Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Musculoskeletal and connective tissue disorders	
Common	Elevations of CPK
Common	Muscle disorders, including myalgia and cramps*
Not known	Rhabdomyolysis

* In Phase III studies frequency observed in the lamivudine treatment group was not greater than observed in the placebo group In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paresthesia) have been reported. In patients with chronic hepatitis B there was no observed difference in incidence of these events between placebo and lamivudine treated patients.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been rare reports of lactic acidosis in patients receiving lamivudine for hepatitis B.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

4.9 Overdose

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

If overdose occurs the patient should be monitored and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group - Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors, ATC Code: J05AF05.

Lamivudine is an antiviral agent which is active against hepatitis B virus in all cell lines tested and in experimentally infected animals.

Lamivudine is metabolised by both infected and uninfected cells to the triphosphate (TP) derivative which is the active form of the parent compound. The intracellular half-life of the triphosphate in hepatocytes is 17-19 hours in vitro. Lamivudine-TP acts as a substrate for the HBV viral polymerase.

The formation of further viral DNA is blocked by incorporation of lamivudine-TP into the chain and subsequent chain termination.

Lamivudine-TP does not interfere with normal cellular deoxynucleotide metabolism. It is also only a weak inhibitor of mammalian DNA polymerases alpha and beta. Furthermore, lamivudine-TP has little effect on mammalian cell DNA content.

In assays relating to potential substance effects on mitochondrial structure and DNA content and function, lamivudine lacked appreciable toxic effects. It has a very low potential to decrease mitochondrial DNA content, is not permanently incorporated into mitochondrial DNA, and does not act as an inhibitor of mitochondrial DNA polymerase gamma.

Clinical experience

Experience in patients with HBeAg positive CHB and compensated liver disease: in controlled studies, 1 year of lamivudine therapy significantly suppressed HBV DNA replication [34-57 % of patients were below the assay detection limits (Abbott Genostics solution hybridization assay, LLOD < 1.6pg/ml)}, normalised ALT level (40-72 % of patients), induced HBeAg seroconversion (HBeAg loss and HBeAb detection with HBV DNA loss [by conventional assay], 16-18 % of patients), improved histology (38-52 % of patients had a ≥ 2 point decrease in the Knodell Histologic Activity Index [HAI]) and reduced progression of fibrosis (in 3-17 % of patients) and progression to cirrhosis.

Continued lamivudine treatment for an additional 2 years in patients who had failed to achieve HBeAg seroconversion in the initial 1 year controlled studies resulted in further improvement in bridging fibrosis. In patients with YMDD mutant HBV, 41/82 (50 %) patients had improvement in liver inflammation and 40/56 (71 %) patients without YMDD mutant HBV had improvement. Improvement in bridging fibrosis occurred in 19/30 (63 %) patients without YMDD mutant and 22/44 (50 %) patients with the mutant. Five percent (3/56) of patients without the YMDD mutant and 13 % (11/82) of patients with YMDD mutant showed worsening in liver inflammation compared to pre-treatment. Progression to cirrhosis occurred in 4/68 (6 %) patients with the YMDD mutant, whereas no patients without the mutant progressed to cirrhosis.

In an extended treatment study in Asian patients (NUCB3018) the HBeAg seroconversion rate and ALT normalisation rate at the end of the 5 year treatment period was 48 % (28/58) and 47 % (15/32), respectively. HBeAg seroconversion was increased in patients with elevated ALT levels; 77 % (20/26) of patients with pre-treatment ALT > 2 x ULN seroconverted. At the end of 5 years, all patients had HBV DNA levels that were undetectable or lower than pre-treatment levels.

Further results from the trial by YMDD mutant status are summarised in Table 2.

