

# **Public Assessment Report**

## **Decentralised Procedure**

**Phenytoin Sodium 100mg Capsules**

**Procedure No: UK/H/2203/001/DC**

**UK Licence No: PL 20620/0021**

**NRIM LIMITED**

## LAY SUMMARY

On 13 September 2011, the MHRA granted a Marketing Authorisation to NRIM Limited for a medicine called Phenytoin Sodium 100mg Capsules.

This product is a prescription-only medicine (POM) used for the following:

- to control a variety of epileptic conditions
- to control or prevent seizures during or after brain surgery or severe head injury
- to treat trigeminal neuralgia (facial nerve pain).

The active ingredient, phenytoin sodium, belongs to a group of medicines called anti-epileptic drugs.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Phenytoin Sodium 100mg Capsules outweigh the risks; hence a Marketing Authorisation was granted.

## TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 4
Module 2: Summary of Product Characteristics	Page 5
Module 3: Product Information Leaflet	Page 13
Module 4: Labelling	Page 15
Module 5: Scientific Discussion	Page 17
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6	Steps taken after initial procedure

# Module 1

## Information about the initial procedure

<b>Product Names</b>	Phenytoin Sodium 100mg Capsules
<b>Type of Application</b>	Generic, Article 10(1)
<b>Active Substance</b>	Phenytoin sodium
<b>Form</b>	Capsule, hard
<b>Strength</b>	100mg
<b>MA Holder</b>	NRIM Limited, Unit 15 Moorcroft, Harlington Road, Hillingdon, UB8 3HD, United Kingdom
<b>Reference Member State (RMS)</b>	UK
<b>Concerned Member States (CMS)</b>	Spain and Ireland
<b>Procedure Number</b>	UK/H/2203/001/DC
<b>Timetable</b>	Day 210 – 18 August 2011

## Module 2

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1 NAME OF THE MEDICINAL PRODUCT

Phenytoin Sodium 100mg Capsules

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100mg of phenytoin sodium.

Each capsule also contains 85.50 mg of lactose

For a full list of excipients, see section 6.1

#### 3 PHARMACEUTICAL FORM

Capsule, Hard (capsules)

Size "3" Hard gelatin capsule with orange transparent coloured cap printed with "146" and white coloured body, containing white granular powder.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Phenytoin Sodium 100mg Capsules are indicated for the following:

- Control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these
- The prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Phenytoin Sodium 100mg Capsules have also been employed in the treatment of trigeminal neuralgia but should only be used as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

##### 4.2 Posology and method of administration

###### Posology

Dosage should be individualised as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. Phenytoin should be introduced in small dosages with gradual increments until control is achieved or until toxic effects appear. In some cases serum level determinations may be necessary for optimal dosage adjustments - the clinically effective level is usually 10-20mg/l (40-80 micromoles/l) although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin. With recommended dosage a period of seven to ten days may be required to achieve steady state serum levels with phenytoin and changes in dosage should not be carried out at intervals shorter than seven to ten days. Maintenance of treatment should be the lowest dose of anticonvulsant consistent with control of seizures.

###### *Adults:*

Initially 3 to 4mg/kg/day with subsequent dosage adjustment if necessary. For most adults a satisfactory maintenance dose will be 200 to 500mg daily in single or divided doses. Exceptionally, a daily dose outside this range may be indicated. Dosage should normally be adjusted according to serum levels where assay facilities exist.

###### *Elderly:*

Elderly (over 65 years): As with adults the dosage of phenytoin should be titrated to the patient's individual requirements using the same guidelines. As elderly patients tend to receive multiple drug therapies, the possibility of drug interactions should be borne in mind.

###### *Paediatric patients*

###### *Infants and Children:*

Initially, 5mg/kg/day in two divided doses, with subsequent dosage individualised to a maximum of 300mg daily. A recommended daily maintenance dosage is usually 4-8mg/kg.

*Neonates:*

The absorption of phenytoin following oral administration in neonates is unpredictable. Furthermore, the metabolism of phenytoin may be depressed. It is therefore especially important to monitor serum levels in the neonate.

Method of Administration

Oral only

**4.3 Contraindications**

Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin, or its excipients, or other hydantoins

**4.4 Special warnings and precautions for use**

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic 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 Sodium. 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.

