AUSTRALIAN PRODUCT INFORMATION

DILANTIN®

(phenytoin sodium) capsules

1 NAME OF THE MEDICINE

Phenytoin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DILANTIN 30 mg capsules: each capsule contains 30 mg phenytoin sodium.

DILANTIN 100 mg capsules: each capsule contains 100 mg phenytoin sodium.

Excipients with known effect: Lactose and sugars.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

30 mg capsules: size 4 hard gelatin capsule with a white, opaque body and cap printed with "VTRS" on one side and "VLE 30" on the other in black ink.

100 mg capsules: size 3 hard gelatin capsule with white, opaque body and orange cap, printed with a "VTRS" on one side and "VLE 100" on the other in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DILANTIN is indicated for the control of generalised tonic-clonic (grand mal) and psychomotor seizures. DILANTIN 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, DILANTIN frequently improves the mental condition and outlook of epileptic patients and there is also increasing evidence that DILANTIN is valuable in the prevention of seizures occurring during or after neurosurgery. Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

4.2 DOSE AND METHOD OF ADMINISTRATION

Serum concentrations should be monitored and care should be taken when switching a patient from the sodium salt to the free acid form.

DILANTIN capsules (30 mg, 100 mg) are formulated with the sodium salt of phenytoin.

The free acid form of phenytoin is used in DILANTIN INFATABS (50 mg) and DILANTIN PAEDIATRIC SUSPENSION (30 mg/5 mL).Because there is approximately an 8% increase in drug content with 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 and vice versa.

Dosage

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 micrograms/mL and 20 micrograms/mL 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 DILANTIN, 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 micrograms/mL to 20 micrograms/mL (40 micromoles/L to 80 micromoles/L). Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable, at high plasma levels small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range.

Method of Administration

Oral administration.

Although phenytoin has a relatively long plasma half-life, thrice daily dosing may reduce the incidence of gastric irritation since lower doses can be administered with thrice daily dosing as compared with twice daily dosing. Recent studies suggest that a better correlation is achieved between plasma levels and dose by expressing the latter on a body-weight basis.

Adult

Initiate therapy with 4 mg/kg/day to 5 mg/kg/day in 2 to 3 divided doses and assess plasma levels. A further upward dosage adjustment may be required to a maximum of 600 mg/day, dosage increments should be made at about 2week intervals. Plasma phenytoin levels should be monitored should higher doses be required.

An initial dose of 6 mg/kg/day to 7 mg/kg/day would be more likely to ensure therapeutic levels however, there is a risk that such a dose may achieve levels exceeding 20 micrograms/mL and increase the risk of toxicity.

Paediatric

Initiate therapy with 5 mg/kg/day in 2 to 3 equally divided doses not to exceed 300 mg daily. A recommended daily maintenance dosage is usually 4 mg/kg to 8 mg/kg. Children over 6 years may require the minimum adult dose (300 mg/day).

Paediatric dosage forms available include DILANTIN INFATABS chewable tablets and DILANTIN PAEDIATRIC SUSPENSION.

Dosage Adjustment

Patients with Renal or Hepatic Disease: (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE, General).

Elderly Patients: Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE, Use in the Elderly).

4.3 CONTRAINDICATIONS

Patients with a history of hypersensitivity to phenytoin, or other hydantoin products, or other inactive ingredients in this product.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

Phenytoin is not indicated for seizures due to hypoglycaemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus, hence any need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication should be implemented gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of an alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

In some individuals, the rate of phenytoin metabolism has been shown to be slower than normal. This slow rate of degradation may be due to enzymatic unavailability or to defective induction mechanisms, effects that appear to be genetically determined.

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

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminaemia, the interpretation of total phenytoin plasma concentrations should be made with caution. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinaemia. Unbound phenytoin concentrations may be more useful in these patient populations.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), including phenytoin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED 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 AEDs showed that patients randomised to one of the AEDs 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 AED-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 AEDs was observed as early as one week after starting drug treatment with AEDs 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 AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 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 AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs 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 AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or 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.