Table 2: Efficacy results 5 years by YMDD status (Asian Study) NUCB3018

Subjects, % (no.)		
YMDD mutant HBV status	YMDD [1]	Non-YMDD [1]
HBeAg seroconversion		
• All patients	38 (15/40)	72 (13/18)
• Baseline ALT ≤ 1 x ULN [2]	9 (1/11)	33 (2/6)

• Baseline ALT > 2 x ULN	60 (9/15)	100 (11/11)
Undetectable HBV DNA		
• Baseline [3]	5 (2/40)	6 (1/18)
• Week 260 [4]		
o Negative	8 (2/25)	0
o positive < baseline	92 (23/25)	100 (4/4)
o positive > baseline	0	0
ALT normalisation		
• Baseline		
o normal	28 (11/40)	33 (6/18)
o above normal	73 (29/40)	67 (12/18)
• Week 260		
o normal	46 (13/28)	50 (2/4)
o above normal < baseline	21 (6/28)	0
o above normal > baseline	32 (9/28)	50 (2/4)

1 Patients designated as YMDD mutant were those with ≥5% YMDD mutant HBV at any annual time-point during the 5-year period. Patients categorised as non-YMDD mutant were those with > 95% wild-type HBV at all annual time-points during the 5-year study period

2 Upper limit of normal

3 Abbott Genostics solution hybridisation assay (LLOD < 1.6 pg/ml

4 Chiron Quantiplex assay (LLOD 0.7 Meq/ml)

Comparative data according to YMDD status were also available for histological assessment but only up to three years. In patients with YMDD mutant HBV, 18/39 (46 %) had improvements in necroinflammatory activity and 9/39 (23 %) had worsening. In patients without the mutant, 20/27 (74 %) had improvements in necroinflammatory activity and 2/27 (7 %) had worsening.

Following HBeAg seroconversion, serologic response and clinical remission are generally durable after stopping lamivudine. However, relapse following seroconversion can occur. In a long-term follow-up study of patients who had previously seroconverted and discontinued lamivudine, late virological relapse occurred in 39 % of the subjects. Therefore, following HBeAg seroconversion, patients should be periodically monitored to determine that serologic and clinical responses are being maintained. In patients who do not maintain a sustained serological response, consideration should be given to retreatment with either lamivudine or an alternative antiviral agent for resumption of clinical control of HBV.

In patients followed for up to 16 weeks after discontinuation of treatment at one year, post-treatment ALT elevations were observed more frequently in patients who had received lamivudine than in patients who had received placebo. A comparison of post-treatment ALT elevations between weeks 52 and 68 in patients who discontinued lamivudine at week 52 and patients in the same studies who received placebo throughout the treatment course is shown in Table 3. The proportion of patients who had post-treatment ALT elevations in association with an increase in bilirubin levels was low and similar in patients receiving either lamivudine or placebo.

Table 3: Post-treatment ALT Elevations in 2 Placebo-Controlled Studies in Adults

Abnorma Value	Patients with ALT Elevation / Patients with Observations*	
	Lamivudine	Placebo
ALT ≥ 2 x baseline value	37/137 (27 %)	22/116 (19 %)
ALT ≥ 3 x baseline value†	29/137 (21 %)	9/116 (8 %)
ALT ≥ 2 x baseline value and absolute ALT > 500 IU/l	21/137 (15 %)	8/116 (7 %)

ALT ≥2 x baseline value; and bilirubin >2 x ULN and ≥2 x baseline value	1/137 (0.7 %)	1/116 (0.9 %)

* Each patient may be represented in one or more category.

† Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.

ULN Upper limit of normal.

Experience in patients with HBeAg negative CHB: initial data indicate the efficacy of lamivudine in patients with HBeAg negative CHB is similar to patients with HBeAg positive CHB, with 71 % of patients having HBV DNA suppressed below the detection limit of the assay, 67 % ALT normalization and 38 % with improvement in HAI after one year of treatment. When lamivudine was discontinued, the majority of patients (70 %) had a return of viral replication. Data is available from an extended treatment study in HBeAg negative patients (NUCAB3017) treated with lamivudine. After two years of treatment in this study, ALT normalisation and undetectable HBV DNA occurred in 30/69 (43 %) and 32/68 (47 %) patients respectively and improvement in necroinflammatory score in 18/49 (37 %) patients. In patients without YMDD mutant HBV, 14/22 (64 %) showed improvement in necroinflammatory score and 1/22 (5 %) patients worsened compared to pre-treatment. In patients with the mutant, 4/26 (15 %) patients showed improvement in necroinflammatory score and 8/26 (31 %) patients worsened compared to pre-treatment. No patients in either group progressed to cirrhosis.

