

Public Assessment Report

PHENYTOIN 250MG/5ML SOLUTION FOR INJECTION

(PHENYTOIN SODIUM)

PL 18157/0010

PHENYTOIN 250MG/5ML SOLUTION FOR INJECTION

(Phenytoin Sodium)

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UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Beacon Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Phenytoin 250mg/5ml Solution for Injection (PL 18157/0010).

Phenytoin sodium is an imidazolin derivative. It is used primarily as a medicine to control (prevent) seizures (convulsions) or stop an ongoing series of seizures in the treatment of epilepsy. This is a prescription only medicine [POM].

The data presented to the MHRA, before licensing, demonstrated that Phenytoin 250mg/5ml Solution for Injection is interchangeable with the reference product, Epanutin Ready Mixed Injection. Epanutin has been marketed in the UK by Warner Lambert Limited (PL 00019/0135) since 1986.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Phenytoin 250mg/5ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.

PHENYTOIN 250MG/5ML SOLUTION FOR INJECTION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Phenytoin 250mg/5ml Solution for Injection (PL 18157/0010) to Beacon Pharmaceuticals Limited on 21st August 2006. This product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC as amended. The application is cross referred to Epanutin Ready Mixed Injection, marketed in the UK by Warner Lambert Limited (PL 00019/0135) since 1986.

The product contains the active Phenytoin sodium. Phenytoin Solution for Injection is indicated for:

The control of status epilepticus of the tonic-clonic (grand mal type) and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Phenytoin is also used in the treatment of cardiac arrhythmias where first line therapy is not effective. It is of particular value when these are digitalis induced.

Phenytoin appears to stabilise rather than raise the seizure threshold and prevents spread of seizure activity rather than abolish the primary focus of seizure discharge.

The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated, however, possible contributory effects include:

1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation.
2. Post-synaptic action to enhance GABA-mediated inhibition and reduce excitatory synaptic transmission.
3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 18157/0010
PROPRIETARY NAME: Phenytoin Sodium 250mg/5ml for Injection
ACTIVE(S): Phenytoin Sodium
COMPANY NAME: Beacon Pharmaceuticals Limited
E.C. ARTICLE: Article 10.1 [formerly Article 10.1(a)(iii) of Directive 2001/83/EC]
LEGAL STATUS: POM

1. INTRODUCTION

1.1 Legal Basis

This national, abridged, standard Marketing Authorisation Application is for parenteral presentation (solutions for injection) of phenytoin sodium and is submitted under Article 10.1 [formerly Article 10.1(a)(iii) of Directive 2001/83/EC]. The application is cross referred to Epanutin Ready Mixed Injection, marketed in the UK by Warner Lambert Limited (PL 00019/0135) since 1986.

1.2 Use

Phenytoin sodium is an imidazolin derivative. It is used primarily as an anticonvulsant for the treatment of epilepsy.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Phenytoin Sodium 250mg/5ml for Injection. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains Phenytoin Sodium equivalent to 250mg per 5ml of solution. The product is packaged in type I clear glass 5 ml ampoules that conforms to Ph Eur specification. The glass ampoule is packaged into cardboard carton. Packs contain 1 ampoule or 50 ampoules (clinical pack). The proposed shelf-life (24 months) and storage conditions (Do not store above 25°C. Store in the original package) are consistent with the details registered for the cross-reference products.

2.3 Legal status

These products will be subject to a medical prescription.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Beacon Pharmaceuticals Limited, 85 High Street, Tunbridge Wells, Kent, TN1 1YG, United Kingdom.

The Qualified Person responsible for pharmacovigilance is stated and their CV is included.

2.5 TSE

The applicant has provided a declaration that no material of animal origin used in manufacture of the finished product.

DRUG SUBSTANCE

One drug substance supplier is approved. The drug substance from this source is the subject of a Drug Master File (DMF). Full assessment of the DMF has been performed. Active from this source is currently in use in two other licensed phenytoin sodium injections in the UK

A copy of the current DMF edition of the applicant's part has been provided in the CTD format. An appropriate letter of access is provided.

A satisfactory drug substance specification is included within the DMF.

The finished product manufacturer has also provided a drug substance specification. A certificate of Analysis (CoA) for batches of the drug substance tested upon receipt has been provided.

Analytical Procedures

Analytical procedures are described.

Validation of Analytical Procedures

Satisfactory validation data are provided for the analytical procedures.

Batch Analysis

Results of industrial scale batches of phenytoin sodium are within specification.

Stability

Batches stored under ICH real time conditions show compliance with set limits during the approved retest period.

DOSAGE FORM

Composition

The composition is satisfactory and tabulated below.

