

# NEW ZEALAND DATASHEET

## Phenytoin Sandoz

*Phenytoin Sodium Ph Eur solution for injection, 50 mg/ml*

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### Presentation

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Phenytoin Sandoz injection is a sterile clear, colourless solution with a pH between 11.5 to 12.1 and contains phenytoin sodium 50 mg/ml. Phenytoin Sandoz injection is packaged in glass ampoules containing phenytoin sodium 100 mg in 2 ml or 250 mg in 5 ml.

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### Uses

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#### **Actions**

Phenytoin sodium is a hydantoin derivative anticonvulsant.

#### **Pharmacotherapeutic group**

N03AB02 Antiepileptics: hydantoin derivatives, phenytoin.

#### **Mechanism of action**

Phenytoin sodium inhibits the spread of seizure activity in the motor cortex. Epileptic seizures are thought to occur through the development of excessive central excitability due to post tetanic potentiation, which is blocked by phenytoin.

The antiarrhythmic action of phenytoin sodium may be attributed to the normalisation of influx of sodium and calcium to cardiac Purkinje fibres. Abnormal ventricular automaticity and membrane responsiveness are decreased. It also shortens the refractory period, and therefore shortens the QT interval and the duration of the action potential.

#### **Pharmacodynamic effects**

The primary target of phenytoin in the central nervous system appears to be sodium channels in depolarising neurones, where phenytoin binds and blocks sodium influx, reducing neuronal excitability and the spread of electrical activity characteristic of epileptic seizures. Phenytoin may also suppress sodium action potentials by stimulating the sodium pump. It appears that by promoting sodium efflux from neurons, phenytoin sodium tends to stabilise the threshold against hyperexcitability caused by environmental changes or excessive stimulation capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation of synapses. Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin thereby reduces the over-activity of brain stem centres responsible for the tonic phase of grand mal seizures.

Other mechanisms possibly contributing to the antiepileptic activity of phenytoin include inhibition of neuronal calcium influx, enhancement of GABA neurotransmission, block of ionotropic receptors for glutamate (a transmitter implicated in seizure activity) and an action at central sigma binding sites.

Hydantoin induces production of liver microsomal enzymes, thereby accelerating the metabolism of concomitantly administered drugs.

#### **Onset and duration of action**

The onset of action after an intravenous dose is 30 to 60 minutes and the effect persists up to 24 hours.

## **Pharmacokinetics**

Optimum control without clinical signs of toxicity occurs most often with plasma levels between 10 and 20 mcg/ml. In renal failure or hypoalbuminaemia, 5 to 12 mcg/ml or even less may be therapeutic.

### **Absorption**

Absorption from an intravenous dose of phenytoin is immediate and bioavailability from the intravenous route is essentially 100%.

### **Distribution**

Phenytoin is distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile, and breast milk. Phenytoin also diffuses across the placenta, with foetal serum concentrations equal to those of the mother. Phenytoin is about 90% protein bound. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Protein binding may be lower in neonates and hyperbilirubinaemic infants; also altered in patients with hypoalbuminaemia, uraemia or acute trauma, and in pregnancy. Therapeutic concentrations of free (unbound) phenytoin, which are frequently monitored in patients with altered protein binding, usually fall in the range of 0.8 to 2 mcg/ml (3 to 8 micromoles/l).

### **Biotransformation**

Phenytoin is metabolised in the liver, the major inactive metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH). The rate of metabolism is increased in younger children, pregnant women, in women during menses and in patients with acute trauma. The rate decreases with advancing age. Phenytoin may be metabolised slowly in a small number of individuals due to genetic polymorphism, which may cause isoenzyme mutations (e.g. CYP2C9/19), limited enzyme availability and lack of induction.

### **Elimination**

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly by glomerular filtration but more importantly by tubular secretion.

