levels is especially helpful.

4.3 Contraindications

Phenytoin is contra-indicated in patients who are hypersensitive to phenytoin or other hydantoin. It is also contra-indicated in sinus bradycardia, sino-atrial block, and second and third degree A-V block, and patients with Adams Stokes syndrome. Intra-arterial injection must be avoided because of the high pH of the solution.

4.4 Special warnings and precautions for use

In adults, intravenous administration should not exceed a rate of 50mg per minute. In neonates, phenytoin should be administered at a rate of 1 - 3mg/kg/min.

The most significant signs of toxicity with the intravenous use of phenytoin are cardiovascular collapse and/or central nervous system depression. Severe cardiotoxic reactions and fatalities due to depression of atrial and ventricular conduction and ventricular fibrillation, respiratory arrest and tonic seizures have been reported, particularly in elderly or gravely ill patients, if the preparation is given too rapidly or in excess. Hypotension usually occurs with rapid administration of phenytoin by the intravenous route.

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

Therefore 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.

Irritation and inflammation of soft tissue has occurred at the injection site with and without extravasation of phenytoin. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing and in rare instances has led to amputation.

Subcutaneous or perivascular injection should be avoided because of the highly alkaline nature of the solution.

The intramuscular route is not recommended for the treatment of status epilepticus because of slow absorption and the resultant delay in achieving serum levels of phenytoin in the therapeutic range.

Intravenous phenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency.

Phenytoin 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 this drug 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 reinstatement of therapy, further phenytoin medication is contraindicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present together, combined drug therapy is needed.

Serum levels of phenytoin 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 drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with phenytoin is recommended.

Because phenytoin is highly protein bound and extensively metabolised by the liver, reduced maintenance dosage may be required in patients with impaired liver function to prevent accumulation and toxicity. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, as the pharmacologically active free drug concentration is unlikely to be altered, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range 10 - 20mg/l. Dosage should not exceed the minimum needed to control convulsions.

Biotransformation of phenytoin occurs mainly in the liver. Patients with impaired hepatic function, the elderly, or those who are gravely ill may show early signs of toxicity. Phenytoin may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported. Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes. Caution is advised when treating patients with diabetes.

There are isolated reports associating phenytoin with exacerbation of porphyria, therefore, caution should be exercised when using phenytoin in patients with porphyria. Herbal preparations containing St John's Wort (*Hypericum perforatum*) should not be used while taking phenytoin due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin (see section 4.5)

Laboratory tests: It may be necessary to measure serum phenytoin levels to achieve optimal dosage adjustments.

This product contains a number of excipients known to have a recognized action or effect. These are:

Propylene glycol (may cause alcohol-like symptoms)

Sodium: This medicinal product contains less than 1mmol sodium (23mg) per dose i.e. essentially 'sodium-free'

Ethanol (395.75 mg/5 ml):- This may be harmful for those suffering from alcoholism and should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy

4.5 Interaction with other medicinal products and other forms of interaction

1) Drugs which may increase phenytoin serum levels include: amiodarone, antifungal agents (including amphotericin B, fluconazole, ketoconazole, miconazole and itraconazole), azapropazone, chloramphenicol, chlordiazepoxide, diazepam, dicoumarol, disulfiram, ethosuximide, fluoxetine, H₂-antagonists, halothane, isoniazid, methylphenidate, oestrogens, omeprazole, phenothiazines, phenylbutazone, salicylates, succinimides, sulphonamides, trazodone, viloxazine, diltiazem, tolbutamide and nifedipine.

2) Drugs which may decrease phenytoin serum levels include: folic acid, reserpine, rifampicin, sucralfate, theophylline and vigabatrin. Serum levels of phenytoin can be reduced by concomitant use of the herbal remedy St. John's Wort (*Hypericum perforatum*), and this effect may persist for at least two weeks after cessation of treatment with St. John's Wort.