Frequency of emergence of YMDD mutant HBV and impact on the treatment response: lamivudine monotherapy results in the selection of YMDD mutant HBV in approximately 24 % of patients following one year of therapy, increasing to 69 % following 5 years of therapy. Development of YMDD mutant HBV is associated with reduced treatment response in some patients, as evidenced by increased HBV DNA levels and ALT elevations from previous on-therapy levels, progression of signs and symptoms of hepatitis disease and/or worsening of hepatic necroinflammatory findings. The optimal therapeutic management of patients with YMDD mutant HBV has not yet been established (see section 4.4).

In a double-blind study in CHB patients with YMDD mutant HBV and compensated liver disease (NUC20904), with a reduced virological and biochemical response to lamivudine (n=95), the addition of adefovir dipivoxil 10 mg once daily to ongoing lamivudine 100mg for 52 weeks resulted in a median decrease in HBV DNA of 4.6 log10 copies/ml compared to a median increase of 0.3 log10 copies/ml in those patients receiving lamivudine monotherapy. Normalisation of ALT levels occurred in 31 % (14/45) of patients receiving combined therapy versus 6 % (3/47) receiving lamivudine alone. Viral suppression was maintained (follow-on study NUC20917) with combined therapy during the second year of treatment to week 104 with patients having continued improvement in virologic and biochemical responses.

In a retrospective study to determine the factors associated with HBV DNA breakthrough, 159 Asian HBeAg-positive patients were treated with lamivudine and followed up for a median period of almost 30 months. Those with HBV DNA levels greater than 200 copies/mL at 6 months (24 weeks) of lamivudine therapy had a 60 % chance of developing the YMDD mutant compared with 8 % of those with HBV DNA levels less than 200 copies/mL at 24 weeks of lamivudine therapy. The risk for developing YMDD mutant was 63% versus 13% with a cut off of 1000 copies/ml (NUCB3009 and NUCB3018).

Experience in patients with decompensated liver disease: placebo controlled studies have been regarded as inappropriate in patients with decompensated liver disease, and have not been undertaken. In non-controlled studies, where lamivudine was administered prior to and during transplantation, effective HBV DNA suppression and ALT normalisation was demonstrated. When lamivudine therapy was continued post transplantation there was reduced graft re-infection by HBV, increased HBsAg loss and on one-year survival rate of 76 – 100 %.

As anticipated due to the concomitant immunosuppression, the rate of emergence of YMDD mutant HBV after 52 weeks treatment was higher (36 % - 64 %) in the liver transplant population than in the immunocompetent CHB patients (14 % - 32 %).

Forty patients (HBeAg negative or HBeAg positive) with either decompensated liver disease or recurrent HBV following liver transplantation and YMDD mutant were enrolled into an open label arm of study NUC20904. Addition of 10 mg adefovir dipivoxil once daily to ongoing lamivudine 100mg for 52 weeks resulted in a median decrease in HBV DNA of 4.6 log10 copies/ml. Improvement in liver function was also seen after one year of therapy. This degree of viral suppression was maintained (follow-on study NUC20917) with combined therapy during the second year of treatment to week 104 and most patients had improved markers of liver function and continued to derive clinical benefit.

Experience in CHB patients with advanced fibrosis or cirrhosis: in a placebo-controlled study in 651 patients with clinically compensated chronic hepatitis B and histologically confirmed fibrosis or cirrhosis, lamivudine treatment (median duration 32 months) significantly reduced the rate of overall disease progression (34/436, 7.8 % for lamivudine versus 38/215, 17.7 % for placebo, p=0.001), demonstrated by a significant reduction in the proportion of patients having increased Child-Pugh scores (15/436, 3.4 % versus 19/215, 8.8 %, p=0.023) or developing hepatocellular carcinoma (17/436, 3.9 % versus 16/215, 7.4 %, p=0.047). The rate of overall disease progression in the lamivudine group was higher for subjects with detectable YMDD mutant HBV DNA (23/209, 11 %) compared to those without detectable YMDD mutant HBV (11/221, 5 %). However, disease progression in YMDD subjects in the lamivudine group was lower than the disease progression in the placebo group (23/209, 11 % versus 38/214, 18 % respectively). Confirmed HBeAg seroconversion occurred in 47 % (118/252) of subjects treated with lamivudine and 93 % (320/345) of subjects receiving lamivudine became HBV DNA negative (VERSANT [version 1], bDNA assay, LLOD < 0.7 MEq/ml) during the study.

