SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenytoin Hikma 50 mg / ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 50 mg phenytoin sodium, equivalent to 46 mg phenytoin.

One 5 ml ampoule contains 250 mg phenytoin sodium, equivalent to 230 mg phenytoin.

Excipients with known effect:

Each 5 ml ampoule contains:

Ethanol (394 mg)

Propylene glycol (2072 mg)

Sodium (0.517 mg - 0.776 mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear and colourless solution with pH range of 11.5 12.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- *Status epilepticus* and series of seizures

- Prophylaxis of seizures occurring in connection with neurosurgery.

N.B.

Phenytoin Hikma is not effective in absence status epilepticus or in the prophylaxis and treatment of febrile convulsions.

4.2 Posology and method of administration

Dosage instructions
The therapeutic range for plasma concentration is generally between 10 and 20 micrograms/ml phenytoin; concentrations over 25 micrograms/ml phenytoin may be in the toxic range.

***Status epilepticus* and series of seizures**
Continuous monitoring of ECG, blood pressure and neurological status and regular determination of plasma phenytoin concentrations is essential. In addition, resuscitation facilities should be readily available.

Adults and adolescents over 12 years of age
The initial dose is 1 ampoule of Phenytoin Hikma (equivalent to 230 mg phenytoin), administered at a maximum rate of 0.5 ml/min (equivalent to 23 mg phenytoin per minute). If the seizures do not stop after 20 to 30 minutes, the dose can be repeated.

If the seizures stop, a dose of 1 ampoule Phenytoin Hikma (equivalent to 230 mg phenytoin) can be given every 1.5 to 6 hours up to a maximum daily dose of 17 mg/kg bodyweight (or 6 ampoules - equivalent to 1380 mg phenytoin), to achieve rapid saturation.

At a maximum daily dose of 17 mg/kg bodyweight, this is equivalent to

Bodyweight	*Ampoules*	*Phenytoin*
41 kg	3	690 mg
54 kg	4	920 mg
68 kg	5	1150 mg
81 kg	6	1380 mg

Children up to 12 years of age
On day 1 the maximum daily dose is 30 mg/kg bodyweight, on day 2 20 mg/kg bodyweight, on day 3 10 mg/kg bodyweight. The maximum injection rate is 1 mg/kg bodyweight per minute.

Day 1
At a maximum daily dose of 30 mg/kg bodyweight, this is equivalent to

Bodyweight	*Ampoules*	*Phenytoin*
8 kg	1	230 mg
15 kg	2	460 mg
23 kg	3	690 mg
31 kg	4	920 mg
38•kg	5	1150 mg
46 kg	6	1380 mg

Day 2
At a maximum daily dose of 20 mg/kg bodyweight, this is equivalent to

Bodyweight	*Ampoules*	*Phenytoin*
12 kg	1	230 mg
23 kg	2	460 mg

35 kg	3	690 mg
46 kg	4	920 mg

Day 3
At a maximum daily dose of 10 mg/kg bodyweight, this is equivalent to

Bodyweight	*Ampoules*	*Phenytoin*
23 kg	1	230 mg
46 kg	2	460 mg

Prophylaxis of seizures
Adults and adolescents over 12 years of age receive 1 to 2 ampoules of Phenytoin Hikma (equivalent to 230 to 460 mg phenytoin) daily at a maximum rate of injection of 0.5 ml/min (equivalent to 23 mg phenytoin per minute).

Children up to 12 years of age receive 5 to 6 mg/kg bodyweight. Rate of injection is reduced according to the weight/age of the child.

At a daily dose of 5 mg/kg bodyweight, this is equivalent to

Bodyweight	*ml*	*Phenytoin*
9 kg	1	46 mg
18 kg	2	92 mg
28 kg	3	138 mg
37 kg	4	184 mg
46 kg	5	230 mg

At a daily dose of 6 mg/kg bodyweight, this is equivalent to

Bodyweight	*ml*	*Phenytoin*
8 kg	1	46 mg
15 kg	2	92 mg
23 kg	3	138 mg
31 kg	4	184 mg
38 kg	5	230 mg
46 kg	6	276 mg

Duration of administration
Duration of administration is dependent on the underlying disease and the course of the illness. If the medicinal product is well-tolerated, it can be used indefinitely.