The plasma half-life is normally from 10 to 15 hours. Because phenytoin exhibits saturable or dose-dependent pharmacokinetics, the apparent half-life of phenytoin changes with dose and plasma concentration. At therapeutic concentrations of the drug, the enzyme system responsible for metabolising phenytoin becomes saturated. Thus a constant amount of drug is metabolised, and small increases in dose may cause disproportionately large increases in plasma concentrations and apparent half-life, possibly causing unexpected toxicity.

Conventionally, with drugs following linear pharmacokinetics the half life is used to determine the dose rate, drug accumulation and the time to reach steady state. Phenytoin, however, demonstrates non-linear pharmacokinetics. Therefore, the half life is affected by the degree of absorption, saturation of metabolic pathways, dose and degree of metabolic enzyme induction. This results in considerable inter- and intra-patient variability in phenytoin pharmacokinetics. As a consequence the clinical relevance of reported phenytoin half life values are limited and cannot be used in the conventional manner to estimate the dosage regimen.

### **Therapeutic serum concentrations**

When administering phenytoin to a patient, it is necessary to measure the serum levels as this provides the most accurate means of deriving a suitable dosage regimen. Serum level determinations should originally be obtained at least 7 to 10 days after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady state will have been achieved. Further serum level determinations may be required to further refine the dosage regimen. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose related side effects and are obtained at the time of expected peak concentration.

Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and

20 mcg/ml. In renal failure or hypoalbuminaemia, 5 to 12 mcg/ml or even less may be therapeutic. Occasionally a patient may have seizure control with plasma concentrations of 6 to 9 mcg/ml. Effective treatment, therefore, should be guided by clinical response, not drug concentrations. In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide inter-patient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be non-compliant or hypermetabolisers of phenytoin. Unusually high levels of phenytoin result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful.

### **Indications**

For the control of status epilepticus, tonic-clonic (grand mal), psychomotor seizures and the prevention of seizures occurring during or following neurosurgery. Phenytoin will prevent or effectively decrease the incidence and severity of convulsive seizures in a high percentage of cases, with patients exhibiting little tendency to become resistant to its action. Besides its effectiveness in controlling seizures, phenytoin frequently improves the mental condition and outlook of epileptic patients.

It has also been used in the treatment of certain cardiac arrhythmias, particularly in those patients who do not respond to conventional antiarrhythmic agents or to cardioversion.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (refer to Dosage and administration).

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## **Dosage and administration**

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### **Dosage**

#### **General considerations**

Dosage should be individualised to obtain maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments. Serum levels between 10 and 20 mcg/ml (40 to 80 micromoles/l) are considered to be clinically effective. With the recommended dosage, a period of at least 7 to 10 days may be required to achieve therapeutic blood levels of phenytoin unless therapy is initiated with a loading dose. After the initial dose has been prescribed, plasma levels should be determined and the dosage adjusted if necessary to obtain a level in the therapeutic range; 10 to 20 mcg/ml (40 to 80 micromoles/l).

Because there is approximately an 8% increase in drug content in the free form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt to the form or vice versa.

Continuous monitoring of the electrocardiogram and blood pressure is essential. The patient should be observed for signs of respiratory depression. Determination of phenytoin plasma levels is advised when using phenytoin in the management of status epilepticus and the subsequent establishment of maintenance dosage. Cardiac resuscitative equipment should be available.

#### **Status epilepticus**

For the control of status epilepticus in adults, a loading dose of 10 to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg/minute. This will require approximately 20 minutes in a 70 kg patient. The loading dose should be followed by maintenance doses of 100 mg orally or intravenously every 6 to 8 hours.

For neonates and children a loading dose of 10 to 20 mg/kg intravenously will usually provide a plasma concentration of phenytoin within the generally accepted therapeutic range (10 to 20 mcg/ml).

The drug should be administered intravenously at a rate not exceeding 1 to 3 mg/kg/min, maximum of 50 mg/min (refer to [Warnings and precautions](#)). Children tend to metabolise phenytoin more rapidly than adults, which may affect dosage regimens. Therefore, serum level monitoring may be particularly beneficial in such cases.