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anti-epileptic 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 anti-epileptic drug not belonging to the hydantoin chemical class.

Phenytoin is highly protein bound and extensively metabolised by the liver. Reduced dosage to prevent accumulation and toxicity may therefore be required in patients with impaired liver function. 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 (40-80 micromoles/l). Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity.

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

Phenytoin may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported in association with toxic levels. Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes.

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).

Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare drug induced, multiorgan syndrome which is potentially fatal and occurs in some patients taking anticonvulsant medication. It is characterized by fever, rash, lymphadenopathy, and other multiorgan pathologies, often hepatic. The mechanism is unknown. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals. If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.

**Serious skin reactions**

Phenytoin can cause rare, serious skin adverse events such as exfoliative dermatitis, Stevens- Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstatement of therapy, further phenytoin medication is contraindicated. Published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, and hepatotoxicity in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B\*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLAB\* 1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of drugs associated with SJS/TEN, including phenytoin, in HLA-B\*1502 positive patients when alternative therapies are otherwise equally available.

HLAB\* 1502 may be associated with an increased risk of developing Stevens Johnson Syndrome (SJS) in individuals of Thai and Han Chinese Origin when treated with phenytoin. If these patients are known to be positive for HLAB\*1502, the use of phenytoin should only be considered if the benefits are thought to exceed risks.

In the Caucasian and Japanese population, the frequency of HLAB\*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not available.

**Musculoskeletal Effect**

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose metabolism should not take this medicine

**4.5 Interaction 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, chlorthalidone, diazepam, dicoumarol, diltiazem, disulfiram, fluoxetine, H<sub>2</sub>-antagonists, halothane, isoniazid, methylphenidate, nifedipine, omeprazole, oestrogens, 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*). This is due to induction of drug metabolising enzymes by St John's wort. 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.  
A pharmacokinetic interaction study between nelfinavir and phenytoin both administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively. Therefore, phenytoin concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

- 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 alcohol intake may increase phenytoin serum levels while chronic alcoholism 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.
- Drugs whose effect is impaired by phenytoin include: Antifungal agents, antineoplastic agents, calcium channel blockers, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, furosemide, lamotrigine, methadone, neuromuscular blockers, oestrogens, oral contraceptives, paroxetine, quinidine, rifampicin, theophylline and vitamin D.
- Drugs whose effect is altered by phenytoin include: Warfarin; 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, and gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

#### 4.6 Pregnancy and lactation

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 with 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.

Anticonvulsants including phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients. The exact role of drug therapy in these abnormalities is unclear and genetic factors, in some studies, have also been shown to be important. Phenytoin should only be used during pregnancy, especially early pregnancy, if in the judgement of the physician the potential benefits clearly 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 more recently been reports of a foetal hydantoin syndrome. This consists of prenatal growth deficiency, micro-encephaly 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, and this may be due to 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, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K<sub>1</sub> 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 phenytoin because phenytoin appears to be secreted in low concentrations in human milk.

#### 4.7 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 phenytoin may cause central nervous system adverse effects such as dizziness and drowsiness (see Section 4.8).

#### 4.8 Undesirable effects

##### *Immune system reactions:*

Anaphylactoid reaction, and anaphylaxis.

##### *Central Nervous System:*

The most common manifestations encountered with phenytoin therapy are referable to this system 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 twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdosage. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

##### *Gastrointestinal:*

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

##### *Dermatological:*

Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash is the most common; dermatitis is seen more rarely. Other more serious and rare forms have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome and toxic epidermal necrolysis (see Section 4.4).

##### *Connective Tissue:*

Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely.

##### *Haemopoietic:*

Haemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, 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 and 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, eg 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.

Frequent blood counts should be carried out during treatment with phenytoin.

*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, polyarteritis 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.

*Musculoskeletal System:*

Bone fractures and osteomalacia have been associated with longterm (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported.

#### 4.9 **Overdose**

The lethal dose in children is not known. The mean lethal dose for adults is estimated to be 2 to 5g. The initial symptoms are nystagmus, ataxia and dysarthria. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus on lateral gaze usually appears at 20mg/l, and ataxia at 30mg/l, dysarthria and lethargy appear when the serum concentration is greater than 40mg/l, but a concentration as high as 50mg/l has been reported without evidence of toxicity.