Switching preparations
Due to the relatively narrow therapeutic range and the varying bioavailability of the numerous pharmaceutical preparations, when changing from one preparation to another containing phenytoin, the phenytoin-plasma concentrations must be monitored closely. If the dose is kept the same, steady state (constant plasma concentration) can be expected after 5 to 14 days.

After switching to an oral formulation, treatment should be monitored monthly during the first three months, and then six-monthly. Phenytoin-plasma concentration, blood count, liver enzymes (GOT, GPT, gamma-GT), alkaline phosphatase and additionally in children thyroid function should be monitored.

Therefore the dose (if possible) should be reduced slowly and the new antiepileptic medicinal product started at a low dose and gradually increased. Abrupt withdrawal of Phenytoin Hikma may increase seizure frequency or lead to *status epilepticus*.

Additional information on special populations

Patients with renal/hepatic impairment:
There is no reference for dosage adjustment for this special group; however, caution should be taken in patients with renal and hepatic disease (see section 4.4). Impaired renal and hepatic functions require careful monitoring.
Phenytoin Hikma should be used with caution in patients with hypoproteinaemia, as reduced plasma protein binding may lead to an increase in the free phenytoin fraction (without increasing the total serum concentration of phenytoin). Increase in the free phenytoin fraction may enhance the risk of nervous system disorders.

Elderly (over 65 years):
As for adults; however, complications may occur more readily in elderly patients.

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

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

Method of administration
The solution for injection is for intravenous use only as absorption is delayed and unreliable after intramuscular administration. Phenytoin Hikma should be injected slowly directly into a large vein through a large-gauge needle or intravenous catheter. Subcutaneous or venous perivascular or intra-arterial injection should be avoided, as the alkaline phenytoin solution for injection can cause tissue necrosis. The solution for injection must not be mixed with other solutions, as phenytoin can crystallise out.

Before use, the ampoules should be checked for precipitation and discolouration. The product should not be used if a precipitate or haziness develops in the solution in the ampoule.
Phenytoin Hikma is suitable for use as long as it remains free of haziness and precipitate. A precipitate might form if the product has been kept in a refrigerator or freezer. This precipitate will dissolve if allowed to stand at room temperature. The product will then be suitable for use.
Only a clear solution should be administered. A slight yellow discoloration has no effect on the efficacy of this solution.

For single use only.
Once it has been broken open, Phenytoin Hikma should be used immediately.

Because of the risk of local toxicity, intravenous phenytoin should be administered directly into a large peripheral or central vein through a large-gauge catheter. Prior to the administration, the patency of the IV catheter should be tested with a flush of sterile saline. Each injection of parenteral phenytoin should then be followed by a flush of sterile saline through the same catheter to avoid local venous irritation due to the alkalinity of the solution (see 4.4. Special warnings and precautions for use, Local Toxicity (including Purple Glove Syndrome)).

4.3 Contraindications

Phenytoin Hikma is contraindicated in patients who are hypersensitive to phenytoin, or any of the excipients listed in section 6.1, or other hydantoins. Intra-arterial administration must be avoided in view of the high pH of the preparation.

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

Co-administration of phenytoin is contraindicated with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

Phenytoin Hikma should not be administered:

- if the patient already has severe damage to the blood cells and bone marrow
- within the first three months after myocardial infarction and in case of cardiac output failure (left ventricular ejection fraction < 35%).

4.4 Special warnings and precautions for use

Phenytoin Hikma should not be used in case of:

- cardiac insufficiency
- impaired pulmonary function
- severe hypotension (systolic blood pressure less than 90 mm Hg)
- Bradycardia (less than 50 beats per minute)
- sinuatrial block and grade I AV block
- atrial fibrillation and atrial flutter

General:

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

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

Phenytoin Hikma is not indicated for seizures due to hypoglycaemia or other metabolic causes.

The most notable signs of toxicity associated with the intravenous use of this drug are cardiovascular collapse and/or central nervous system depression. Severe cardiotoxic reactions and fatalities due to depression of atrial and ventricular conduction and ventricular fibrillation, respiratory arrest and tonic seizures have been reported particularly in older people or gravely ill patients, if the preparation is given too rapidly or in excess.