Name of constituents	Function	Reference to Standards
Active constituent		
Phenytoin Sodium	Active	Ph. Eur
Other constituents		
Propylene glycol	Solvent	Ph. Eur
Ethanol (96%)	Solvent	Ph. Eur
Sodium Hydroxide	Solvent	Ph. Eur
Water For Injection	Solvent	Ph. Eur

PHARMACEUTICAL DEVELOPMENT

Drug Substance

Phenytoin Sodium is soluble in water and in alcohol.

Excipients

The excipients; water for injection, propylene glycol, ethanol 96%, and sodium hydroxide are stated to conform to Ph Eur monographs. Satisfactory in-house Certificates of Analysis are provided for typical batches of excipients issued by the Drug Product Manufacturer testing the excipients to their relevant pharmacopoeia monographs. Nitrogen gas is Ph Eur grade and is sterile filtered prior to use. Satisfactory supplier's specification and C of A are provided for excipients.

Container Closure System

The product is packaged in type I clear glass 5 ml ampoules that conforms to Ph Eur specification. The glass ampoule is packaged into cardboard carton. Packs contain 1 ampoule or 50 ampoules (clinical pack).

Compatibility

Stated 'not relevant' but can be inferred from the product stability data, and accepted.

MANUFACTURE

GMP Statement and Manufacturing Chain

The site of manufacture, batch release and assembly is Laboratorio Reig Jofre S.A. Sant Joan Despi, Barcelona, Spain. A satisfactory copy of the manufacturers licence is issued by the Medicamento Agency in Spain has been provided.

Description of the Manufacturing Process

A satisfactory formula and description of manufacture are provided.
There are no re-processing data provided.

Critical phases of the manufacturing process have been satisfactorily identified and appropriate in-process controls are in place.

The analytical methods and limits are the same as those used in finished product testing and comply with current guidelines and accepted. The product is packaged with satisfactory in-process controls.

In-process batch data for validation batches are satisfactory. The validation results demonstrate homogeneity of blends and consistent manufacture.

The validation protocol provided is considered adequate for the purpose.

Control of Excipients

The list of excipients, complying with Ph. Eur. requirements, is given under “Composition of the medicinal product” above.

Satisfactory Certificates of Analysis have been provided for each excipient and are accepted. The compendial methodology is used in testing.

Specifications

A satisfactory finished product specification is provided.

Analytical Procedures

Satisfactory validation data are provided.

Batch data

Satisfactory data are provided for batches manufactured at the proposed site and are considered representative of the product to be marketed.

Characterisation of Impurities

This is satisfactory.

Container Closure System

Satisfactory details of supplier specification, product construction, standards and compliance statements are provided. In-house specification giving details of tests performed on receipt are provided.

Standard Storage Conditions

Based on stability data at normal, intermediate and accelerated conditions; a product shelf-life of 24 months and the storage direction ‘do not store above 25°C, store in the original package’ is approved.

The samples provided for stability studies are representative of the product to be marketed in the proposed pack.

The programme is ongoing. The stability programme is satisfactory as the applicant has agreed to place the first commercial batches on stability.

The results of the stability studies support the proposed shelf life.

Bioanalytical Methods and Validation

The note for guidance on the investigation of bioavailability and bioequivalence states that for parenteral solutions, if the product is of the same type of solution (aqueous or oily), contains the same concentration of the same active and the same or comparable excipients as the reference medicinal product currently approved, then bioequivalence testing is not required.

Quality Overall Summary

This is satisfactory.

PRODUCT PARTICULARS

Product Brand Name

This is considered satisfactory.

Summary of Product Characteristics

Satisfactory SPC provided.

Patient Information Leaflet

Satisfactory coloured mock-ups are provided. The applicant has until 1st July 2008 to amend the order in which the information appears in the leaflet and provide user testing data (both parts of Article 59, Directive 2004/27/EC must be complied with at the same time).

Labelling

Satisfactory.

MARKETING AUTHORISATION APPLICATION (MAA) form

This is satisfactory.

ADDITIONAL DATA REQUIREMENTS

Satisfactory.

CONCLUSION

A product licence may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

This is a generic application for Phenytoin 250mg/5ml Solution for Injection. The original product referred to is Epanutin Ready Mixed Injection, marketed in the UK by Warner Lambert Limited (PL 00019/0135) since 1986.

Phenytoin is an anticonvulsant well characterised in the literature. It is effective in generalised convulsive disorders and partial seizures but relatively ineffective in myoclonic seizures and ineffective in absence seizures. It appears to stabilise rather than raise the seizure threshold and prevents spread of seizure activity rather than abolish the primary focus of seizure discharge.

2. INDICATIONS

The UK has approved the following indications:

Phenytoin Solution for Injection is indicated for

The control of status epilepticus of the tonic-clonic (grand mal type) and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Phenytoin is also used in the treatment of cardiac arrhythmias where first line therapy is not effective. It is of particular value when these are digitalis induced.

The above is essentially identical to the SPC text for the licensed indications of the reference product and is satisfactory.