As much as 25 times therapeutic dose has been taken to result in serum concentration over 100mg/l (400 micromoles/l) with complete recovery.

*Treatment:*

Treatment is non-specific since there is no known antidote. If ingested within the previous 4 hours the stomach should be emptied. If the gag reflex is absent, the airway should be supported. Oxygen, and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular depression. Haemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been utilised 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; Hydantoin derivatives

ATC Code: N03AB02

Phenytoin is effective in various animal models of generalised convulsive disorders, 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:

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

## 5.2 Pharmacokinetic properties

Phenytoin is absorbed from the small intestine after oral administration. Various formulation factors may affect the bioavailability of phenytoin; however, non-linear techniques have estimated absorption to be essentially complete. After absorption it is distributed into body fluid 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).

The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours. Steady state therapeutic drug levels are achieved at least 7 to 10 days after initiation of therapy.

Phenytoin is hydroxylated in the liver by an enzyme system which 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

Pre-clinical safety data do not add anything of further significance to the prescriber.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Capsules shell components

Gelatin

Water

Erythrosine (E127)

Quinoline yellow (E104)

Titanium dioxide (E171)

Sodium lauryl sulfate

Printing Ink Composition

Shellac

Propylene glycol

Black Iron Oxide (E172)

Potassium Hydroxide

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Keep the container tightly closed in order to protect from light and moisture.

### 6.5 Nature and contents of container

HDPE white opaque tablet container with a 38mm white polypropylene child resistant cap.

Pack size: 84 capsules.

### 6.6 Special precautions for disposal

No special requirements.

- 7      MARKETING AUTHORISATION HOLDER**  
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Hillingdon,  
UB8 3HD, United Kingdom
- 8      MARKETING AUTHORISATION NUMBER(S)**  
PL 20620/0021
- 9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
13/09/2011
- 10     DATE OF REVISION OF THE TEXT**  
13/09/2011

# Module 3

## Patient Information Leaflet



### NRIM PHENYTOIN SODIUM 100MG CAPSULES PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Phenytoin Capsules are and what they are used for
2. Before you take Phenytoin Capsules
3. How to take Phenytoin Capsules
4. Possible side effects
5. How to store Phenytoin Capsules
6. Further Information

#### 1. WHAT PHENYTOIN CAPSULES ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Phenytoin sodium 100mg Capsules (referred to as Phenytoin Capsules or as Phenytoin throughout this leaflet).

Phenytoin belongs to a group of medicines called anti-epileptic drugs; these medicines are used to treat epilepsy.

Phenytoin can be used to control a variety of epileptic conditions, to control or prevent seizures during or after brain surgery or severe head injury. Phenytoin can also be used to treat trigeminal neuralgia (facial nerve pain). You should ask your doctor if you are unsure why you have been given Phenytoin capsules.

#### 2. BEFORE YOU TAKE PHENYTOIN CAPSULES

You should not take Phenytoin until you are sure it is safe for you to do so.

##### Do not take Phenytoin

- If you are allergic (hypersensitive) to phenytoin, other hydantoin products or any of the other ingredients of Phenytoin capsules.

##### Take special care with Phenytoin

Medicines are not always suitable for everyone. Your doctor needs to know before you take phenytoin if you suffer from or have suffered in the past from any of the following conditions:

- Liver disease.
- Porphyria (an inherited disease that affects haemoglobin biosynthesis).

A small number of people being treated with antiepileptics such as phenytoin sodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Serious skin side effects can rarely occur during treatment with Phenytoin. This risk may be associated with a variant in genes in a subject with Chinese or Thai origin. If you are of such origin and have been tested previously carrying this genetic variant (HLA-B\*1502), discuss this with your doctor before taking Phenytoin.