3) Drugs which may either increase or decrease phenytoin serum levels include: certain antacids, antineoplastic agents, carbamazepine, ciprofloxacin, phenobarbital, sodium valproate, valproic acid and zidovudine. The effect of phenytoin on phenobarbital, carbamazepine, sodium valproate and valproic acid serum levels is also unpredictable. Acute alcoholic intake may increase phenytoin serum levels whereas chronic alcoholic use may decrease serum levels.

4) Tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted. Phenytoin increases the clearance of quetiapine and thus impairing the effect of it. Neurotoxicity has been reported during concomitant use of phenytoin and lithium.

5) Drugs whose effect is impaired by phenytoin include: antifungal agents, antineoplastic agents, amprenavir, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, disopyramide, doxycycline, felodipine, furosemide, haloperidol, levodopa, methadone, methoxsalen, mexiletine, neuromuscular blockers, oestrogens, oral contraceptives, quinidine, rifampicin, theophylline, thyroxine, vitamin D, calcium channel blockers, lamotrigine and paroxetine.

6) Drugs whose effect may be enhanced by phenytoin include warfarin. The interaction between phenytoin and warfarin may lead to increased INR. The effect of phenytoin on warfarin is variable and prothrombin times should be determined when these agents are combined.

Serum level determinations are especially helpful when possible drug interactions are suspected.

Drug/laboratory test interactions

Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result of enhanced peripheral metabolism. These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hypothyroidism. Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. Phenytoin may affect blood sugar metabolism tests.

It is recommended that serum folate concentrations be measured at least every 6 months, and folic acid supplements given if necessary.

4.6 Pregnancy and lactation

The following information should be taken into account when considering the intravenous use of phenytoin in the management of status epilepticus in pregnancy. It is essential to control the condition as quickly as possible in order to reduce the potential adverse effects, specifically hypoxia, of status epilepticus upon the foetus.

There are difficulties in obtaining meaningful data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in the development of birth defects. Most mothers on anticonvulsant therapy deliver normal infants. In patients receiving an anticonvulsant drug to prevent major seizures, it is important that the drug should not be discontinued because of the strong possibility of precipitating status epilepticus and attendant hypoxia and threat to life if the drug was withdrawn. In individual cases, where the frequency and severity of the seizure disorder are such that cessation of therapy does not pose a serious risk to the patient, discontinuation of the drug may be considered prior to and during pregnancy. However, it cannot be stated with certainty that even minor seizures do not pose some hazard to the developing embryo or foetus.

There is some evidence that phenytoin may produce congenital abnormalities in the offspring of a small number of patients with epilepsy. Therefore, phenytoin should not be used as a first-line drug during pregnancy, especially in early pregnancy, unless the physician considers that the potential benefits outweigh the risk.

More recent to the reports of an increased incidence of congenital malformations such as cleft lip/palate and cardiac malformations in children of women who received phenytoin and other antiepileptic agents, there have been reports of foetal hydantoin syndrome. The syndrome consists of prenatal growth deficiency, microencephaly and mental deficiency in the children of women who received phenytoin, alcohol, barbiturates or trimethadione. However, all of these features are interrelated and are frequently associated with intrauterine growth retardation due to other causes.

There are isolated reports of malignancies, including neuroblastoma, in the children of women who received phenytoin during pregnancy.

Because of altered phenytoin absorption or metabolism during pregnancy, a proportion of patients experience an increase in seizure frequency; periodic estimations of serum phenytoin levels serve as a valuable guide to appropriate dosage adjustment in the management of epilepsy during pregnancy. However, restoration of the original dosage will probably be indicated postpartum.

There have been reports of neonatal coagulation defects occurring within the first 24 hours in babies born to women receiving phenytoin. Vitamin K can be used to prevent or correct this defect and may be administered to the mother prior to delivery and to the neonate after birth. Phenytoin is excreted in small quantities in breast milk and breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

Patients are acutely ill and hospitalised.

4.8 Undesirable effects

Signs of toxicity are associated with cardiovascular and central nervous system depression.

Cardiovascular: Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are seen most commonly in elderly or seriously ill patients.

Respiratory: Alterations in respiratory function including respiratory arrest may occur.