Cardiac Effects

Cases of bradycardia and asystole/cardiac arrest have been reported, most commonly in association with phenytoin toxicity (see Section 4.9 OVERDOSE), but also at recommended phenytoin doses and levels.

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms

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 interval between the first drug exposure and symptoms is usually 2 to 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 should be discontinued if an alternative aetiology for the signs and symptoms cannot be established, and appropriate supportive measures provided.

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 immunosuppressed patients. The syndrome is more severe in previously sensitised individuals.

Serious Dermatologic Reactions

Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP) (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), Dermatologic System), exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS, which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, itching and other signs and symptoms of HSS/DRESS (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE, Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms), and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin, including skin rash, SJS, TEN, hepatotoxicity, and HSS 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 human leucocyte antigen B (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.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally caution should be exercised if using structurally similar compounds (e.g. barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Angioedema

Angioedema has been reported in patients treated with phenytoin. Phenytoin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Immunologic).

Hepatic Injury

The main site of biotransformation of phenytoin is the liver.

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 WARNING AND PRECAUTIONS FOR USE, Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). Patients with impaired liver function, elderly patients or those gravely ill, may show early signs of toxicity on standard dosage. Care should be exercised with dose adjustment in these patients.

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 Effect

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.

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 signs and symptoms resembling HSS/DRESS (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR, Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). 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.

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.

It is recommended that patients receiving long-term DILANTIN therapy should undergo regular blood counts as serious haematological abnormalities have been reported (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Metabolic Effect

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.

Hyperglycaemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Hypoalbuminaemia, from any cause, may be potentially toxic through its effect on increasing unbound phenytoin levels.

Musculoskeletal Effect

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

Women of Childbearing Potential

Phenytoin may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy).

Phenytoin should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. Before the initiation of treatment with phenytoin in a woman of childbearing potential, pregnancy testing should be considered.

Women of childbearing potential, women planning pregnancy and pregnant women should be fully informed of the potential risk to the fetus if they take phenytoin during pregnancy. Women of childbearing potential should be counselled regarding the need to consult their physician as soon as they are planning pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy).

Women of childbearing potential should be counselled to contact their doctor immediately if they become pregnant or think they may be pregnant and are taking phenytoin.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy).

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 and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, determination of plasma drug levels is recommended. Dose reduction of phenytoin therapy is indicated if plasma drug levels are excessive, if symptoms persist, termination of phenytoin therapy is recommended.

Use in the Elderly

Phenytoin clearance tends to decrease with increasing age. Phenytoin dosing requirements are highly variable and must be individualised.

Paediatric Use

No data available.

Effects on Laboratory Tests

Phenytoin may cause decreased serum levels of protein bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT). Raised glucose levels appear to be due to inhibition of insulin secretion.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are many drugs that may increase or decrease phenytoin levels or that phenytoin may affect. Mechanisms of drug interaction with phenytoin may be complex. In assessing drug-interactions, serum phenytoin concentrations and the clinical status of the patient will be helpful.

In general, phenytoin is a potent inducer of the hepatic cytochrome P450 microsomal isoenzymes CYP3A4, CYP2D6, CYP1A2, CYP2C9 and CYP2C19. However, a patient's susceptibility to enzyme-inducing interactions may be influenced by factors such as age, cigarette smoking, or the presence of liver disease. Phenytoin is metabolised primarily by CYP2C9 (major) and CYP2C19 (minor), thus several drugs may inhibit or induce the metabolism of phenytoin.

Oral phenytoin absorption may be reduced by a number of drugs. Phenytoin is highly plasma-protein bound and may be displaced by other drugs, increasing unbound ('free') phenytoin levels. Phenytoin 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.