##### Taking other medicines

Some medicines can affect the way Phenytoin works, or Phenytoin itself can reduce the effectiveness of other medicines taken at the same time. These include:

- Medicines used for heart and circulation problems (dicoumarol, digitoxin, amiodarone, furosemide, quinidine, reserpine, warfarin, and calcium channel blockers e.g. diltiazem and nifedipine).
- Medicines used for epilepsy (carbamazepine, lamotrigine, phenobarbital, sodium valproate and valproic acid, succinimides e.g. ethosuximide and vigabatrin).

- Medicines used to treat fungal infections (e.g. amphotericin B, fluconazole, itraconazole, ketoconazole and miconazole).
- Medicines used for tuberculosis and other infections (chloramphenicol, isoniazid, rifampicin, sulphonamides, doxycycline, ciprofloxacin and nelfinavir).
- Medicines used for stomach ulcers (omeprazole, sucralfate, the medicines known as H2 antagonists e.g. cimetidine, ranitidine, famotidine and some antacids).
- Medicines used for asthma and bronchitis (theophylline).
- Medicines used for pain and inflammation (phenylbutazone, salicylates e.g. aspirin and steroids).
- Medicines used for sleeplessness, depression and psychiatric disorders (chlordiazepoxide, clozapine, diazepam, disulfiram, fluoxetine, methylphenidate, paroxetine, phenothiazines, trazodone, tricyclic antidepressants and viloxazine).
- Medicines used for diabetes (tolbutamide).
- Some hormone replacement therapies (oestrogens), oral contraceptives (the birth control pill).
- Medicines used for organ and tissue transplants, to prevent rejection (cyclosporin).
- Medicines used for cancer (antineoplastic agents).
- Muscle relaxants used for surgery (neuromuscular blockers), some anaesthetic drugs (halothane) and methadone.
- Some products available without a prescription (folic acid, theophylline, vitamin D).

Your doctor may need to test the amount of Phenytoin in your blood to help decide if any of these medicines are affecting your treatment.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The herbal preparation St John's wort (*Hypericum perforatum*) should not be taken at the same time as this medicine. If you already take St John's wort, consult your doctor before stopping the St John's wort preparation.

Phenytoin capsules may also interfere with certain laboratory tests that you may be given.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Phenytoin.

##### Taking Phenytoin with food or drink

Phenytoin can be taken before or after food and drinks. Drinking a lot of alcohol can also affect the concentration of Phenytoin in your blood.

##### Pregnancy or breast-feeding

If you think you might be pregnant, or are planning to get pregnant, tell your doctor before you take Phenytoin.

You should not take phenytoin if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

##### Driving and using machines

Phenytoin may cause dizziness or drowsiness, especially during the first few weeks of treatment. If you experience these symptoms, do not drive or operate tools or machinery or carry out other hazardous activities.

Important information about some of the ingredients of Phenytoin  
Phenytoin contains lactose, a type of sugar. If you have been told that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE PHENYTOIN CAPSULES

Always take Phenytoin exactly as your doctor has told you. You should check with your doctor if you are not sure.

It is best to take Phenytoin at the same time each day. Swallow the capsules whole, with plenty of water.

#### Adults

The amount of Phenytoin needed varies from one person to another. Most adults need between 200mg and 500mg a day either as a single or divided dose. Occasionally higher doses are needed.

#### Children

Infants and children usually start on a dose that depends on their weight (5mg per day for every kg they weigh) and is given as a divided dose, twice a day. The dose is then adjusted up to a maximum of 300mg a day.

#### Elderly

The dose of Phenytoin for elderly patients who may be taking other medicines may also need careful consideration and adjustment by their doctor.

#### If you take more Phenytoin than you should

Phenytoin is dangerous in overdose. If you or someone else accidentally takes too much phenytoin contact your doctor at once or go to the nearest hospital casualty department. Always take the labelled medicine package with you, whether there is any Phenytoin left or not, as this will allow easier identification of the medicine.

#### If you forget to take Phenytoin

If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do not take a double dose to make up for a missed dose.

#### If you stop taking Phenytoin

Do not stop taking phenytoin unless your doctor tells you to. If you suddenly stop taking this medicine you may have a seizure. Should you need to stop taking phenytoin, your doctor will have decided which the best method is for you.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Phenytoin can cause side effects although not everybody gets them.

**Tell your doctor immediately** if you experience any of the following symptoms after taking this medicine. Although they are very rare, these symptoms can be serious.

- Sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body).
- If you develop a severe skin rash that causes blistering, (this can also affect the mouth and tongue). These may be signs of a condition known as Stevens Johnson Syndrome, or toxic epidermal necrolysis (TEN). **Your doctor will stop your treatment in these cases.**
- If you notice bruising, fever, you are looking pale or you have a severe sore throat. These may be the first signs of an abnormality of the blood, including decreases in the number of red cells, white cells or platelets. Your doctor may take regular blood samples to test for these effects.
- Skin rash and fever with swollen glands, particularly in the first two months of treatment, as these may be signs of a hypersensitivity reaction. If these are severe and you also experience pain and inflammation of the joints this could be related to a condition called systemic lupus erythematosus.
- If you experience confusion or have a severe mental illness, as this may be a sign that you have high amounts of phenytoin in your blood. On rare occasions, when the amount of phenytoin in the blood remains high, irreversible brain injury has occurred. Your doctor may test your blood to see how much phenytoin is in the blood and may change your dose.

Other side-effects that may occur are:

- **Effects on your nervous system:** Unusual eye movements, unsteadiness, difficulty in controlling movements, shaking, abnormal or uncoordinated movements, slurred speech, confusion, pins and needles or numbness, drowsiness, dizziness, vertigo, sleeplessness, nervousness, twitching muscles, headaches.
- **Effects on your skin:** skin rash including measles-like reactions which are mild.
- **Effects on your stomach and intestines:** feeling sick, being sick and constipation.
- **Effects on your blood and lymph system:** swelling of the lymph glands.
- **Effects on your liver and kidney:** inflammation of the kidneys and liver, liver damage (seen as yellowing of the skin and whites of the eye).
- **Effects on your reproductive system and breasts:** changes in the shape of the penis, painful erection.
- **Effects on your hands, face and body:** changes in the hands with difficulty in straightening the fingers, changes in facial features, enlarged lips or gums, increased or abnormal body or facial hair.
- **Effects on your respiratory system:** problems breathing, inflammation of the lining of the lung.
- **Effects on your immune system:** problems with the body's defence against infection, inflammation of the wall of the arteries.
- **Effects on medical tests:** increased levels of blood sugar, or decreased levels of blood calcium, folic acid and vitamin D. If you also do not get enough vitamin D in your diet or from exposure to sunlight, you may suffer from bone pain or fractures.

If any of the side effects get serious or lasts longer than a few days, or if you notice other unwanted effects, tell your doctor or pharmacist.

### 5. HOW TO STORE PHENYTOIN CAPSULES

- Keep out of the reach and sight of children.
- Do not use Phenytoin after the expiry date, which is printed on the end of the carton and also on the bottle label. The expiry date refers to the last day of the month.
- Do not store above 25°C. Store in the original package. Keep the container tightly closed in order to protect from light and moisture
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

### 6. FURTHER INFORMATION

#### What Phenytoin Capsules contain

The name of this medicine is Phenytoin sodium 100mg Capsules. The active substance in your capsules is phenytoin sodium. Each hard capsule contains 100mg of the active ingredient phenytoin sodium. Other ingredients include lactose monohydrate and magnesium stearate. The capsule shell is made of gelatin, water, erythrosine (E127), quinoline yellow (E104), titanium dioxide (E171), sodium lauril sulfate and black edible printing ink, which contains shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide.

#### What Phenytoin Capsules look like and contents of the pack

Phenytoin sodium 100mg Capsules are hard gelatin capsules with an orange transparent coloured cap printed with "146" and white coloured body, containing white granular powder. Phenytoin sodium 100mg Capsules are supplied in a HDPE capsule container with a child-resistant polypropylene cap. Each bottle contains 84 capsules.