Central nervous system: The most common reactions associated with phenytoin therapy involve the C.N.S. and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased co-ordination, mental confusion, paraesthesia, drowsiness and vertigo. Dizziness, insomnia, transient nervousness, motor twitching, and headache have also been observed. There have also been rare reports of phenytoin-induced dyskinesia, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy. Tonic seizures have also been reported.

Injection site: Local reactions reported include irritation, inflammation and tenderness. Necrosis and sloughing have been reported after subcutaneous or perivascular injection and subcutaneous or perivascular injection should, therefore, be avoided. Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of intravenous phenytoin.

Dermatological system: 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.

Haemopoietic system: Haemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression and aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. There have been a number of reports suggesting a relationship between phenytoin 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.

All cases of lymphadenopathy require follow-up for an extended period and every effort should be made to achieve seizure control using alternative anticonvulsant agents.

Gastrointestinal system: Nausea, vomiting, constipation, toxic hepatitis, and liver damage have been reported.

Connective tissue system: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's disease and Dupuytren's contracture may occur rarely.

Immune system: Hypersensitivity syndrome has been reported and may in rare cases be fatal (the syndrome may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities may occur. 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.

Other: Polyarthropathy, interstitial nephritis, pneumonitis.

4.9 Overdose

The mean lethal dose in adults is estimated to be 2 to 5 grams. The lethal dose in children is not known. The initial signs are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperflexia, lethargy, nausea, vomiting. Overdosage may lead to hypotension, coma and respiratory depression. Death is due to respiratory and circulatory depression. Attempts to relate serum levels of the drug to

toxic effects have shown wide interpatient variation.

Nystagmus on lateral gaze usually appears at 20mg/l and ataxia at 30mg/l.

Dysarthria and lethargy appear when the serum concentration is above 40mg/l, although a serum concentration as high as 50mg/l has been reported without evidence of toxicity.

As much as 25 times the therapeutic dose, which resulted in a serum concentration of 100mg/l was taken with complete recovery.

Treatment : There is no known antidote and treatment is symptomatic and supportive.

Particular attention should be paid to circulatory and respiratory function and appropriate supportive measures employed. Haemodialysis can be considered, since phenytoin is not completely bound to plasma proteins.

Total exchange transfusion has been used in the treatment of severe intoxication in children. In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Phenytoin is an anticonvulsant which appears to stabilise rather than elevate the seizure threshold and to limit the spread of seizure activity rather than abolish the primary focus of seizure discharge. Phenytoin exerts a stabilising effect on excitable membranes of a variety of cells, including neurons and cardiac myocytes.

5.2 Pharmacokinetic properties

A small percentage of recipients appear to metabolise phenytoin more slowly than normal and this appears to be genetically determined.

Absorption of phenytoin is slow from the gastro-intestinal tract and is even slower from the intramuscular site. Phenytoin is widely distributed throughout the body and is extensively (about 90%) bound to plasma proteins. It has a very variable dose dependent half-life but the mean appears to be about 22 hours at steady-state.

Phenytoin is extensively metabolised in the liver to inactive metabolites. It undergoes enterohepatic recycling and is excreted in the urine, mainly as metabolites. Phenytoin crosses the placenta and small amounts are excreted in breast milk.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol B.P.

Ethanol B.P.

Sodium Hydroxide B.P.
Water for Injections B.P.

6.2 Incompatibilities

Phenytoin 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). The mixing of phenytoin sodium injection with other drugs is not recommended.

6.3 Shelf life

3 years.
If only part used, discard the remaining solution.

6.4 Special precautions for storage

Do not store above 30°C.
Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

5ml, clear glass ampoules, glass type I, Ph. Eur. packed in cardboard cartons to contain 10 x 5ml ampoules.

6.6 Special precautions for disposal

For I.V. and I.M. administration.
Use as directed by the physician.
Solutions in which a haziness or precipitate develops should not be used.
Do not mix with other drugs because of precipitation of phenytoin acid.

7 MARKETING AUTHORISATION HOLDER

Antigen International Ltd.,
Roscrea,
Co. Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 02848/0164

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 29/11/91.

10 DATE OF REVISION OF THE TEXT

13 August 2010