Effects of Other Drugs on Phenytoin

Table 2. Drugs That May Increase Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)*
Alcohol	Alcohol (acute intake).
Analgesic / Anti-inflammatory agents	Salicylates.
Antibacterial agents	Chloramphenicol, erythromycin, isoniazid, sulfadiazine, sulfamethoxazole-trimethoprim, sulfonamides.
Anticonvulsants	Oxcarbazepine, sodium valproate, succinimides (ethosuximide), topiramate.
Antifungal agents	Amphotericin B, fluconazole, itraconazole, ketoconazole, miconazole, voriconazole.
Antineoplastic agents	Capecitabine**, fluorouracil**.
Antiplatelet agents	Clopidogrel.
Benzodiazepines / Psychotropic agents	Chlordiazepoxide, diazepam, disulfiram, methylphenidate, trazodone.
Calcium channel blockers / Cardiovascular agents	Amiodarone, diltiazem, nifedipine, ticlopidine.
H2-antagonists	Cimetidine.
HMG-CoA reductase inhibitors	Fluvastatin.
Hormones	Estrogens.
Immunosuppressant drugs	Tacrolimus.
Oral hypoglycaemic agents	Tolbutamide.
Proton pump inhibitors	Omeprazole.
Serotonin re-uptake inhibitors	Fluoxetine, fluvoxamine, sertraline.

* This list is not intended to be inclusive or comprehensive. Individual drug Product Information should be consulted.

** Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil (5FU). Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine. Patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels.

Table 3. Drugs That May Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)*
Alcohol	Alcohol (chronic intake).
Antibacterial agents / fluoroquinolones	Ciprofloxacin, rifampicin.
Anticonvulsants	Vigabatrin.
Antineoplastic agent	Bleomycin, carboplatin, cisplatin, doxorubicin, methotrexate.
Antiulcer agents	Sucralfate.
Antiretrovirals	Fosamprenavir, nelfinavir**, ritonavir.
Bronchodilators	Theophylline.

Drug Classes	Drugs in each Class (such as)*
Folic acid	Folic acid.
Hyperglycaemic agents	Diazoxide.
St John's wort	Hypericum perforatum (St John's wort).

* This list is not intended to be inclusive or comprehensive. Individual drug Product Information should be consulted.

** A pharmacokinetic interaction study between nelfinavir and phenytoin both administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28% respectively. Therefore, phenytoin concentration should be monitored during co-administration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

Calcium ions may interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

Table 4. Drugs That May Either 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	Antineoplastic agents.
Psychotropic agents	Chlordiazepoxide, diazepam, phenothiazines.

* This list is not intended to be inclusive or comprehensive. Individual drug Product Information should be consulted.

** The effect of phenytoin on carbamazepine, phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.

Effect of Phenytoin on Other Drugs

Table 5. Drugs Whose Serum Levels and/or Effects May be Altered by Phenytoin

Drug Classes	Drugs in each Class (such as)*
Antibacterial agents	Doxycycline, rifampicin, tetracycline.
Anticoagulants	Warfarin, apixaban, dabigatran, edoxaban, rivaroxaban.
Anticonvulsants	Carbamazepine, lamotrigine, phenobarbital, sodium valproate#, valproic acid#, lacosamide.
Antifungal agents	Azoles, posaconazole, voriconazole.
Antihelminthics	Albendazole, praziquantel.
Antineoplastic agents	Teniposide.
Antiplatelets	Ticagrelor.
Antiretrovirals	Delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir/ritonavir, ritonavir, saquinavir.
Bronchodilators	Theophylline.

Drug Classes	Drugs in each Class (such as)*
Calcium channel blockers / Cardiovascular agents	Digitoxin, digoxin, disopyramide, mexiletine, nicardipine, nimodipine, quinidine, verapamil.
Corticosteroids	Corticosteroids.
Ciclosporin	Ciclosporin.
Diuretics	Furosemide.
HMG-CoA reductase inhibitors	Atorvastatin, fluvastatin, simvastatin.
Hormones	Estrogens, oral contraceptives (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Women of Childbearing Potential and 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy).
Hyperglycaemic agents	Diazoxide.
Immunosuppressant drugs	Immunosuppressant drugs.
Neuromuscular blocking agents	Cisatracurium, pancuronium, rocuronium, vecuronium.
Opioid analgesics	Methadone.
Oral hypoglycaemic agents	Chlorpropamide, glibenclamide, tolbutamide.
Psychotropic agents / Antidepressants	Clozapine, paroxetine, quetiapine, sertraline.
Vitamin D	Vitamin D.
Folic acid	Folic acid.

* This list is not intended to be inclusive or comprehensive. Individual drug Product Information should be consulted.

Sodium valproate and valproic acid are similar medications. The term valproate has been used to represent these medications.

Hyperammonemia with Concomitant Use of Valproate

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

Seizure Threshold Lowering Drugs

Although not a pharmacokinetic drug interaction, antidepressants, antipsychotics, tramadol and other seizure threshold lowering drugs may precipitate seizures in susceptible patients by lowering convulsive threshold. Phenytoin dosage may need to be adjusted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Phenytoin has not been adequately assessed for effects on male or female fertility.

Use in Pregnancy (Category D)

Phenytoin crosses the placenta in humans. Similar concentrations of phenytoin have been reported in the umbilical cord and maternal blood.

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 of approximately 6% compared to a rate in the general population of 2-3%.

Malformations such as orofacial clefts, cardiac defects, dysmorphic facial features, nail and digit hypoplasia, and growth abnormalities (including microcephaly) have been reported either individually or as part of a fetal Hydantoin Syndrome among children born to women with epilepsy who took 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 neurodevelopmental risk in children exposed to phenytoin during pregnancy are contradictory and a risk cannot be excluded.

It is recommended that:

- Women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of congenital malformations or adverse developmental outcomes;
- AEDs should be continued during pregnancy at the lowest effective dose, and monotherapy should be used if appropriate as risk of congenital malformations or adverse developmental outcomes is greater in women taking combined medication;
- Adequate folic acid supplementation should be discussed as part of pre-pregnancy and pregnancy counselling;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be considered.

Phenytoin should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating and counselling epileptic women of childbearing potential.

There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. However, the respective role of antiepileptic drugs and other factors in the increased risk is not determined.

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.

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant. In pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

In neonates

Phenytoin also can cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn infant which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.

Post-natal monitoring/children

In case of exposure during pregnancy, children should be closely monitored in relation to neurodevelopmental disorders in order to provide specialised care as soon as possible, if necessary.

Women of childbearing potential

Phenytoin should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risk of potential harm to the fetus if phenytoin is taken during pregnancy and therefore the importance of planning any pregnancy. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with phenytoin.

Women of childbearing potential should be counselled regarding the need to consult her physician as soon as she is planning pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued.

Contraception

Women should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking phenytoin.

Women of childbearing potential should use effective contraception during treatment and for one month after stopping treatment. Due to enzyme induction, phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

Use in Lactation

Breastfeeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentration in human milk. Phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Body as a Whole

Anaphylactoid reaction and anaphylaxis.

Gastrointestinal System

Nausea, vomiting and constipation. To prevent gastric irritation due to alkalinity, DILANTIN should be taken with at least half a glass of water. Gastric irritation may often be minimised by administering DILANTIN during or following meals.

Haematopoietic System

Some fatal haematopoietic complications have occasionally been reported in association with the administration of phenytoin. Included in these are thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis and pancytopenia with or without bone marrow suppression. Macrocytosis and megaloblastic anaemia have also occurred, these conditions usually respond to folic acid therapy.

Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma and Hodgkin's disease have been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Haematopoietic Effect).

Pure red cell aplasia has also been reported.

Central Nervous System

The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. Cerebellar atrophy has been reported and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Central Nervous System Effect). Cases of dizziness, vertigo, insomnia, transient nervousness, motor twitchings, headache, paraesthesia and somnolence have also been reported.

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. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Immunologic

HSS/DRESS (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa and immunoglobulin abnormalities (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms). Angioedema has been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Angioedema).

Investigations

Thyroid function test abnormal.

Connective Tissue System

Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Musculoskeletal System

Bone fractures and osteomalacia have been associated with long-term (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcaemia, hypophosphataemia and decreased serum levels of vitamin D metabolites have also been reported.

Dermatological System

Dermatological manifestations sometimes associated with fever have included scarlatiniform or morbilliform rashes. The latter case is the most common with other types of dermatitis being more rare. In general, rashes are more frequent in children and young adults. More serious forms that may be fatal have also been reported and they include bullous, exfoliative, or other purpuric dermatitis, lupus erythematosus, AGEP, SJS and TEN (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Serious Dermatologic Reactions). Urticaria has been reported. Hirsutism.