Hypotension usually occurs when the drug is administered rapidly by the intravenous route. Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing and in rare instances has led to amputation.

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

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

The intramuscular route is not recommended for the treatment of status epilepticus because of slow absorption. Serum levels of phenytoin in the therapeutic range cannot be rapidly achieved by this method.

Phenytoin Hikma may precipitate or aggravate absence seizures and myoclonic seizures.

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic 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 antiepileptic drug not belonging to the hydantoin chemical class.

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

Herbal preparations containing St. John's Wort (Hypericum perforatum) should not be used while taking phenytoin due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin (see section 4.5).

Phenytoin Hikma is highly protein bound and extensively metabolised by the liver.

Reduced maintenance 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 10-20 mg/l. Dosage should not exceed the minimum necessary to control convulsions.

Case-control, genome-wide association studies in Taiwanese, Japanese, Malaysian and Thai patients have identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant.

CYP2C9 metabolism:

Phenytoin is metabolised by the CYP450 CYP2C9 enzyme. Patients who are carriers of the decreased function CYP2C9*2 or CYP2C9*3 variants (intermediate or poor metabolisers of CYP2C9 substrates) may be at risk of increased phenytoin plasma concentrations and subsequent toxicity. In patients who are known to be carriers of the decreased function CYP2C9*2 or *3 alleles, close monitoring of clinical response is advised and monitoring of plasma phenytoin concentrations may be required.

Suicide:

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.

Cardiovascular Effect:

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

Local Toxicity (including Purple Glove Syndrome):

Soft tissue irritation and inflammation have occurred at the site of injection with and without extravasation of intravenous phenytoin.

Edema, discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin injection. Soft tissue irritation may vary from slight tenderness to extensive necrosis, and sloughing of skin. The syndrome may not develop for several days after injection. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting, and, in rare cases, amputation.

Improper administration including subcutaneous or perivascular injection should be avoided.

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms (HSS/DRESS):

Hypersensitivity Syndrome (HSS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin. Some of these events have been fatal or life threatening.

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, haematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leucocytosis, and eosinophilia. 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. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin Hikma should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past (with phenytoin or other anticonvulsant drugs), patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Serious Skin Reactions:

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Phenytoin Hikma. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of HSS/DRESS (see section 4.4– HSS/DRESS), occurrence of rash 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, Phenytoin Hikma 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 Phenytoin Hikma, Phenytoin Hikma must not be re-started in this patient at any time.

If the rash is of a milder type (measles-like or scarlantiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher 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 HLA-B*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.

Literature reports suggest that the combination of phenytoin, cranial irradiation, and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme and/or SJS and/or TEN.

Hepatic Injury:

The liver is the chief site of biotransformation of phenytoin.

Toxic hepatitis and liver damage have been reported and may, in rare cases, be fatal.

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually occur within the first 2 months of treatment and may be associated with HSS/DRESS (see section 4.4 Special Warnings and Special Precautions for Use – HSS/DRESS).

Patients with impaired liver function, older patients, or those who are gravely ill may show early signs of toxicity.

The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, phenytoin should be immediately discontinued and not re-administered.

The risk of hepatotoxicity and other hypersensitivity reactions to phenytoin may be higher in black patients.

Haematopoietic System:

Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis and pancytopenia with or without bone marrow suppression.

Central Nervous System Effect:

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.

Metabolic Effect:

Phenytoin may affect glucose metabolism and inhibit insulin release.

Hyperglycaemia has been reported. Caution is advised when treating diabetic patients.

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

Women of childbearing potential:

Phenytoin may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for major congenital malformations and other adverse development outcomes (see Section 4.6). The magnitude of the risk to the foetus is unknown

when phenytoin use is of short duration (emergency situations).

Phenytoin should not be used in women of childbearing potential except where there is a clinical need and when possible, the woman should be informed of the potential risk to the foetus associated with the use of phenytoin during pregnancy. In emergency situations, the risk of harm to the foetus should be assessed in view of the risk of seizures for both the foetus and the pregnant woman.

Before the initiation of treatment with phenytoin in a woman of childbearing potential, pregnancy testing should be considered.