3. DOSE & DOSE SCHEDULE

The proposed posology properly reflects that of the reference product, but with occasional revised wording. It is satisfactory.

4. TOXICOLOGY

No new data are submitted and none are required for this type of application.

5. CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application. Bioequivalence data are not required, as the product is an aqueous solution for intravenous administration.

6. EFFICACY

No new data are submitted and none are required for this type of application.

7. SAFETY

No new data are submitted and none are required for this type of application.

8. EXPERT REPORT

A Clinical Overview has been provided in CTD Module 2.5.

A Clinical Summary has not been provided in CTD Module 2.7.

Information about the Clinical Expert is provided in CTD Module 1.4.3.

9. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is considered satisfactory and is consistent with the SPC for the reference product.

10. PATIENT INFORMATION LEAFLET

The PIL is considered satisfactory and is consistent with the PIL for the reference product.

11. LABELLING

The labelling is considered satisfactory.

12. DISCUSSION

The clinical use of Phenytoin Sodium 250mg/5ml for Injection is well established in the indications proposed. No new clinical efficacy and safety data has been submitted and none is required.

13. CONCLUSIONS

Overall, there is no clinical objection to the grant of marketing authorisations for this application. No new or unexpected safety concerns arise from this application. Phenytoin Sodium 250mg/5ml for Injection is considered to be interchangeable with the reference product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Phenytoin Sodium is a well known drug and has been used as an anticonvulsant for many years. Essential similarity has been demonstrated between the applicant's product and the innovator product, Epanutin Ready Mixed Injection. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product which, in turn, has been shown to be interchangeable with the innovator product. Extensive clinical experience with phenytoin sodium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

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STEPS TAKEN FOR ASSESMENT

	Step Name	Effective Date	Result
1.	Received	24/06/2003	Done
2.	Validate Case	07/03/2006	Submission Validated
3.	Start Quality Assessment	07/03/2006	Start Assessment
4.	Start Clinical Assessment	17/05/2006	Start Assessment
5.	Clinical Assessment	17/08/2006	Done
6.	Quality Assessment	17/08/2006	Done
7.	Check Site Status	17/08/2006	Determine Case
8.	Determination	21/08/2006	Grant
9.	Application Complete	21/08/2006	End

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

PHENYTOIN 250MG/5ML SOLUTION FOR INJECTION

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Phenytoin 250mg/5ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml ampoule contains 250 mg phenytoin sodium.
for excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, sterile, solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Phenytoin Solution for Injection is indicated for

The control of status epilepticus of the tonic-clonic (grand mal type) and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Phenytoin is also used in the treatment of cardiac arrhythmias where first line therapy is not effective. It is of particular value when these are digitalis induced.

4.2. Posology and method of administration

for intravenous administration.

Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Phenytoin Solution for Injection is suitable for use as long as it remains clear and free of 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 this 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 occurs most often with serum levels between 10 and 20mg/l (40-80 micromoles/l).

Phenytoin Solution for Injection should be injected slowly directly into a large vein through a large-gauge needle or intravenous catheter.

Each injection or infusion of intravenous phenytoin should be preceded and followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to alkalinity of the solution. (See section 4.4.)

for infusion administration the phenytoin solution should be diluted in 50-100ml of normal saline, with the final concentration of phenytoin not exceeding 10mg/ml, the infusion mixture should not be refrigerated. Administration should begin immediately after the infusion mixture has been prepared and must be completed within one hour. An in-line filter (0.22-0.50 microns) should be used.

The diluted form is suitable for use as long as it remains clear and free of precipitate.

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

Use in Status Epilepticus:

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

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 in adults (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.

In neonates, it has been 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 10-20 mg/l phenytoin which is within the generally accepted therapeutic range. The drug should be injected slowly intravenously at a rate of 1-3mg/kg/min.

It is advised that the serum levels of phenytoin are determined in the management of status epilepticus and to establish a maintenance dose. The clinically effective level 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 the attainment of peak plasma levels may require up to 24 hours.

Use in Cardiac Arrhythmias:

3.5-5mg per kg of bodyweight intravenously initially, repeated once if necessary. The solution should be injected slowly, intravenously and at a uniform rate which should not exceed 1ml (50mg) per minute.

Other clinical conditions:

The intravenous route of administration is preferred. Dosage and dosing interval will, of necessity, be determined by the needs of the individual patient. Factors such as previous antiepileptic therapy, seizure control, age and general medical condition must be considered.

Phenytoin is slowly absorbed when administered intramuscularly; this may be appropriate for the treatment of 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 necessary to maintain these levels. When returned to oral administration, the dose should be reduced by 50% of the original oral dose, for the same period of time the patient received phenytoin intramuscularly. This is to prevent excessive serum levels due to continued release from intramuscular tissue sites

Neurosurgery:

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

If the patient requires more than a week of intramuscular phenytoin, alternative routes should be explored such as gastric intubation. 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. Measurement of serum levels is of value as a guide to an appropriate adjustment of dosage.