Hepatic System

Potentially fatal cases of acute hepatic failure, toxic hepatitis and liver damage may occur (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hepatic Injury). This effect may be the result of a hypersensitivity reaction.

Special Senses

Taste perversion.

Miscellaneous

Gingival hyperplasia occurs frequently and its incidence may be reduced by good oral hygiene, including gum massage, frequent brushing and appropriate dental care.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus or lateral gaze, usually appears at 20 micrograms/mL, ataxia at 30 micrograms/mL, dysarthria and lethargy appear when the plasma concentration is over 40 micrograms/mL, but as high a concentration as 50 micrograms/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration above 100 micrograms/mL with complete recovery. The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 g to 5 g.

The cardinal initial symptoms are nystagmus, ataxia, dysarthria and CNS depression. Other signs that may be seen are tremor, hyperreflexia, somnolence, drowsiness, lethargy, hallucinations, confusion, mental status changes, slurred speech, blurred vision, nausea, vomiting, choreoathetosis, dyskinesias, hyperglycaemia and mild hypoglycaemia. Severe poisoning may result in respiratory depression. Cardiotoxicity has not been reported with oral overdoses. Irreversible cerebellar dysfunction and atrophy have been reported as a delayed effect following severe overdoses. The patient may become comatose and hypotensive. Bradycardia and asystole/cardiac arrest have been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Cardiac Effects). Death is due to respiratory and circulatory depression.

Pharmacokinetic Information

In overdose settings, saturation of the hepatic hydroxylation system occurs and zero order kinetics predominate. Elimination follows a Michaelis-Menten model with a prolonged half-life. As phenytoin is continually excreted, elimination changes from zero order to first order kinetics and drug levels decrease more.

Serial plasma phenytoin concentrations should be monitored. In acute overdose, peak levels are frequently delayed for 24 to 48 hours, and occasionally as long as 7 days.

The proportion of phenytoin in plasma not bound to protein is an important measure of potential toxicity with free phenytoin levels of <1.5 micrograms/mL indicating no signs of toxicity; 1.5 micrograms/mL to 5 micrograms/mL seen with mild to moderate intoxication; and levels above 5 micrograms/mL associated with severe intoxication.

Treatment of Overdosage

Treatment is non-specific since there is no known antidote. Most cases of overdosage may be managed conservatively with symptomatic and supportive care. Signs and symptoms of toxicity may persist up to 7 to 10 days after ingestion.

Phenytoin is poorly absorbed in the stomach, therefore although routine use of activated charcoal is not recommended, it may be considered in the rare patient with a life threatening ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Administration of a further dose of activated charcoal may be considered in patients with rising serum phenytoin levels or worsening clinical condition despite initial decontamination.

Peritoneal dialysis, diuresis, haemodialysis, plasmapheresis, haemofiltration and total exchange transfusion may be of little benefit although the latter has been used in the treatment of severe intoxication in children.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

DILANTIN is an anticonvulsant drug, which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex, where the spreading of seizure activity is inhibited. It is likely that by promoting sodium efflux from neurones, DILANTIN tends to stabilise the threshold against hyperexcitability caused by excessive stimulation or those environmental changes capable of reducing the gradient of sodium ions through membranes. This also applies to the reduction of post-tetanic potentiation at synapse level. Losing post-tetanic potential prevents the cortical seizure foci from deteriorating neighbouring cortical areas. In this sense, DILANTIN reduces the maximal activity of brain centres associated with the tonic phase of generalised tonic-clonic (grand mal) seizures.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In general the reported plasma half-life of phenytoin averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5 to 7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

DILANTIN Capsules *in vivo* performance is characterised by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 hours.

Distribution

For DILANTIN Capsules, peak serum levels occur 4 to 12 hours after administration.