#### Marketing Authorisation Holder and Manufacturer

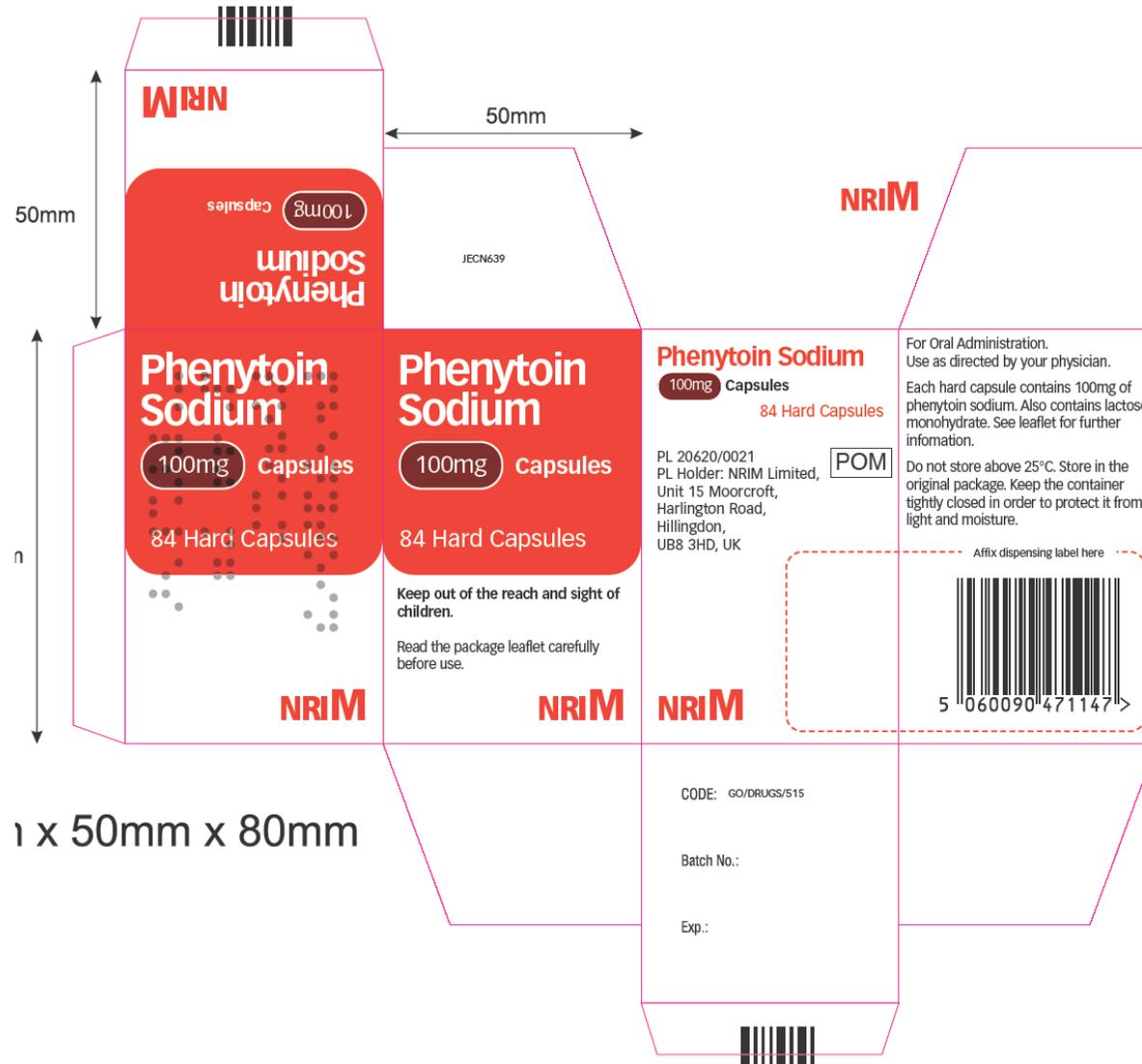
The Marketing Authorisation holder and manufacturer of these capsules is NRIM Limited, Unit 15 Moorcroft, Harlington Road, Hillingdon, UB8 3HD, United Kingdom.

This leaflet was prepared in 08/2011

GO/DRUGS/515

JELT234

# Module 4 Labelling



# Phenytoin Sodium

100mg Capsules

84 Hard Capsules **NRIM**

For Oral Administration.  
Use as directed by your physician.  
Each hard capsule contains 100mg of phenytoin sodium. See leaflet for further information.

Do not store above 25°C. Store in the original package. Keep the container tightly closed to protect from light and moisture.