Elderly (over 65 years):

As for adults. However, complications may occur more readily in elderly patients.

Neonates:

In neonates it has been shown that absorption of phenytoin is unreliable after oral administration. Phenytoin should be injected slowly intravenously at a rate of 1-3mg/kg/min at a dose of 15-20mg/kg. This will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range of 10-20mg/l.

Infants and children:

As for adults. Children tend to metabolise phenytoin more rapidly than adults. This should be considered when determining dosage regimens; monitoring serum levels is therefore particularly beneficial in such cases.

4.3. Contraindications

Phenytoin is contra-indicated in patients who are hypersensitive to phenytoin or other hydantoin. Intra-arterial administration must be avoided in view of the high pH of the preparation.

Because of its effect on ventricular automaticity, phenytoin is contra-indicated in sinus bradycardia, sino-atrial block, and second and third degree A-V block, and patients with Adams-Stokes syndrome.

4.4. Special warnings and precautions for use

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

The most notable signs of toxicity associated with the intravenous use of this drug 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.

When the drug is administered rapidly by the intravenous route hypotension usually occurs.

Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous 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. Serum levels of phenytoin in the therapeutic range cannot be rapidly achieved by this method.

General:

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.

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).

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

Biotransformation of phenytoin occurs mainly in the liver. Patients with impaired liver function, elderly patients, 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. Therefore it is advised that caution be taken when treating diabetic patients.

It has been rarely reported that the use of phenytoin exacerbates porphyria, therefore caution should be exercised in using this medication in patients suffering from this disease.

Laboratory Tests:

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

4.5. Interactions with other medicinal products and other forms of interaction

Drugs which may increase phenytoin serum levels include: amiodarone, antifungal agents (such as, but not limited to, amphotericin B, fluconazole, ketoconazole, miconazole and itraconazole), chloramphenicol, chlordiazepoxide, diazepam, dicoumarol, diltiazem, disulfiram, oestrogens, fluoxetine, H₂-antagonists, halothane, isoniazid, methylphenidate, nifedipine, omeprazole, phenothiazines, phenylbutazone, salicylates, succinimides, sulphonamides, tolbutamide, trazodone, and viloxazine.

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 preparations containing St John's wort (*Hypericum perforatum*). St John's wort induces enzymes that metabolise phenytoin. Herbal preparations containing St John's wort should therefore not be combined with phenytoin. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort. If a patient is

already taking St John's wort check the anticonvulsant levels and stop St John's wort. Anticonvulsant levels may increase on stopping St John's wort. The dose of anticonvulsant may need adjusting. Drugs, which may either increase or decrease phenytoin serum levels, include carbamazepine, phenobarbital, valproic acid, sodium valproate, antineoplastic agents, certain antacids and ciprofloxacin. Similarly the effect of phenytoin on carbamazepine, phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

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

Although not a true pharmacokinetic interaction, tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

Phenytoin impairs the effect of the following drugs: antifungal agents, antineoplastic agents, calcium channel blockers, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, frusemide, lamotrigine, methadone, neuromuscular blockers, oestrogens, oral contraceptives, paroxetine, quinidine, rifampicin, theophylline and vitamin D.

The effect of warfarin is enhanced by phenytoin. 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. It may, however, 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. It is recommended that serum folate concentrations be measured at least every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

4.6. Pregnancy and lactation

In considering the use of phenytoin intravenously in the management of status epilepticus in pregnancy, the following information should be weighed in assessing the risks and the benefits. The potential adverse effects upon the foetus of status epilepticus, specifically hypoxia, make it imperative to control the condition in the shortest possible time.

There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus and attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence 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 epileptic patients, therefore it should not be used as the first drug during pregnancy, especially early pregnancy, unless in the judgement of the physician the potential benefits outweigh the risk.

In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have been recent reports of a foetal hydantoin syndrome. This consists of prenatal growth deficiency, microencephaly and mental deficiency in children born to mothers who have received phenytoin,

barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

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

An increase in seizure frequency during pregnancy occurs in a proportion of patients, because of altered phenytoin 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, post partum 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 phenytoin. Vitamin K has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth.

Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

4.7. Effects on ability to drive and use machines

None known.

4.8. Undesirable effects

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

Central Nervous System:

The most common adverse reactions with phenytoin therapy occur in the central nervous system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, 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.

Cardiovascular:

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

Respiratory:

Alterations in respiratory function including respiratory arrest may occur.

Injection Site:

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

Dermatological System:

Dermatological reactions 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.

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 antiepileptic drugs.

Gastrointestinal System:

Nausea, vomiting, constipation, toxic hepatitis, and liver damage.