Conventionally, with drugs following linear kinetics the half-life is used to determine the dose rate, drug accumulation and the time to reach steady-state. Phenytoin, however, demonstrates non-linear kinetics and therefore the half-life is affected by the degree of absorption, saturation of metabolic pathways, dose and the 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. When administering phenytoin to a patient it is necessary to measure 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 more often with serum levels between 10 micrograms/mL and 20 micrograms/mL. Therapeutic concentrations of free (unbound) phenytoin, which are frequently monitored in patients with altered protein-binding, usually fall in the range of 0.8 micrograms/mL to 2 micrograms/mL.

In most patients maintained at steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolisers of phenytoin.

Unusually high levels of phenytoin result from liver disease, congenital enzyme deficiency or drug interactions, which result in metabolic interference. Patients with large variations in phenytoin plasma levels, despite standard doses, present a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. 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.

Metabolism

Phenytoin is metabolised in the liver primarily by CYP2C9 (major) and CYP2C19 (minor) (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 decreased 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 (e.g. CYP3A4). Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable, at high plasma levels small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range.

Excretion

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 with glomerular filtration but more importantly with tubular secretion.

The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Food Effect of Bioavailability of DILANTIN Capsules

The C_{max} and AUC data from a food-effect study involving administration of DILANTIN 100 mg to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Phenytoin was negative in the Ames test and in the *in vitro* clastogenicity assay in Chinese hamster ovary (CHO) cells. In studies reported in the literature, phenytoin was negative in the *in vitro* mouse lymphoma assay and the *in vivo* micronucleus assay in mouse. Phenytoin was clastogenic in the *in vitro* sister chromatid exchange assay in CHO cells.

Carcinogenicity

In carcinogenicity studies, phenytoin was administered in the diet to mice (10, 25, or 45 mg/kg/day) and rats (25, 50, or 100 mg/kg/day) for 2 years. The incidences of hepatocellular tumors were increased in male and female mice at the highest dose. No increases in tumor incidence were observed in rats. The highest doses tested in these studies were associated with peak serum phenytoin levels below human therapeutic concentrations.

In carcinogenicity studies reported in literature, phenytoin was administered in the diet for 2 years at doses up to 300 ppm (approximately 60 mg/kg/day) and 600 ppm (approximately 160 mg/kg/day) to male and female mice respectively, and up to 2400 ppm (approximately 120 mg/kg/day) to rats. The incidence of hepatocellular tumors were increased in female mice at all but the lowest dose tested. No increases in tumor incidence were observed in rats. Phenytoin-induced hepatic tumors in mice may be secondary to hepatic enzyme induction in those species and are of uncertain clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

DILANTIN 30 mg capsules contain lactose monohydrate, Confectioner's Sugar (ID 1749), magnesium stearate, purified talc, titanium dioxide, carbon black and gelatin.

DILANTIN 100 mg capsules contain lactose monohydrate, Confectioner's Sugar (ID 1749), purified talc, magnesium stearate, titanium dioxide, sunset yellow FCF, erythrosine, carbon black and gelatin.

6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

30 mg and 100 mg capsules are packaged in HDPE bottles with a child-resistant polypropylene cap. One bottle contains 200 capsules.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 295264 - DILANTIN phenytoin sodium 30 mg capsule bottle

AUST R 295265 - DILANTIN phenytoin sodium 100 mg capsule bottle

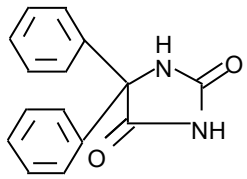
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

The molecular structure of phenytoin is shown below:



Chemical name: 5,5-diphenylimidazolidine-2,4-dione

Molecular formula: C15H12N2O2

Molecular weight: 252.272

Phenytoin is a white, or almost white, odourless or almost odourless, crystalline powder. It is practically insoluble in water and soluble 1 in 70 alcohol.

Phenytoin sodium is the sodium salt of phenytoin. It is a white, odourless, slightly hygroscopic crystalline powder. It is soluble in water and alcohol.

CAS Number

CAS registry number: 57-41-0.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

11/12/2017

10 DATE OF REVISION

26/10/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Separate PI for DILANTIN Capsules Minor editorial changes to PI

DILANTIN® is a Viatris company trade mark

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