Due to enzyme induction, Phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives (see Sections 4.5 and 4.6).

Laboratory Tests:

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

Important information regarding treatment

Patients who suffer from genetically determined slow hydroxylation may develop signs of overdose even at moderate doses. The dose should be reduced and phenytoin-plasma concentrations checked.

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

• Sodium: Phenytoin Hikma contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially “sodium-free”

• Propylene glycol

May cause alcohol-like symptoms

• Ethanol: This medicinal product contains 10 vol % ethanol (alcohol), i.e. up to 394 mg per dose, equivalent to 10 ml beer, 4.17 ml wine per dose.

Harmful to those suffering from alcoholism.

To be taken into account in pregnant of breast-feeding women, children and high risk groups such as patients with liver disease, or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions:

Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome (CYP) P450 enzymes CYP2C9 and CYP2C19 and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes and may reduce the levels of drugs metabolized by these enzymes.

Concomitant administration of phenytoin and valproate has been associated with an increased risk of valproate-associated hyperammonaemia. Patients treated concomitantly with these two drugs should be monitored for signs and symptoms of hyperammonaemia.

There are many drugs which may increase or decrease serum phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

The most commonly occurring drug interactions are listed below.

Drugs which may increase phenytoin serum levels

Table 1 summarizes the drug classes which may potentially increase phenytoin serum levels.

Table 1 Drugs Which May Increase Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
Analgesic/Anti-inflammatory agents	azapropazone phenylbutazone salicylates

Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides topiramate
Antifungal agents	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastic agents	fluorouracil capecitabine
Benzodiazepines/Psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine
Calcium channel blockers/Cardiovascular agents	amiodarone dicumarol diltiazem nifedipine ticlopidine
H_2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	oestrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

Drugs which may decrease phenytoin serum levels

Table 2 summarizes the drug classes which may potentially decrease phenytoin serum levels.

Table 2 Drugs Which May Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (chronic intake)	
Antibacterial agents	rifampin ciprofloxacin
Anticonvulsants	vigabatrin
Antineoplastic agents	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiretrovirals	fosamprenavir nelfinav ritonavir
Bronchodilators	theophylline
Cardiovascular agents	reserpine
Folic Acid	folic acid
Hyperglycemic agents	diazoxide
St. John's Wort	St. John's wort

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. Johns 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.

Drugs which may increase or decrease phenytoin serum levels

Table 3 summarizes the drug classes which may either increase or decrease phenytoin serum levels.

Table 3 Drugs Which May Increase or Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Antibacterial agents	ciprofloxacin
Anticonvulsants	carbamazepine phenobarbital sodium valproate valproic acid
Antineoplastic agents	
Psychotropic agents	chlordiazepoxide diazepam phenothiazines

Drugs whose serum levels and/or effects may be altered by phenytoin

Table 4 summarizes the drug classes whose serum levels and/or effects may be altered by phenytoin.

Table 4 Drugs Whose Serum Levels and/or Effects May be Altered by Phenytoin

Drug Classes	Drugs in each Class (such as)
Antibacterial agents	doxycycline rifampin tetracycline
Anticonvulsants	carbamazepine lamotrigine phenobarbital sodium valproate valproic acid lacosamide
Antifungal agents	azoles posaconazole voriconazole
Antihelmintics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	oestrogens oral contraceptives

Hyperglycemic agents	diazoxide
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral anticoagulants	rivaroxaban dabigatran apixaban edoxaban
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Platelet aggregation inhibitors	ticagrelor
Psychotropic agents/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamin D	vitamin D

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:

Eslicarbazepine: In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite, eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of Zebinix may need to be increased and the dose of phenytoin may need to be decreased".

*Zonisamide:*Enzyme induction: Exposure to zonisamide is lower in epileptic patients receiving
CYP3A4-inducing agents such as phenytoin. These effects are unlikely to be of clinical significance when zonisamide is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the zonisamide dose may be required.
Topiramate: Phenytoin and carbamazepine decrease the plasma concentration of topimarate. The addition or withdrawal of phenytoin or carbamazepine to Topamax therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect.
Tigabine: Anti-epileptic agents which induce hepatic enzymes (CYP 450) such as phenytoin, enhance the metabolism of tiagabine. In case of combination with one or several of these drugs (anti-epileptic agents, rifampicine), the dose of

tiagabine could be adapted: increase of daily dose and/or more frequent administration in order to achieve the clinical response.

Drug/Laboratory Test Interactions:
Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result of enhanced peripheral metabolism.

These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hypothyroidism.

It may, however, produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

Additional administration of valproic acid or increasing the dose of valproic acid can increase the amount of free phenytoin (concentration of non protein-bound portion) without increasing the serum level of total phenytoin. This can increase the risk of undesirable effects, especially brain damage (see section 4.8).
Patients on anticoagulants are advised to have regular checks of blood coagulation time (INR). The toxicity of methotrexate can be increased. The effect of phenytoin can be reduced by simultaneous intake of folic acid.

4.6 Fertility, pregnancy and lactation

Pregnancy

Phenytoin crosses the placenta in humans.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, phenytoin exposure during pregnancy is associated with a frequency of major malformations 2 to 3 times higher than that of the general population, which has a frequency of 2-3%. Malformations such as orofacial clefts, cardiac defects, craniofacial defects, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Fetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used phenytoin alone or in combination with other AEDs during pregnancy. Studies related to the risk of

neurodevelopmental disorders in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded.

Phenytoin should not be used during pregnancy except where there is a clinical need and when possible, the woman is made aware of the risk of potential harm to the foetus.

Women of childbearing potential should be advised of the necessity of carefully planning and regular monitoring of any pregnancy and that the efficacy of oral contraceptives may be reduced (see section 4.5).
If treatment is considered essential, phenytoin should preferably be prescribed as monotherapy and at the lowest effective dose, because the incidence of birth defects increases with multiple antiepileptic therapy and/or increasing dose.
No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.
In considering the use of Phenytoin Hikma intravenously in the management of status epilepticus in pregnancy, the following information should be weighed in assessing the risks and the benefits. The potential adverse effects upon the foetus of status epilepticus, specifically hypoxia, make it imperative to control the condition in the shortest possible time.

An increase in seizure frequency during pregnancy occurs in a proportion of patients, because of altered phenytoin absorption or metabolism.

The plasma concentration of phenytoin may decline during pregnancy, while reaching original levels postpartum. Therefore, periodic measurements of phenytoin plasma concentrations should be performed to guide appropriate dose adjustments for maintaining adequate seizure control.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth.

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

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

4.7 Effects on ability to drive and use machines

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machines) as treatment with phenytoin may cause central nervous system adverse effects such as dizziness and drowsiness (see section 4.8).

4.8 Undesirable effects

The following adverse reactions have been reported with phenytoin (frequency unknown – cannot be estimated from available data):

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

Blood and lymphatic system disorders:
Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression and aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. Pure red cell aplasia has been reported with a frequency not known.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g. fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.
Frequent blood counts should be carried out during treatment with phenytoin.

Immune system reactions:
Anaphylactoid reaction and anaphylaxis.

Hypersensitivity syndrome/Drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) (see section 4.4) 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.

Endocrine disorders
Disturbance of thyroid function may occur, especially in children

Nervous system disorders:
Adverse reactions in this body system are common and are usually dose-related. Reactions include nystagmus, diplopia, ataxia, slurred speech, decreased coordination, mental confusion, memory disorder, cognitive disorder, paraesthesia, somnolence, drowsiness and vertigo. Dizziness, insomnia, transient nervousness,

increasing irritability, motor twitchings, taste perversion and headache have also been observed.

There have also been rare reports of phenytoin-induced dyskinesia, including chorea, dystonia, tremor, and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdosage or long-term plasma concentrations of phenytoin above 25 μg/ml. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.
Long-term treatment with phenytoin concomitant with other anticonvulsive drugs, especially velproic acied, may lead to signs of encephalopathy: increased seizure frequency, listlessness, stupor, muscular hypoptonia, choreatiform dyskinesias and severe general changes on the EEG.
Tonic seizures have also been reported.