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 lethal dose in children is not known. The mean lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperflexia, lethargy, nausea, vomiting. The patient may become comatose and hypotensive. 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 >40mg/l, but a 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:

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 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 the presence of other CNS depressants, including alcohol, should be borne in mind.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics
ATC code: N03AB 01

Phenytoin is effective in various animal models of generalised convulsive disorders and reasonably effective in models of partial seizures but relatively ineffective in models of myoclonic seizures.

It appears to stabilise rather than raise the seizure threshold and prevents spread of seizure activity rather than abolish the primary focus of seizure discharge.

The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated, however, possible contributory effects include:

1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation.
2. Post-synaptic action to enhance GABA-mediated inhibition and reduce excitatory synaptic transmission.
3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter.

5.2. Pharmacokinetic properties

After injection phenytoin is distributed into body fluids including CSF. Its volume of distribution has been estimated to be between 0.52 and 1.19 litres/kg, and it is highly protein bound (usually 90% in adults).

In serum, phenytoin binds rapidly and reversibly to proteins. About 90% of phenytoin in plasma is bound to albumin. The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours.

Phenytoin is hydroxylated in the liver by an enzyme system that is saturable. Small incremental doses may produce very substantial increases in serum levels when these are in the upper range of therapeutic concentrations.

The parameters controlling elimination are also subject to wide interpatient variation. The serum level achieved by a given dose is therefore also subject to wide variation.

5.3. Preclinical safety data

There are no preclinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propylene glycol
Ethanol (96%)
Sodium hydroxide
Water for injection.

6.2. Incompatibilities

Phenytoin solution for injection should not be mixed with other drugs because of precipitation of phenytoin acid.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 25°C.

Store in the original package.

Keep out of sight and reach of children.

The product should not be used if a precipitate or haziness is noticed in the ampoule

6.5. Nature and contents of container

Transparent, type I glass ampoules.

Each 5ml ampoule contains 250mg phenytoin sodium.

Packs contain 1 ampoule or 50 ampoules (clinical pack)

6.6. Instruction for use and handling (, and disposal)

Should be used immediately after opening. Discard any unused product once opened.

Refer also to 4.2 above.

7. MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Ltd.

Tunbridge Wells

Kent TN1 1YG

8. MARKETING AUTHORISATION NUMBER

PL 18157/0010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/08/2006

10. DATE OF REVISION OF THE TEXT

21/08/2006

PHENYTOIN 250MG/5ML SOLUTION FOR INJECTION (Phenytoin Sodium) PL 18157/0010

PRODUCT INFORMATION LEAFLET

<p>Phenytoin, phenytoin sodium, other similar drugs (hydantoin) or any of the other ingredients in this medicine</p> <p>Special care will be taken before giving you Phenytoin 250mg/5ml Solution for Injection:</p> <ul style="list-style-type: none"> • If you have a heart condition called heart block • If you have low blood pressure or heart failure • If you drink large amounts of alcohol • If you have liver disease • If you have diabetes • If you have porphyria (an inherited blood disease) • If you are on hormone replacement therapy (oestrogens), taking the pill (oral contraceptive) • If you are due to have a surgical procedure as the effectiveness of muscle relaxants used for surgery can be reduced by phenytoin, or if you are to be given the anaesthetic agent halothane as this may increase phenytoin levels • If you are taking methadone • If you are taking vitamin supplements such as Vitamin D and folic acid • If you are taking the herbal preparation St John's wort (Hypericum perforatum). <p>Please tell your doctor if you are taking, or have recently taken, any other medicines, including ones you have bought yourself.</p> <p>You should tell your doctor if you are (or drink you might be) pregnant or are breast-feeding.</p> <p>Phenytoin may also interfere with certain laboratory tests that you may be given.</p> <p>You should limit the amount of alcohol you drink whilst being treated with this medicine as the concentration of phenytoin in your blood can be altered with excess alcohol.</p> <p>How much Phenytoin is given? You will be in hospital when you are given this medicine. A diluted solution will be either injected into one of your veins (intravenously) or into your muscle (intramuscularly). Phenytoin must not be given by rapid intravenous injection. The medicine is injected slowly into your vein or given as an infusion over a period of time. If you are unable to take phenytoin by mouth it may be injected into a muscle. Usually Phenytoin is only given intramuscularly for a week. As this medicine will be given too little or too much, however tell your doctor or pharmacist if you have</p>	<p>Phenytoin 250mg/5ml Solution for Injection</p> <p>Please read this leaflet carefully before receiving Phenytoin 250mg/5ml Solution for Injection. If you have already received Phenytoin Solution for Injection because of the urgency of your condition, you should still read this leaflet. Keep the leaflet in case you want to refer to it again.</p> <p>If you want to know more about Phenytoin 250mg/5ml Solution for Injection or have any questions, you should ask your doctor.</p> <p>The name of this medicine is Phenytoin 250mg/5ml Solution for Injection. The active substance is phenytoin sodium.</p> <p>Each 5ml ampoule contains 250mg of phenytoin sodium. The other ingredients are propylene glycol, ethanol, sodium hydroxide and water. Phenytoin 250mg/5ml Solution for Injection comes in packs of 1 or 50 ampoules.</p> <p>Product Licence Holder: Becon Pharmaceuticals Ltd, Tunbridge Wells, Kent TN11 1YQ</p> <p>Manufacturer: The medicine is manufactured for the Product Licence Holder by Laboratorios Reig Jofre, S.A., Spain.</p> <p>What is Phenytoin 250mg/5ml Solution for Injection? Phenytoin belongs to a group of medicines called anti-epileptic drugs. These medicines are used to treat epileptic seizures or fits. It can also be used to treat irregular heart rhythms when given by injection.</p> <p>What is Phenytoin 250mg/5ml Solution for Injection used for? Phenytoin is used to treat severe epileptic seizures or fits (status epilepticus). It is also used to treat and prevent seizures for short periods of time when anti-epileptic drugs can not be taken by mouth. Phenytoin can be used to prevent or treat seizures during or after brain surgery and/or severe head injury. Phenytoin can be used to treat specific changes in the rhythm of the heart (cardiac arrhythmias), particularly when these are caused by the drug.</p> <p>Your doctor may have already given you phenytoin to control status epilepticus, as the urgent need for treatment may have been more important than the normal cautions. In this case the doctor would have considered the following information, you can read this leaflet after you have had phenytoin, this is particularly important if you are to continue to be given phenytoin.</p> <p>You should not be given Phenytoin 250mg/5ml Solution for Injection in the following circumstances:</p> <ul style="list-style-type: none"> • If you have shown signs of hypersensitivity (severe allergy) to
<p>Technical Leaflet : Phenytoin 250mg/5ml Solution for Injection</p> <p>Please read this information carefully before using Phenytoin 250mg/5ml Solution for Injection. Further information is contained in the Summary of Product Characteristics.</p> <p>Presentation: Phenytoin 250 mg/5 ml Solution for Injection contains 250 mg phenytoin sodium in each 5 ml ampoule. Packs contain 1 or 50 ampoules.</p> <p>Dosage and Method of Administration: Phenytoin solution is clear and colourless, it is suitable for use as long as it remains clear and free of precipitate. Upon refrigeration or freezing a precipitate might form; this will dissolve again after the solution is allowed to stand at room temperature. Only a clear solution should be used. A faint yellow colouration may develop but this has no effect on potency. Phenytoin Solution should be injected slowly, directly into a large vein through a large-gauge needle or intravenous catheter.</p> <p>Rapid intravenous administration may cause serious cardiovascular toxicity and death. In adults, intravenous administration should not exceed 50mg per minute. In neonates the drug should be administered at a rate of 1-3mg/kg/min.</p> <p>Each injection or infusion of intravenous phenytoin should be preceded and followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to alkalinity of the solution.</p> <p>For infusion administration the Phenytoin Solution should be diluted in 50-100ml of normal saline, with the final concentration of phenytoin not exceeding 10mg/ml. The infusion mixture should not be refrigerated and is suitable for use as long as it remains clear and free of precipitate. Administration should begin immediately after preparation of the infusion mixture and must be completed within one hour. An in-line filter (0.22-0.50 microns) should be used.</p> <p>Use in Status Epilepticus: In a patient having continuous</p>	<p>seizure i.e. serial epilepsy, injection of intravenous diazepam or a short acting barbiturate is recommended because of their rapid onset of action, prior to administration of phenytoin. A loading dose of phenytoin 10-15mg/kg should then be slowly injected intravenously (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. The intra-muscular route is not recommended.</p> <p>Use in Cardiac Arrhythmias: 3.5-5mg per kg of bodyweight intravenously initially, repeated once if necessary. The solution should be injected slowly, intravenously and at a uniform rate.</p> <p>Neurosurgery: In a patient who has not previously received the drug, 100-200mg (2-4ml) of phenytoin may be given intramuscularly at approximately 4-hour intervals prophylactically during neurosurgery and continued during the postoperative period for 48-72 hrs. The dosage should then be reduced to a maintenance dose of 300mg and adjusted according to serum level estimations.</p> <p>Elderly (over 65 years): As for adults. However, complications may occur more readily in elderly patients.</p> <p>Neonates: In neonates, the absorption of phenytoin is unreliable after oral administration. Phenytoin should be slowly injected intravenously at a rate of 1-3mg/kg/min at a dose of 15-20mg/kg. This will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range of 10-20mg/l.</p> <p>Infants and children: As for adults. Children tend to metabolise phenytoin more rapidly than adults. This should be considered when determining dosage regimens; monitoring serum levels is therefore particularly beneficial in such cases.</p> <p>Contra-Indications: Phenytoin is contra-indicated in patients who are hypersensitive to phenytoin or other hydantoin. Intra-arterial administration must be avoided in view of the high pH of the preparation.</p>