Experience in children and adolescents: lamivudine has been administered to children and adolescents with compensated CHB in a placebo controlled study of 286 patients aged 2 to 17 years. This population primarily consisted of children with minimal hepatitis B. A dose of 3 mg/kg once daily (up to a maximum of 100 mg daily) was used in children aged 2 to 11 years and a dose of 100 mg once daily in adolescents aged 12 years and above. This dose needs to be further substantiated. The difference in the HBeAg seroconversion rates (HBeAg and HBV DNA loss with HBeAb detection) between placebo and lamivudine was not statistically significant in this population (rates after one year were 13 % (12/95) for placebo versus 22 % (42/191) for lamivudine; p=0.057). The incidence of YMDD mutant HBV was similar to that observed in adults, ranging from 19 % at week 52 up to 45 % in patients treated continuously for 24 months.

5.2 Pharmacokinetic properties

Absorption: Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85 %. Following oral administration, the mean time (tmax) to maximal serum concentrations (Cmax) is about an hour. At therapeutic dose levels i.e. 100 mg once daily, Cmax is in the order of 1.1-1.5 µg/ml and trough levels were 0.015-0.020 µg/ml.

Co-administration of lamivudine with food resulted in a delay of tmax and a lower Cmax (decreased by up to 47 %). However, the extent (based on the AUC) of lamivudine absorbed was not influenced, therefore lamivudine can be administered with or without food.

Distribution: From intravenous studies the mean volume of distribution is 1.3 l/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding to albumin.

Limited data shows lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean lamivudine CSF/serum concentration ratio 2-4 hours after oral administration was approximately 0.12.

Biotransformation: Lamivudine is predominately cleared by renal excretion of unchanged substance. The likelihood of metabolic substance interactions with lamivudine is low due to the small (5-10 %) extent of hepatic metabolism and the low plasma protein binding.

Elimination: The mean systemic clearance of lamivudine is approximately 0.3 l/h/kg. The observed half-life of elimination is 5 to 7 hours. The majority of lamivudine is excreted unchanged in the urine via glomerular filtration and active secretion (organic cationic transport system). Renal clearance accounts for about 70 % of lamivudine elimination.

Special populations:

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction in patients with a creatinine clearance of < 50 ml/min is necessary (see section 4.2).

The pharmacokinetics of lamivudine are unaffected by hepatic impairment. Limited data in patients undergoing liver transplantation show that impairment of hepatic function does not impact significantly on the pharmacokinetics of lamivudine unless accompanied by renal dysfunction.

In elderly patients the pharmacokinetic profile of lamivudine suggests that normal ageing with accompanying renal decline has no clinically significant effect on lamivudine exposure, except in patients with creatinine clearance of < 50 ml/min (see section 4.2).

5.3 Preclinical safety data

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reduction in liver weights. Reduction of erythrocytes and neutrophil counts were identified as the

effects most likely to be of clinical relevance. These events were seen infrequently in clinical studies.

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues showed activity in an in vitro cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic in vivo at doses that gave plasma concentrations around 60-70 times higher than the anticipated clinical plasma levels. As the in vitro mutagenic activity of lamivudine could not be confirmed by in vivo tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

Reproductive studies in animals have not shown evidence of teratogenicity and showed no effect on male or female fertility. Lamivudine induces early embryolethality when administered to pregnant rabbits at exposure levels comparable to those achieved in man, but not in the rat even at very high systemic exposures.

The results of long term carcinogenicity studies with lamivudine in rats and mice did not shown any carcinogenic potential.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Isomalt (E953)

Crospovidone Type A

Magnesium stearate (E572)

Coating

Hypromellose 6cp (E464)

Titanium dioxide (E171)

Macrogol 400

Polysorbate 80 (E433)

Iron oxide red (E172)

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Alu-Alu blister pack: 14, 28, 30, 56, 60, 84, 90 and 120 film-coated tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Sandoz Limited

Frimley Business Park,

Frimley,

Camberley,

Surrey,

GU16 7SR.

