Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epanutin 100 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg Phenytoin Sodium
Each capsule also contains lactose monohydrate

For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard.
Product imported from the UK:
Half white and half orange capsules marked with “EPANUTIN 100” containing a white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Epanutin has also been employed in the treatment of trigeminal neuralgia but it 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

For oral administration only.

Dosage:

Dosage should be individualized as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. Epanutin 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 Epanutin 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.

Epanutin Capsules, Suspension and Infatabs:

Epanutin Capsules contain phenytoin sodium whereas Epanutin Suspension and Epanutin Infatabs contain phenytoin. Although 100mg of phenytoin sodium is equivalent to 92mg of phenytoin on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent.

Physicians should therefore exercise care in those situations where it is necessary to change the dosage form and serum level monitoring is advised.

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 the 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 Epanutin 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.

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.

4.3 Contraindications

Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin, or its inactive ingredients, 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.

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.

Drug rash with eosinophilia and systemic symptoms (DRESS) reflects a serious hypersensitivity reaction to drugs, characterized by skin rash, fever, lymph node enlargement, and internal organ involvement. Cases of DRESS have been noted in patients taking phenytoin.

Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals. If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.

Integumentary Effect

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Epanutin. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of skin rash and blisters, fever or other signs of hypersensitivity such as itching and should be monitored closely for skin reactions. Patients should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Epanutin treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Epanutin, Epanutin must not be re-started in this patient at any time.

If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further 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, hepatotoxicity, and Anticonvulsant Hypersensitivity Syndrome in black patients.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLAB gene, in patients using carbamazepine.

HLA-B*1502 may be associated with increased risk of developing SJS/TEN in patients of Thai and Han Chinese ancestry taking drugs associated with SJS/TEN, including 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 the 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 D_3. 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.

Phenytoin may cause lowered serum levels of folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary.

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

4.5 Interaction with other medicinal products and other forms of interaction

1. Drugs which may <u>increase</u> 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, fluoxetine, fluvoxamine, sertraline, H2-antagonists (e.g. cimetidine), halothane, isoniazid, methylphenidate, nifedipine, omeprazole, oestrogens, phenothiazines, phenylbutazone, salicylates, succinimides, sulphonamides, tolbutamide, trazodone, antineoplastic agents (such as fluorouracil) and viloxazine.

2. Drugs which may <u>decrease</u> 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 (see section **5.2 Pharmacokinetic Properties** – Pharmacokinetic Interaction).

3. Drugs which may either <u>increase</u> or <u>decrease</u> 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.

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

5. Drugs whose effect is <u>impaired</u> by phenytoin include:

Antifungal agents (e.g. azoles), antineoplastic agents (e.g. teniposide), calcium channel blockers, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, furosemide, lamotrigine, methadone, neuromuscular blockers, oestrogens, oral contraceptives, paroxetine, sertraline, quinidine, rifampicin, theophylline and vitamin D.

6. 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 Fertility, 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. Epanutin 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, 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, 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 K1 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

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

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, somnolence, drowsiness and vertigo. Dizziness, insomnia, transient nervousness, motor twitchings, taste perversion 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. Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported very rarely (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, 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.

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.

Drug rash with eosinophilia and systemic symptoms (DRESS). (see Section 4.4 **Special warnings and precautions for use,** under Anticonvulsant Hypersensitivity Syndrome (AHS).

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:
There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenytoin. The mechanism by which phenytoin affects bone metabolism has not been identified. Other disorders of bone metabolism such as hypocalcemia, hypophophatemia 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

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:

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

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.

Pharmacokinetic Interaction
Co-administration of nelfinavir tablets (1,250 mg twice a day) with phenytoin capsule (300 mg once a day) did not change the plasma concentration of nelfinavir. However, coadministration of nelfinavir reduced the AUC values of phenytoin (total) and free phenytoin by 29% and 28%, respectively (see section **4.5 Interaction with other medicinal products and other forms of interaction**).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Magnesium stearate
Sodium laurilsulfate

Shell
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)
Quinoline yellow (E104)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light

6.5 Nature and contents of container

White plastic container with white plastic cap, containing 84 capsules

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare,
Unit 4, Bradfield Road
Ruislip
Middlesex
HA4 0NU
UK

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/147/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th April 2011

10 DATE OF REVISION OF THE TEXT

December 2013