skin conditions occur such as Stevens Johnson Syndrome, which causes blistering and can also affect the mouth and tongue. A rash may be the first sign of other side effects, your doctor may stop giving you phenytoin until the rash clears up. If the rash does not clear up or recurs or you show signs of serious reaction your doctor may advise you not to take phenytoin again. Swelling of the lymph glands (part of your bodies defence system) and other lymph disorders may occur. Blood disorders, which may be noticed as bruising, paleness, fever or sore throat. Your doctor may take blood samples to test for this. Liver damage or hepatitis (inflammation of the liver), which may be recognised by yellowing of the eyes and skin. Inflammation of the kidneys. Breathing problems (mainly inflammation of the lung lining). Nausea, vomiting or constipation. Increased levels of blood sugar, decreased levels of folic acid and calcium. The amount of vitamin D in your body may be altered. If you do not get enough vitamin D in your diet or from exposure to the sun you may suffer from bone pain or fractures. Rickets (abnormal bone development) may occur if the effect is prolonged. Other rare side effects have been reported such as changes in the hand with difficulty straightening the fingers, changes to facial features, enlarged gums or lips, abnormal facial or body hair, changes to the shape of the penis and painful erection, pain in the joints. Tell your doctor or nurse if you become unwell or feel discomfort that you do not understand. **Storage:** Keep out of the sight and reach of children. Keep in the original packaging. Do not use after the expiry date printed on the carton. **Further information:** This leaflet does not include all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or nurse. **Date of last revision:** February 04.

Does this medicine cause undesirable effects? As with all medicines, phenytoin may cause some undesirable effects in some patients. Intermittent phenytoin may cause irritation at the site of the injection particularly if it escapes from a vein into the surrounding tissue. If this happens tell a doctor or nurse immediately. If the injection is given too quickly blood pressure may drop and a severe reaction involving the heart, blood vessels and the central nervous system may occur. Rarely this has resulted in death in elderly or very ill patients. **Severe allergic reaction or hypersensitivity syndrome** – this may be recognised by an itchy rash, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), or you may feel you are going to faint. Rarely a condition called systemic lupus erythematosus may also occur (inflammation of various parts of the body including the joints, skin and kidneys). Changes of liver function, increase numbers of white blood cells and joint pains may also occur. Inflammation of the walls of the arteries and problems with the body's defence system (immune system) have also been reported. Although still rare, you may be likely to get this syndrome, skin rash or liver damage. If you are black. These are very serious side effects and you may need urgent medical attention. **If you experience any of the following tell your doctor or nurse as soon as possible:** Effects on the central nervous system include: difficulty in controlling movements, unsteadiness, shaking, uncoordinated movements, unusual eye movements, confusion, slurred speech, pins and needles, drowsiness, dizziness or vertigo (dizziness in high places), nervousness, sleeplessness, twitching muscles, loss of feeling in the hands and feet, headaches. These effects may also occur when the amount of phenytoin in your blood is too high. Very high amounts of phenytoin in the blood can cause extreme confusion e.g. delirium, psychosis or encephalopathy (a brain disease). Rarely irreversible brain injury has occurred when the amount of phenytoin in the blood has remained high for a long period of time. Your doctor should test your blood to measure the amount of phenytoin and adjust your dose if necessary. If you suffer side effects at lower doses of phenytoin. **Minor skin rashes** such as measles-like or dermatitis. Rarely serious

Phenytoin is contra-indicated in sinus bradycardia, sinoatrial block, and second and third degree A-V block, and patients with Adams-Stokes syndrome. **Special Warnings and Precautions:** Rapid intravenous administration may cause serious cardiovascular toxicity and death. The most notable signs of toxicity associated with the intravenous use of this drug are hypotension, cardiovascular collapse and/or central nervous system depression. Adverse reactions are more likely in elderly or gravely ill patients, or if the preparation is given too rapidly or in excess. Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Subcutaneous or perivascular injection should be avoided because of the highly alkaline nature of the solution. Phenytoin should be discontinued if a skin rash appears. If signs of acute toxicity appear, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive and, if symptoms persist, termination of therapy with phenytoin is recommended. **Interactions with other Medicinal Products and other Forms of Interaction:** Drugs that may increase phenytoin serum levels include: amiodarone, antifungal agents (such as, but not limited to, amphotericin B, fluconazole, ketoconazole, miconazole and itraconazole), chloramphenicol, chlorthalidopoxide, diazepam, dicoumarol, diltiazem, disulfiram, oestrogens, fluoxetine, H2-antagonists, halothane, isoniazid, methylphenidate, nifedipine, omeprazole, phenothiazines, phenylbutazone, salicylates, succinimides, sulphonamides, tolbutamide, trazodone, and viloxazine. Drugs that may decrease phenytoin serum levels include: folic acid, reserpine, rifampicin, sucralfate, theophylline, vigabatrin and herbal preparations containing St John's wort (Hypericum perforatum). Drugs, which may either increase or decrease phenytoin serum levels, include carbamazepine, phenobarbital, valproic acid, sodium valproate, antineoplastic agents,

certain antacids and ciprofloxacin. Similarly the effect of phenytoin on carbamazepine, phenobarbital, valproic acid and sodium valproate serum levels is unpredictable. Acute alcoholic intake may increase phenytoin serum levels, chronic alcoholic use may decrease serum levels. Tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted. Phenytoin impairs the effect of the following drugs: antifungal agents, antineoplastic agents, calcium channel blockers, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, frusemide, lamotrigine, methadone, neuromuscular blockers, oestrogens, oral contraceptives, paroxetine, quinidine, rifampicin, theophylline and vitamin D. The effect of warfarin is enhanced by phenytoin. 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. **Pharmaceutical Information:** Excipients: propylene glycol, ethanol (96%), sodium hydroxide, water for injection. Incompatibilities: Phenytoin Solution for Injection should not be mixed with other drugs because of precipitation of phenytoin acid. Shelf-life: 2 years. Storage Precautions: Do not store above 25°C. Store in the original package. Keep out of sight and reach of children. Nature of Container: Transparent, type 1 glass 5ml ampoules. Instructions for Use and Handling: After administration, discard any unused solution.

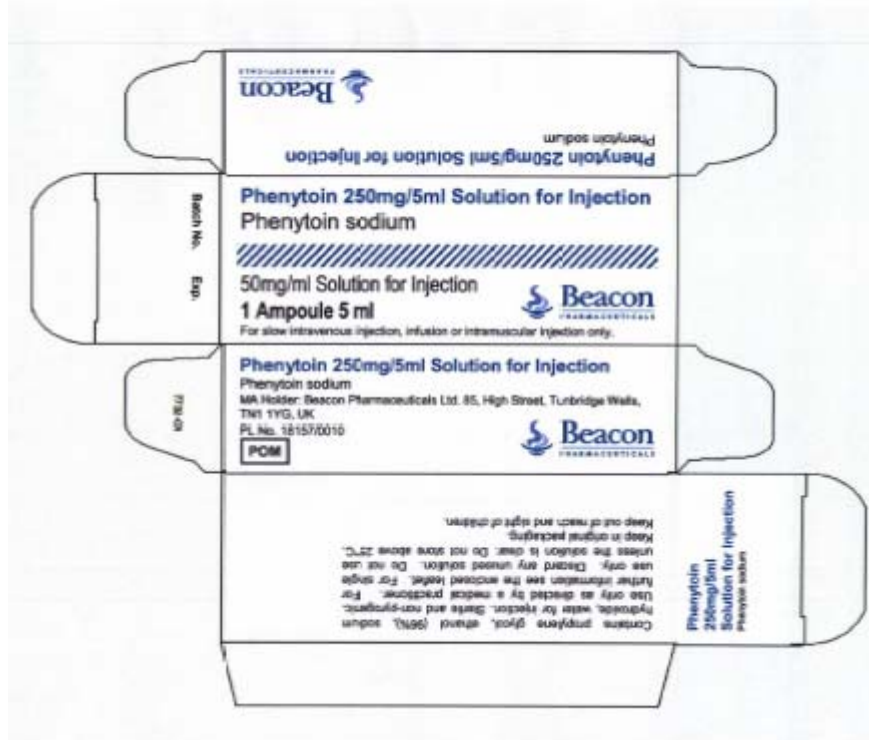
PHENYTOIN 250MG/5ML SOLUTION FOR INJECTION

(Phenytoin Sodium)

PL 18157/0010

LABELLING

Pack label



50 AMPOULE PACK LABEL

Phenytoin 250mg/5ml Solution for Injection
Phenytoin sodium



50mg/ml Solution for Injection
50 Ampoules 5 ml


For slow intravenous injection, infusion or intramuscular injection only.

Contains propylene glycol, ethanol (96%), sodium hydroxide, water for injection. Sterile and non-pyrogenic.
Use only as directed by a medical practitioner. For further information see the enclosed leaflet.

For single use only. Discard any unused solution. Do not use unless the solution is clear. Do not store above 25°C. Keep in original packaging.
Keep out of reach and sight of children.

MA Holder: Beacon Pharmaceuticals Ltd.
85, High Street, Tunbridge Wells,
TN1 1YG, UK
PL No. 18157/0010



Batch No. Exp.

Ampoule label

Phenytoin 50mg/ml
Solution for Injection
5ml - Injectable Solution L.v. or I.m.
Beacon Pharmaceuticals Ltd
Exp. Ex No.