**Keep out of the reach and sight of children.**

Read the package leaflet before use.

**POM**

PL Number: 20620/0021  
PL Holder: NRIM Limited,  
Unit 15 Moorcroft,  
Harlington Road,  
Hillingdon, UB8 3HD, UK

CODE: GO/DRUGS/515

Batch:

Exp.:

JIE10057

## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Phenytoin Sodium 100mg Capsules (PL 20620/0021; UK/H/2203/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for the following:

- control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these
- the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Phenytoin Sodium 100mg Capsules have also been employed in the treatment of trigeminal neuralgia, but should be only used as second-line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Spain and Ireland as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Epanutin 100mg Hard Capsules (Pfizer Limited UK), which was first authorized in 25 October 1989.

Phenytoin is an anticonvulsant drug used in the treatment of epilepsy. It acts to suppress the abnormal brain activity seen in seizures by reducing electrical conductance between brain cells, by stabilising the inactive state of voltage-gated sodium channels. It is also useful in trigeminal neuralgia as second-line therapy.

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.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support this application, comparing the test product Phenytoin Sodium 100mg Capsules (NRIM Limited, U.K.) with the reference product Epanutin 100mg Hard Capsules (Pfizer Limited, U.K.). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of

current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 08 August 2011. After a subsequent national phase, a licence was granted in the UK on 13 September 2011.

**II. ABOUT THE PRODUCT**

<b>Name of the product in the Reference Member State</b>	Phenytoin Sodium 100mg Capsules
<b>Name(s) of the active substance(s) (INN)</b>	Phenytoin sodium
<b>Pharmacotherapeutic classification (ATC code)</b>	Hydantoin derivatives (N03AB)
<b>Pharmaceutical form and strength(s)</b>	Capsule, hard 100 mg
<b>Reference numbers for the Decentralised Procedure</b>	UK/H/2203/001/DC
<b>Reference Member State (RMS)</b>	United Kingdom
<b>Concerned Member States (CMS)</b>	Spain and Ireland
<b>Marketing Authorisation Number(s)</b>	PL 20620/0021
<b>Name and address of the Authorisation Holder</b>	NRIM Limited Unit 15 Moorcroft, Harlington Road, Hillingdon, UB8 3HD, United Kingdom

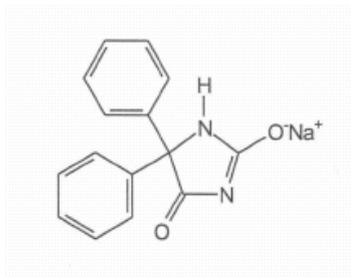
### III SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 QUALITY ASPECTS

##### ACTIVE SUBSTANCE

INN: Phenytoin sodium  
Chemical names: Sodium 4-oxo-5,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-olate  
2,4-imidazolidinedione, 5,5-diphenyl-, monosodium salt  
5,5-diphenylimidazolidine-2,4-dione, sodium salt  
5,5-diphenylhydantoin, sodium salt

Structure:



Molecular formula:  $C_{15}H_{11}N_2NaO_2$   
Molecular Mass: 274.3  
Appearance: A white or almost white crystalline, hygroscopic powder. Soluble in water and alcohol, practically insoluble in ether and methylene chloride.

Phenytoin sodium is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

#### MEDICINAL PRODUCT

##### Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely lactose monohydrate, magnesium stearate, gelatin, water, erythrosine (E127), quinoline yellow (E104), titanium dioxide (E171), sodium lauril sulphate, shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide. Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of quinoline yellow, erythrosine, shellac, potassium hydroxide, black iron oxide and propylene glycol, all excipients comply with their respective European Pharmacopoeia monograph. Propylene glycol complies with United States Pharmacopoeia monograph. Quinoline yellow and erythrosine are controlled to suitable in-house specifications. Black iron oxide (E172), shellac, and potassium hydroxide are controlled to National Formulary specifications. Quinoline yellow, erythrosine and black iron oxide are also in compliance with current European Directives concerning use of colouring agents in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin and lactose monohydrate, none of the excipients used contain materials of animal or human origin. All suppliers of gelatin have provided TSE Certificates of Suitability to show that appropriate measures are taken to reduce the risk of transmission of BSE/TSE, in line with current EU regulations. The supplier of lactose monohydrate has confirmed that milk is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

### **Pharmaceutical Development**

The objective of the development programme was to produce a safe, efficacious product that could be considered a generic medicinal product of Epanutin 100mg Hard Capsules (Pfizer Limited UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative dissolution profiles have been provided for this product and its respective reference product.