Cardiac disorders:
Rare – asystole due to inhibition of the sinus node, conduction blockade and suppression of the ventricular escape rhythm in patients with total AV block, especially when phenytoin is administered intravenously. Proarhythmic effects in the form of changes or increases in cardiac arrythmias can occur which can lead to severe impairment of cardiac activity or even cardiac arrest. With intravenous administration in particular, decreased blood pressure, deterioration in existing heart and respiratory failure can occur. In isolated cases ventricular fibrillation has been triggered. Atrial fibrillation and flutter is not cured by phenytoin. However, as AV node refractory time can be shortened, acceleration in ventricular rate is possible.
Severe cardiotoxic reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in older people or gravely ill patients.

Respiratory, thoracic and mediastinal disorders:
Alterations in respiratory function including respiratory arrest may occur.
Pneumonitis.

Gastrointestinal disorders:
Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, constipation.

Skin and subcutaneous tissue disorders:
Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common. Other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus. Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis
(TEN) have been reported very rarely (see section 4.4).
Hyperpigmentation (chloasma).

Musculoskeletal and connective tissue disorders:
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.

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

Renal and urinary disorders:
Interstitial nephritis.

General disorders and administration site conditions:
Local irritation, inflammation, tenderness, necrosis, and sloughing of skin have been reported with or without extravasation of intravenous phenytoin. Edema, discoloration and pain distal to the site of injection (described as “purple glove syndrome”) have also been reported (see section **4.4**).
Exhaustion

Paediatric population
The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

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, Website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of an 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, diplopia, tremor, vertigo, nausea, stomach trouble, cerebellar ataxia and dysarthria. Longer lasting overdose may present with stare gaze, loss of appetite, vomiting, weight loss, apathia, sedation, disturbance of perception and/or consciousness, seizures. Irreversible cerebellar impairment may occur. 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.

Attempts to relate serum levels of the drug to toxic effects have shown wide interpatient variation. Nystagmus on lateral gaze usually appears at 20 mg/l, and ataxia at 30 mg/l, dysarthria and lethargy appear when the serum concentration is >40 mg/l, but a concentration as high as 50 mg/l has been reported without evidence of toxicity.

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

Treatment of overdose:
Treatment is non-specific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed.

Haemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of the presence of other CNS depressants, including alcohol, should be borne in mind.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC-Code: N03AB02.

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

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

The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated, however, possible contributory effects include:
1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation.
2. Post-synaptic action to enhance GABA-mediated inhibition and reduce excitatory synaptic transmission.
3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter.

5.2 Pharmacokinetic properties

Absorption
After injection phenytoin is distributed into body fluids including CSF.

Distribution
Its volume of distribution has been estimated to be between 0.52 and 1.19 litres/kg, and it is highly protein bound (usually 90% in adults).

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

Biotransformation
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.

Elimination
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

Effects in non-clinical studies were observed only at exposures considered 3-4 times in excess of the maximum human exposure indicating limited relevance to clinical use (see also sections 4.8 and 4.9).

Apart from a number of negative findings on mutagenicity, there is evidence that phenytoin induces chromosome mutations. It was not possible to make any further evaluation from these studies owing to their poor quality. Malignant and benign proliferative changes of the lymphatic system have been observed in long-term studies in mice. The significance of this observation in humans is unclear.

Phenytoin is teratogenic in a variety of species including humans (see also section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol

Ethanol (96%)

Sodium hydroxide (for pH-adjustment)

Water for injection

6.2 Incompatibilities

Phenytoin Hikma must not be mixed with other medicinal products as the phenytoin acid precipitates out.

6.3 Shelf life

2 years

After first opening: Phenytoin Hikma should be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent breakable ampoules made from type I glass.

Pack sizes: 5 ampoules or 50 (10x5) ampoules.

6.6 Special precautions for disposal

Before use, the ampoules should be checked for precipitation and discolouration.

The product should not be used if a precipitate or haziness develops in the solution in the ampoule.

Phenytoin Hikma is suitable for use as long as it remains free of haziness and precipitate. A precipitate might form if the product has been kept in a refrigerator or freezer. This precipitate will dissolve if allowed to stand at room temperature. The product will then be suitable for use.

Only a clear solution should be administered. A slight yellow discoloration has no effect on the efficacy of this solution.

For single use only. Any unused product should be discarded.

7 MARKETING AUTHORISATION HOLDER

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