In the treatment of status epilepticus an intravenous benzodiazepine such as diazepam or an intravenous short acting barbiturate, is usually given initially for the rapid control of seizures and is then followed by the slow intravenous administration of phenytoin. Intramuscular administration of phenytoin is unsuitable for the emergency treatment of status epilepticus due to very slow and erratic absorption from the intramuscular site.

### **Neurosurgery**

For the prevention of seizures during or following neurosurgery, cautious intravenous administration of 250 mg every six to twelve hours is recommended until oral dosage is possible. Plasma levels should be monitored to ensure optimal efficacy and to minimise toxicity. Phenytoin should not be given by intramuscular injection for the prevention of seizures following neurosurgery.

### **Cardiac arrhythmias**

Phenytoin sodium can be useful in ventricular arrhythmias, especially those due to digitalis. Although not a cardiac depressant, it has a positive inotropic effect and enhances conduction, though it generally decreases automaticity. The recommended dosage is one intravenous injection of Phenytoin Sandoz solution for injection 3 to 5 mg/kg body weight initially, repeating if necessary.

### **Administration**

Phenytoin Sandoz solution for injection must be administered slowly. Intravenous administration should not exceed 50 mg/min in adults. In neonates and children, the drug should be administered at a rate not exceeding 1 to 3 mg/kg/min, maximum of 50 mg/min.

Dilution of Phenytoin Sandoz solution for injection into intravenous infusion is not recommended due to lack of solubility and resultant precipitation.

Intra-arterial administration must be avoided in view of the high pH of the preparation.

The solution 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.

Phenytoin injection should be injected slowly and directly into a large vein through a large-gauge needle or intravenous catheter. Each injection should be followed by an injection of sodium chloride intravenous infusion 0.9% through the same needle or catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided.

Product is for single dose in one patient only. Discard any remaining contents.

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## **Contraindications**

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Known hypersensitivity to phenytoin, other hydantoin or to any of the inactive ingredients listed in [Further information](#).

Sinus bradycardia, sino-atrial block, second and third degree AV block or Stokes-Adams syndrome due to its effect on ventricular automaticity.

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## **Warnings and precautions**

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Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When the need arises for a dosage reduction of phenytoin, or discontinuation or substitution of alternative

anticonvulsant therapy is required, this should be done gradually. In hypersensitivity reactions, where rapid substitution of therapy is warranted, the alternative drug should be one not belonging to the hydantoin class of compounds.

Soft tissue irritation and inflammation, varying from slight tenderness to extensive necrosis and sloughing, has been noted at the site of injection with and without the extravasation of intravenous phenytoin. Each injection of phenytoin should be followed by an injection of sodium chloride intravenous infusion 0.9% through the same needle or catheter to avoid the irritation caused by the alkalinity of the solution.

The injection must be administered slowly, at a rate not exceeding 50 mg/min in adults. In children and neonates, the drug should be administered at a rate not exceeding 1 to 3 mg/kg/min, (maximum of 50 mg/min). Administration at faster rates may result in cardiac arrhythmias, impaired cardiac conduction, hypotension, cardiovascular collapse or CNS depression attributed to the propylene glycol diluent.

The response to phenytoin may be significantly altered by the concomitant use of other drugs (refer to [Interactions](#)).

Phenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency. Hypotension usually occurs when phenytoin is administered rapidly by the intravenous route.

In patients with cardiovascular disease, parenteral administration may result in atrial and ventricular conduction depression, ventricular fibrillation or reduced cardiac output.

The intramuscular administration of phenytoin sodium is not recommended due to erratic absorption and local tissue reactions, such as tissue necrosis, caused by the alkalinity of the solution. Erratic absorption is partly caused by tissue precipitation of phenytoin.

While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. If folic acid is added to phenytoin therapy, a decrease in seizure control may occur (refer to [Interactions](#)).

Osteomalacia has been associated with phenytoin therapy and is attributed to interference with vitamin D metabolism (refer to [Adverse effects](#)).

It is recommended that patients receiving long term phenytoin therapy should undergo regular blood counts as serious adverse haematological reactions have been reported (refer to [Adverse effects](#)).

Caution should also be used when administering phenytoin to patients suffering from porphyria. There have been isolated reports linking phenytoin to exacerbation of this disease.

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

A small percentage of individuals who have been treated with phenytoin have been shown to metabolise the drug slowly. Slow metabolism appears to be due to limited enzyme availability and lack of or defective induction, which may be genetically determined.

There have been a number of reports suggesting a relationship between phenytoin and the development of local or generalised lymphadenopathy, including benign lymph node hyperplasia, lymphoma, pseudolymphoma and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy requires differentiation from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms resembling serum sickness e.g. rash, fever and liver involvement. In all cases of lymphadenopathy, seizure control should be sought using alternative anticonvulsants and observation of patients for an extended period is recommended.

Plasma levels of phenytoin sustained above the optimal range may produce encephalopathy, or

confusional states (delirium psychosis), or rarely irreversible cerebellar dysfunction. Plasma level determinations are recommended at the first signs of acute toxicity. If plasma levels are excessive, then dosage reduction is indicated. Termination is recommended if symptoms persist (refer to Warnings and precautions).

Literature reports suggest the combination of phenytoin, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme and/or Stevens-Johnson syndrome and/or toxic epidermal necrolysis.

Phenytoin should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, phenytoin treatment should not be resumed. If the rash is mild (measles-like or scarlatiniform), resumption of therapy, after the rash has disappeared completely, will depend on a consideration of the risk/benefit ratio by the treating physician. However, in the case of the rash recurring upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin is not effective for absence (petit mal) seizures as it may increase the frequency of these seizures. Therefore, combined therapy is required if both tonic-clonic (grand mal) and absence (petit mal) seizures are present.

Phenytoin should be used with caution in diabetic patients, as hyperglycaemia may be potentiated. There have been isolated reports of hyperglycaemia occurring in patients receiving phenytoin, resulting from the drug's inhibition of insulin secretion. Phenytoin may also raise the plasma glucose in diabetic patients. Patients with impaired renal function appear to be more susceptible to this effect.

Phenytoin is not indicated for the treatment of seizures due to hypoglycaemia or other metabolic causes. The appropriate diagnostic tests should be performed as indicated.

Caution should also be given in patients with hypoalbuminaemia as this condition can lead to potential toxicity through its effect on increasing unbound phenytoin levels.

### **Suicidal behaviour and ideation**

Anticonvulsants, including phenytoin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any anticonvulsant for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different anticonvulsants showed that patients randomised to one of the anticonvulsants had approximately twice the risk (adjusted relative risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 anticonvulsant-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with anticonvulsants was observed as early as one week after starting drug treatment with anticonvulsants and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with anticonvulsants of varying mechanisms of action and across a range of indications suggests that the risk applies to all anticonvulsants used for any indication. This risk did not vary substantially by age (5 to 100 years) in the clinical trials analysed. The following table shows absolute and relative risk by indication for all evaluated anticonvulsants.

## Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events / 1000 patients	Drug patients with events / 1000 patients	Relative risk: incidence of events in drug patients / incidence in placebo patients	Risk difference: additional drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing phenytoin or any other anticonvulsant must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that anticonvulsants increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

### **Use in the elderly**

Severe complications are most commonly encountered in elderly or gravely ill patients. In these patients, the drug should be administered at a rate not exceeding 25 mg/minute, and if necessary, at a slow rate of 5 to 10 mg/minute. Elderly patients have an increased frequency of toxicity due to their slower rate of phenytoin metabolism and decreased serum albumin concentration, which decreases the degree of protein binding of phenytoin. Therefore, lower doses and subsequent dosage adjustment may be necessary.

### **Use in renal or hepatic impairment**

Patients with renal function impairment should be carefully observed as excretion and protein binding of phenytoin may be altered. Similarly, because the liver is the principal site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity on standard dosage. Accordingly, dosage reduction may be required in patients with extensive hepatic impairment.

## ***Pregnancy and lactation***

### **Use in pregnancy**

Assigned Category D by the Australian Drug Evaluation Committee. This category includes medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the general population. Some of this risk is due to the anticonvulsant medicines taken. Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine. Women with epilepsy should take folic acid supplements of 5 mg daily before, and for 12 weeks after conception.

Phenytoin sodium taken during pregnancy has been associated with distinctive craniofacial abnormalities, fingernail hypoplasia, developmental disability, mental and growth retardation and less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the 'foetal hydantoin syndrome'. There have been reports of neonatal coagulation defects with consequent risk of haemorrhage within the first 24 hours in babies born to mothers receiving phenytoin. Phytomenadione or vitamin K has been shown to correct or prevent this defect and has been recommended to be administered to the mother before delivery and to the baby after birth.

Malignancies such as neuroblastoma have been reported rarely in children whose mothers received phenytoin during pregnancy.

Overall, the risk of having an abnormal child as a result of medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant medicines should not be discontinued in patients in whom the medicine is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated. Some patients may experience a rapid reduction in maternal hepatic phenytoin metabolism at the time of delivery, requiring the dosage to be reduced within 12 hours postpartum.

#### **Use in lactation**

Residual phenytoin may be present in breast milk at levels corresponding to approximately 3.0 to 7.2% of the maternal dose. Phenytoin is considered safe. However the literature reports cases of methaemoglobinaemia, poor suckling and sedation so the infant should be monitored accordingly.

#### ***Effects on ability to drive and use machines***

This medicine is likely to produce severe adverse effects or presumed to be potentially dangerous.

#### ***Other***

##### **Preclinical safety data**

###### *Carcinogenicity*

In two studies in mice, increased incidences of hepatic adenoma were seen when phenytoin sodium was administered at dietary doses of 45 and 90 mg/kg/day. The incidence of hepatic carcinoma was also increased in one of these studies. These effects were seen at plasma phenytoin concentrations slightly lower than the human therapeutic range. In rats, the incidence of hepatic adenoma was marginally increased at 240 mg/kg/day in one study, but was not affected at 100 mg/kg/day in another. In the latter study, plasma concentrations of phenytoin were slightly lower than the human therapeutic range. In two other studies, no carcinogenic effects were seen at low doses (16 mg/kg/day in mice and 20 mg/kg/day in rats). Phenytoin induced hepatic tumours in rodents may be secondary to hepatic enzyme induction, and are of uncertain clinical relevance.

###### *Mutagenicity*

In genotoxicity studies with phenytoin sodium, negative results were obtained in assays for chromosomal damage in mammalian cells *in vitro* and *in vivo* and in a sister chromatid exchange assay *in vivo*. The potential for phenytoin sodium to cause gene mutations has not been investigated.

###### *Impairment of fertility*

In studies in which phenytoin sodium was administered orally to female mice and rats for two weeks before breeding and throughout gestation and lactation, no pregnancies occurred at respective doses of 90 mg/kg/day and 240 mg/kg/day; there were no adverse effects at respective doses of 30 and 80 mg/kg/day.

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## Adverse effects

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The most notable signs of toxicity are cardiovascular collapse and/or CNS depression. Nystagmus is the most frequently reported clinical finding of toxicity and tends to occur when the plasma phenytoin concentration exceeds 20 mg/l. Hypotension does occur when the drug is administered rapidly by the intravenous route. Toxicity should be minimised by following the appropriate directions (refer to [Dosage and administration](#)).

### Cardiovascular

Periarteritis nodosa has been reported. Severe cardiotoxic reactions and fatalities have been reported, most commonly in gravely ill patients or the elderly (refer to [Warnings and precautions](#)).

### CNS

These are the most common reactions encountered with phenytoin and include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Cases of dizziness, insomnia, transient nervousness, stuttering, trembling of hands, unusual excitement, irritability, toxic amblyopia, cognitive impairment, tonic seizures, motor twitchings and headaches have also been reported. These side effects are usually dose related.

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. These may be due to sudden administration of intravenous phenytoin for status epilepticus. The effect usually lasts 24 to 48 hours after discontinuation.

A predominantly sensory peripheral polyneuropathy has been reported for patients on long-term phenytoin therapy.

### Gastrointestinal

Nausea, vomiting, epigastric pain, dysphagia, loss of taste, anorexia, weight loss and constipation.

### Dermatological

A measles-like rash is the most common dermatological manifestation. Rashes are sometimes accompanied by fever, and are generally more common in children and young adults. Other types of rashes are more rare, and more serious forms which may be fatal include bullous, exfoliative or purpuric dermatitis, systemic lupus erythematosus, Stevens-Johnson syndrome, scarlatiniform or morbilliform rashes and toxic epidermal necrolysis (refer to [Warnings and precautions](#)).

### Haemopoietic

Some fatal haemopoietic complications have occasionally been reported in association with the use of phenytoin. These have included thrombocytopaenia, leukopaenia, granulocytopaenia, agranulocytosis, and pancytopaenia with or without bone marrow suppression. Although macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy has also been reported (refer to [Warnings and precautions](#)).

### Hepatic system

Potentially fatal cases of toxic hepatitis and liver damage may occur. This effect may be the result of a hypersensitivity reaction.

### Immunologic

Hypersensitivity syndrome (which may include but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus and immunoglobulin abnormalities.

### Musculoskeletal system

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with vitamin D metabolism. Some patients on high phenytoin doses with poor dietary intake of vitamin D, limited sun exposure and reduced levels of physical activity may require vitamin D

supplementation.

### **Other**

Gingival hyperplasia occurs frequently, usually within the first 6 months, beginning as gingivitis or gum inflammation. Children and young adults do appear more susceptible to gingival hyperplasia than adults. Its incidence may be reduced by maintaining good oral hygiene such as frequent brushing, gum massage and appropriate dental care.

Coarsening of the facial features, enlargement or thickening of the lips, widening of the nasal tip, protrusion of the jaw, gynaecomastia, Dupuytren's contracture, hypertrichosis, immunoglobulin abnormalities, Peyronie's Disease and hirsutism may occur. Younger patients appear more susceptible to bleeding, tender and enlarged gums. Unusual and excessive body hair growth may be more pronounced in young patients. Liver damage may be a manifestation of hypersensitivity to the drug.

Local irritation, inflammation, tenderness, necrosis and sloughing at the injection site have been reported with or without extravasation of intravenous phenytoin.

Rare reports of pulmonary infiltrates or fibrosis, with symptoms including fever, troubled or quick, shallow breathing, unusual tiredness or weakness, loss of appetite and weight and chest discomfort, have also occurred.

Anticonvulsant drugs have been associated with an increased risk of suicidal behaviour, suicidal ideation and emergence or worsening of existing depression.

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## **Interactions**

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### ***Medicines and other pharmacologically active substances***

A number of drugs have been noted to increase or decrease the effects of phenytoin either through an effect on metabolic degradation of phenytoin, interference with protein binding, altered absorption or by unknown mechanisms.

The activities of some enzymes such as, CYP P450 isoenzymes, the uridine diphosphate glucuronosyl transferase (UDPGT) system and epoxide hydrolase enzymes, are significantly increased by phenytoin therapy, which in turn enhances the metabolism of many drugs. Phenytoin may also compete with drugs metabolised by the same CYP isoenzyme (CYP2C9 and CYP2C19), which would decrease the metabolic clearance of these drugs.

### **General interactions**

Drugs that may elevate plasma levels of phenytoin, in some cases to toxic levels, include: allopurinol, amiodarone, amphotericin B, azapropazone, celecoxib, chloramphenicol, chlordiazepoxide, chlorphenamine, cimetidine, clarithromycin, coumarin anticoagulants, diazepam, diltiazem, disulfiram, erythromycin, ethosuximide and other succinimides, felbamate, fluconazole, fluoxetine, halothane, isoniazid, isradipine, itraconazole, ketoconazole, mephenytoin, methylphenidate, miconazole, nifedipine, oestrogens, omeprazole, pheneturide, phenylbutazone, phenothiazines, posaconazole, ranitidine, salicylates, sulfapyrazole, sulphonamides, sultiame, tamoxifen, ticlopidine, tizanidine, tolazamide, tolbutamide, topiramate, trazodone, trimethiadione, trimethoprim, viloxazine and voriconazole.

Drugs that may decrease plasma levels of phenytoin and in some cases, impair seizure control, include: some antacids and ionic calcium preparations, bleomycin, calcium folinate, carbamazepine, carboplatin, carmustine, ciprofloxacin and other fluoroquinolones, cisplatin, clofazamine, diazoxide, dichloralphenazone, folic acid, loxapine, methotrexate, nitrofurantoin, oxacillin, reserpine, rifampicin, St. John's Wort (*Hypericum perforatum*), sucralfate, theophylline, vigabatrin and vinblastine.

Drugs that may either increase or decrease plasma levels of phenytoin and vice versa include: amiodarone, barbiturates, carbamazepine, chlordiazepoxide, diazepam, influenza vaccines,

phenothiazines, primidone, valproic acid and sodium valproate.

Phenytoin impairs the efficacy of several drugs, including: clozapine, corticosteroids, coumarin anticoagulants, cyclosporin, dacarbazine, diazoxide, digoxin, disopyramide, doxycycline, furosemide, glibenclamide, itraconazole, ketoconazole, lamotrigine, L-dopa, lignocaine or lidocaine, methadone, mexiletine, nifedipine, nimodipine, oestrogens, oral contraceptives, pancuronium, paroxetine, praziquantel, quinidine, rifampicin, succinimide, posaconazole, tetracycline, tolbutamide, vecuronium, verapamil, vitamin D, voriconazole and xanthines (e.g. theophylline).

### **Specific drugs and therapeutic categories**

#### *Amide antiarrhythmics and beta-adrenoceptor antagonists*

Concurrent use of intravenous phenytoin with lignocaine (lidocaine) or beta-blockers may produce additive cardiac depressant effects. Phenytoin may also enhance metabolism of lignocaine.

#### *Calcium antagonists*

Caution is advised when nifedipine or verapamil are used concurrently with phenytoin. All are highly protein bound medications and therefore changes in plasma concentrations of the free, unbound fractions may occur. Plasma levels of felodipine and nisoldipine are very markedly reduced by phenytoin (either alone or with carbamazepine).

#### *Capecitabine*

Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil. Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of CYP2C9 isoenzyme system by capecitabine. Plasma levels of phenytoin sustained above the optimal range may produce encephalopathy, or confusional states (delirium psychosis), or rarely irreversible cerebellar dysfunction. Therefore, patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels.

#### *Diazoxide*

Concurrent use of phenytoin and oral diazoxide may decrease the efficacy of phenytoin and the hyperglycaemic effect of diazoxide and is not recommended.

#### *Dopamine*

Phenytoin given intravenously to patients maintained on dopamine may produce sudden hypotension and bradycardia. This appears to be dose-rate dependent. If anticonvulsant therapy is necessary during administration of dopamine, an alternative to phenytoin should be considered.

#### *Insulin and oral antidiabetic agents*

Phenytoin, especially in large doses, may increase plasma glucose levels and therefore dosage adjustments for insulin or oral antidiabetic agents may be necessary.

#### *Lamotrigine*

The plasma clearance of lamotrigine is doubled and its elimination half life is reduced by 50% when given in combination with phenytoin; this requires dosage adjustment.

#### *Metronidazole*

Metronidazole may raise plasma levels and prolong the half life of phenytoin although this has not been consistently observed.

#### *Proton pump inhibitors*

Proton pump inhibitors omeprazole, lansoprazole and esomeprazole, have in some cases, raised plasma levels of phenytoin although these interactions have not been consistently observed.

#### *Psychoactive drugs*

Tricyclic antidepressants, haloperidol, MAO inhibitors and thioxanthenes may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

### *Selective serotonin reuptake inhibitors*

Concomitant use of fluoxetine in patients stabilised on phenytoin has resulted in elevated plasma phenytoin concentrations and signs and symptoms of phenytoin toxicity. Plasma phenytoin concentrations should be monitored closely during concomitant use of fluoxetine, and the dose of phenytoin adjusted if necessary. There are also isolated reports of phenytoin toxicity associated with fluvoxamine treatment. Phenytoin and sertraline do not normally interact, but increased plasma phenytoin levels have been reported. Sertraline and possibly paroxetine levels may be reduced by phenytoin. Note that selective serotonin reuptake inhibitors should be avoided in unstable epilepsy and used with care in other epileptic conditions.

### *Ticlopidine*

Ticlopidine reduces the metabolism of phenytoin. Several case reports describe patients who developed phenytoin toxicity in the presence of ticlopidine.

### *Topiramate*

Co-administration of phenytoin and topiramate reduces topiramate levels by 59% and has the potential to increase phenytoin levels by 25% in some patients.

### *Vigabatrin*

Phenytoin levels may be reduced by 20 to 30% when co-administered with vigabatrin; in some patients this may require a dosage adjustment.

### *Zidovudine*

Although one study found that zidovudine did not alter phenytoin pharmacokinetics, other evidence suggests that some changes possibly occur, although these may be attributed to HIV infection.

## **Abnormal laboratory test results**

Phenytoin increases blood glucose levels due to inhibition of insulin secretion. Raised plasma levels of alkaline phosphatase, hypocalcaemia and osteomalacia have been linked with altered vitamin D metabolism. Elevated plasma levels of gamma glutamyl transpeptidase (GGT) and alkaline phosphatase may be related to hepatic enzyme induction. Phenytoin may also produce lower than normal values for dexamethasone or metyrapone. Folic acid, calcium and free thyroxine concentrations and protein bound iodine (PBI) test values may all be reduced.

## **Food and alcohol**

The absorption of phenytoin can be affected by some foods. A very marked reduction in phenytoin absorption has been reported when it was given with enteral feeds by nasogastric or jejunostomy tubes. Patients who must receive continuous enteral feedings should probably receive phenytoin intravenously.

Acute alcohol intake may increase plasma levels of phenytoin while chronic alcohol use may decrease them.

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## **Overdosage**

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### **Signs and symptoms**

The mean lethal dose in adults is considered to be 2 to 5 grams. The lethal dose in children is not known. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperflexia, lethargy, slurred speech, nausea and vomiting. The patient may become comatose, hypotensive, severely confused, dizzy or drowsy, unusually tired or weak. The patient's pupils may become unresponsive and blurred or double vision may also occur. Other manifestations of accidental intravenous overdosage of phenytoin are bradycardia and heart block. Death is due to respiratory and circulatory depression and apnoea.

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

### ***Management***

Treatment is nonspecific since there is no known antidote. If the gag reflex is absent, the airway should be supported. Oxygen, vasopressors and assisted ventilation may be necessary for CNS, 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 overdose the possibility of other CNS depressants, including alcohol, should be borne in mind.

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## **Pharmaceutical precautions**

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### ***Instructions for use/handling***

The product should be visually inspected for particulate matter and discolouration prior to administration. Product is for immediate and single use only. Discard any residue.

### ***Incompatibilities***

The mixing of phenytoin sodium with other drugs or with intravenous infusion solutions is not recommended because the solubility of phenytoin sodium is such that crystallisation or precipitation may result if the special vehicle is altered or the pH is lowered.

### ***Special precautions for storage***

Store at or below 25°C. Protect from light.

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## **Medicine classification**

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Prescription Medicine.

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## **Package quantities**

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Packs of 5 ampoules.

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## **Further information**

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### ***List of excipients***

Propylene glycol, ethanol, sodium hydroxide and water for injections.

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## **Name and address**

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Novartis New Zealand Limited  
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Telephone: (09) 361 8100

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**Date of preparation**

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