### **Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Process validation studies were conducted on two production-scale batches and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the Marketing Authorisation Holder that full process validation will be conducted on an additional production scale batch in accordance with the process validation protocol.

### **Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

The finished product is packaged in white, opaque high-density polyethylene (HDPE) tablet containers with a 38 mm white polypropylene child-resistant cap, in pack sizes of 84 capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions 'Do not store above 25°C. Store in the original package. Keep the container tightly closed in order to protect from light and moisture.'

**Bioequivalence/Bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**

The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Forms**

The MAA form is satisfactory.

**Expert Report**

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

The grant of a Marketing Authorisation is recommended.

### **III.2 NON-CLINICAL ASPECTS**

As the pharmacodynamic, pharmacokinetic and toxicological properties of phenytoin sodium are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product.

As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated and no Environmental Risk Assessment is necessary. A suitable justification has been provided for non-submission of an environmental risk assessment.

There is no objection to the approval of this product from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS

#### CLINICAL PHARMACOLOGY

##### Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open-label, balanced, randomised, single-dose, two-period, two-treatment, two-sequence, crossover study to compare the pharmacokinetics of the test product Phenytoin Sodium 3 x 100mg Capsules versus the reference product Epanutin 3 x 100mg Hard Capsules (Pfizer Limited, UK) in healthy adult male volunteers under fasted conditions.

All volunteers received a single oral dose (3x100mg) of either the test or the reference product with 240ml of water under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters pre- and up to 144 hours post dose. The washout period between the two treatment arms was at least 14 days.

The pharmacokinetic results for phenytoin sodium are presented below (non-transformed values; arithmetic mean  $\pm$  standard deviation, ratios and 90% confidence intervals):

Treatment	AUC <sub>0-t</sub> (ng/ml/h)	AUC <sub>0-∞</sub> (ng/ml/h)	C <sub>max</sub> (ng/ml)
Test	182231.9821 $\pm$ 78033.35877	192321.0489 $\pm$ 87917.18932	4695.3184 $\pm$ 1275.16953
Reference	183025.3106 $\pm$ 70480.19443	190529.7441 $\pm$ 71881.83704	4892.7116 $\pm$ 1326.43754
*Ratio (90% CI)	98.96 (93.77-104.43)	99.53 (94.23-105.13)	96.23 (91.68-101.00)
AUC <sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity AUC <sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours C <sub>max</sub> maximum plasma concentration			

*\*ln-transformed values*

The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference product for phenytoin sodium are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product Phenytoin Sodium 100mg Capsules (NRIM Limited) is bioequivalent to the reference product Epanutin 100mg Hard Capsules (Pfizer Limited UK).

#### EFFICACY

The efficacy of phenytoin sodium is well-known. No new efficacy data have been submitted and none are required for an application of this type.

#### SAFETY

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for an application of this type. No new or unexpected safety issues were raised by the bioequivalence data.

#### Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labels are clinically acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

### **Clinical Expert Report**

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

### **Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

### **Conclusion**

The grant of a Marketing Authorisation is recommended.

#### **IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT QUALITY**

The important quality characteristics of Phenytoin Sodium 100mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

#### **NON-CLINICAL**

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of phenytoin sodium are well-known, no additional data were required.

#### **EFFICACY**

With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type. Bioequivalence has been demonstrated between the applicant's 100mg capsules and the reference product.

#### **SAFETY**

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for an application of this type. No new or unexpected safety concerns arose from the bioequivalence study

#### **PRODUCT LITERATURE**

The SmPC, PIL and labelling are acceptable. The SmPC is consistent with these for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

#### **BENEFIT/RISK ASSESSMENT**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product is a generic medicinal product of the reference product, Epanutin 100mg Hard Capsules (Pfizer Limited UK). Extensive clinical experience with phenytoin sodium is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome