Public Health Link

From the Chief Medical Officer for Wales

Distribution:	As Appendix 1
From:	Andrew Evans, Directorate of Health Policy
Date:	22 October 2018
Reference:	CEM/CPhA/2018/16b
Category:	Immediate (within 24 hours)
Title:	Epanutin (Phenytoin) 30mg/5ml Oral Suspension - Supply Disruption
What is this about:	Supply Validation Protocols - Full details are set out below.
Why has it been sent:	For your information and to pass on to Colleagues

Issue:
Pfizer will be out of stock of Epanutin (phenytoin) 30mg/5ml oral suspension from the week commencing 29 October 2018 until early December 2018.

This alert gives advice for all healthcare professionals who prescribe, dispense or administer Epanutin oral suspension. The alert also makes reference to unlicensed preparations, the Patient Information Leaflet (PIL) and product monograph is also attached.

Department of Health & Social Care

Supply Disruption Alert

SDA/2018/002 Issued: 22nd October 2018 at 14:30 Valid until: 10th December 2018

Epanutin (phenytoin) 30mg/5ml Oral Suspension– Supply Disruption

Summary

Pfizer will be out of stock of Epanutin (phenytoin) 30mg/5ml oral suspension from w/c 29th October until early December 2018.

Pfizer are the sole licensed UK supplier of this product and alternative phenytoin formulations are not directly interchangeable; switching to alternative formulations may require specialist advice, support, or referral.

For action by

Care Trusts, Mental Health Trusts, Learning Disabilities Trusts, Mental Health & Social Care Trusts, Specialist Trusts, Ambulance Trusts, Acute Trusts, Mental Health & Learning Disabilities, NHS Regional Offices, Community Trust

Action start date: 22/10/2018

Action

Different formulations of phenytoin are not interchangeable and careful management of switching and monitoring is required. All health care professionals in primary, secondary or specialist healthcare services who prescribe, dispense or administer Epanutin oral suspension, should be aware of the following advice:

All Patients

- General Practitioners should identify all patients currently prescribed Epanutin 30mg/5ml oral suspension. Early contact should be made with the patient or patient's parent/carer to determine if the stocks at home will last until early December, or if any switches are likely to be required during the next 7-8 weeks.
- If the patient has sufficient supplies to last them until early December 2018, then no further action is required. These patients should **not** be issued with a repeat prescription during this period.

If a patient does not have sufficient supplies to last until early December, the following advice should be followed:

Paediatric Patients (<18 years of age)

- The patient should be referred to their specialist prescriber. Switching to alternative formulations should be undertaken by specialist prescribers only

Adult Patients (>18 years of age)

- Switching some patients to alternative formulations may be managed in the community with the support of a clinical specialist
- General Practitioners should make early contact with secondary care or tertiary care to seek support on the most suitable management plan for the patient and monitoring requirements if needed
- Prescribers may wish to use advice in later sections of this alert when switching patients to alternative products

Prescribers should work in close collaboration with their pharmacists to understand which phenytoin formulations are available. Prescribers and pharmacists should work together to ensure correct calculation of dosing and monitoring of plasma levels are undertaken when patients are switched to alternative formulations.

Patients should revert to Epanutin 30mg/5ml oral suspension when supplies are back in stock and prescribers should liaise with their pharmacists to be alerted to this.

Deadlines for actions

Actions initiated:	22/10/2018
Actions completed:	10/12/2018

Product details

Pfizer Epanutin® (phenytoin) 30mg/5ml Oral Suspension 500ml bottle.

Background

There is a global short-term supply issue affecting Epanutin suspension due to global manufacturing delays. Pfizer are the sole licensed UK supplier of phenytoin 30mg/5ml oral suspension.

It is anticipated that current stock will be depleted week commencing 29th October 2018. Further deliveries are currently anticipated early December, however exact dates have not been confirmed.

Epanutin oral suspension is licensed for the control of tonic-clonic seizures, partial seizures or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. It has also been employed in the treatment of trigeminal neuralgia as second line therapy. Dosage is individualised as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. In some cases serum level determinations may be necessary for optimal dosage adjustments.[1]

The MHRA has classified phenytoin as a Category 1 antiepileptic drug, which means there are clear indications that clinically relevant differences between different manufacturers' products might occur, even when the pharmaceutical forms are the same and bioequivalence has been shown. Therefore, the patient should be maintained on a specific manufacturer's product.[2]

However, in the event of a shortage of a product, it may not be possible to maintain the patient on their previous preparation, and therefore all product switches should be carried out with care and close monitoring.[3]

Advice on switching patients

It is recommended that patients who require switching should be prescribed an alternative phenytoin oral suspension in the first instance. If a patient is considered for this switch, prescribers should be aware of the following:

- Although phenytoin alternative oral suspensions are unlicensed, expert clinical advice is that it is preferable, where possible, to switch patients to these products.
- The alternative oral suspension may be of a different strength to Epanutin
- As Epanutin oral suspension contains phenytoin **base**, patients switching product should be prescribed an oral suspension containing phenytoin **base**
- Any decision to prescribe an unlicensed medicine must take into account the relevant GMC guidance and NHS Trust governance procedures. Please see link to GMC guidance: https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines

Information on other preparations are discussed below.