United Kingdom

8. Marketing authorisation number(s)
PL 04416/1359

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation: 05 June 2013

10. Date of revision of the text
06/2013

Epanutin capsules 25, 50 and 100mg
Table of Contents
1. Name of the medicinal product
Epanutin 25 mg Hard Capsules

Epanutin 50 mg Hard Capsules

Epanutin 100 mg Hard Capsules

2. Qualitative and quantitative composition
Each capsule contains 25 mg phenytoin sodium.

Each capsule also contains 66.857 mg lactose monohydrate

Each capsule contains 50mg phenytoin sodium

Each capsule also contains 90.71 mg lactose monohydrate

Each capsule contains 100mg phenytoin sodium

Each capsule also contains 96.15 mg lactose monohydrate

For full list of excipients, see Section 6.1

3. Pharmaceutical form
Capsules, hard

Epanutin Capsules 25mg: A white powder in a No 4 hard gelatin capsule with a white opaque body and blue-violet cap, radially printed 'EPANUTIN 25'.

Epanutin Capsules 50mg: A white powder in a No 4 hard gelatin capsule with a white opaque body and a flesh-coloured transparent cap, radially printed 'EPANUTIN 50'.

Each capsule contains 100mg: A white powder in a No 3 hard gelatin capsule with a white opaque body and orange cap, radially printed 'EPANUTIN 100'.

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 individualised 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 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 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 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 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, 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

1. 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, fluoxetine, fluvoxamine, sertraline, H2-antagonists e.g. cimetidine,, halothane, isoniazid, methylphenidate, nifedipine, omeprazole, oestrogens, phenothiazines, phenylbutazone, salicylates, succinimides, sulphonamides, tolbutamide, trazodone and viloxazine.

2. Drugs which may decrease phenytoin serum levels include:

Folic acid, reserpine, rifampicin, sucralfate, theophylline and vigabatrin.

Serum levels of phenytoin can be reduced by concomitant use of the herbal 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.

3. 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.

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

5. Drugs whose effect is impaired by phenytoin include:

Antifungal agents (e.g. azoles), antineoplastic agents, 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 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, 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 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

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, 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, 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: 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.

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

25mg

Core:

Lactose monohydrate

Magnesium stearate

Shell:

Gelatin

Erythrosine (E127)

Patent blue V (E131)

Titanium dioxide (E171)

Sodium laurilsulfate

Printing Ink:

Shellac

Black iron oxide (E172)

Propylene glycol

50mg

Core:

Lactose monohydrate

Magnesium stearate

Shell:

Gelatin

Erythrosine (E127)

Quinoline yellow (E104)

Titanium dioxide (E171)

Sodium laurilsulfate

Printing ink:

Shellac

Black iron oxide (E172)

Propylene glycol

100mg

Core:

Lactose monohydrate

Magnesium stearate

Shell:

Gelatin

Erythrosine (E127)

Quinoline yellow (E104)

Titanium dioxide (E171)

Sodium laurilsulfate

Printing ink:

Shellac

Black iron oxide (E172)

Propylene glycol

6.2 Incompatibilities
None known

6.3 Shelf life
18 months (25mg)

36 months (50mg)

36 months (100mg)

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
25mg

White HDPE container with a white polypropylene child resistant cap, containing 28 or 500 capsules. An activated silica gel dessicant, within the HDPE canister, is included in each bottle

50mg

White HDPE container with a white polypropylene child resistant cap, containing 28, 50, 100 or 500 capsules. An activated silica gel dessicant, within the HDPE canister, is included in each bottle

100mg

White HDPE container with a white polypropylene child resistant cap, containing 50, 84, 100, 500 or 1000 capsules. An activated silica gel dessicant, within the HDPE canister, is included in each bottle

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder
Pfizer Limited
Ramsgate Road

Sandwich

Kent

CT13 9NJ

United Kingdom

8. Marketing authorisation number(s)
PL 00057/0522 (25mg)

PL 00057/0523 (50mg)

PL 00057/0524 (100mg)

9. Date of first authorisation/renewal of the authorisation
1st March 2004 (25mg)

1st March 2004 (50mg)

1st March 2004 (100mg)

10. Date of revision of the text
29 February 2012

Ref: EP 18_0 UK