Dose equivalence and conversion

Doses of the phenytoin base preparations (suspension and Infatabs) require dose conversion when switching formulation from or to the sodium salt preparations (capsules, injection, tablets).[3]

Although 100mg of phenytoin sodium is equivalent to 92mg of phenytoin base on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent. Thus, care should be taken where it is necessary to change the dosage form and serum level monitoring is advised.[1] In practice, the conversion used is, phenytoin sodium 100mg is equivalent to phenytoin base 90mg therefore 45mg of suspension (7.5ml of 30mg/5ml) is equivalent to a 50mg capsule.[4]

Alternative formulations

Licensed preparation

There are a number of alternative licensed phenytoin preparations available (see table). However please note that none of the licensed alternatives are in the form of suspension.

Formulation	Strength	Presentation	Phenytoin sodium OR base
Phenytoin Capsules	25, 50, 100 and 300mg	Oral Capsules	Phenytoin sodium
Phenytoin Tablets	100mg	Oral Tablets	Phenytoin sodium
*Epanutin Infatabs	50mg	Chewable Tablets	Phenytoin base

*please be aware that supplies of Epanutin Infatabs are only available to meet normal market demand, as such **patients should not be switched to Epanutin Infatabs as this may precipitate a shortage of this presentation,**

In the case of the alternative suspensions not being suitable, advice can be sought from pharmacy on emptying out capsules for dispersion[3,5] (unlicensed use). It should be noted that as the capsule contents do not dissolve, they cannot be used for withdrawal of part doses.

Unlicensed Preparations

To help mitigate the shortage, Pfizer has obtained approval from the Medicines and Healthcare Regulatory Agency (MHRA) to import stock of phenytoin oral suspension from Canada. This stock is considered an unlicensed preparation in the UK. It is important to note that supplies of this product are very limited and therefore it may not be possible to access for all patients. The bottle size of this product is half that of Epanutin oral suspension. Further details on Epanutin and Dilantin-30 are below and copies of the Patient Information Leaflet and product monograph have been included with this alert on the CAS website.

Name	Strength	Presentation	Bottle Size	Phenytoin sodium OR base
Epanutin	30mg/5ml	Oral Suspension	500ml	Phenytoin base
*Dilantin-30	30mg/5ml	Oral Suspension	250ml	Phenytoin base

*please be aware that there are some differences in excipients to that in Epanutin

Unlicensed phenytoin suspensions are available from a number of specials manufacturers. In addition, unlicensed specialist importers may be able to source phenytoin oral suspension from abroad. Pharmacists will know how to source these unlicensed and specials products and should be able to advise you further. Before prescribing, you should liaise with your pharmacist to clarify local availability of products.

When prescribing and dispensing unlicensed preparations, prescribers and pharmacists should always ensure the following:

- Ensure patient consent has been sought for use of an unlicensed preparation
- It should be confirmed whether the unlicensed phenytoin oral suspension contains phenytoin **sodium** or phenytoin **base** (Epanutin oral suspension contains phenytoin **base**)
- If a switch is made to a different strength suspension, prescribers, carers and patients must be made aware of the change in strength and ensure the correct dose is being taken
- Patients are supplied sufficient quantity of a specific unlicensed preparation to cover until Epanutin returns in stock in early December 2018

Monitoring Patients After Switching

- A change in formulation should always be overseen by a specialist.
- As different formulations of phenytoin may not be bioequivalent, monitoring of plasma levels of phenytoin is advisable before and one week after any phenytoin product switch. GPs may need to seek local advice on how to do this and access Therapeutic Drug Monitoring services
- Patients who have switched to another product should be referred to a specialist for review if there are changes in seizure control or the product is not tolerated

References

1. Pfizer Limited. Epanutin 30mg/5ml oral Suspension. SPC; date of revision of the text, 09/2018: https://www.medicines.org.uk/emc/product/2257/smpc

2. MHRA. Antiepileptic drugs: updated advice on switching between different manufacturers' products, Published 24 November 2017: https://www.gov.uk/drug-safety-update/antiepileptic-drugs-updated-advice-on-switching-between-different-manufacturers-products
3. The NEWT Guidelines. Phenytoin monograph updated October 2017 http://www.newtguidelines.com/
4. Evelina London Paediatric Formulary. Phenytoin monograph, last published on 03 October, 2014: http://cms.ubqo.com/public/d2595446-ce3c-47ff-9dcc-63167d9f4b80/content/99e5ed1f-8143-453e-a8ea-45984597e32a
5. Handbook of Drug Administration via Enteral Feeding Tube: https://about.medicinescomplete.com/publication/drug-administration-via-enteral-feeding-tubes/

Distribution

If you are responsible for cascading these alerts in your organisation, these are our suggested distribution lists; however, each organisation needs to ensure a senior clinician takes responsibility for coordinating all actions that need to be taken.

- General practitioners
- Practice nurses
- Chief pharmacist
- Allergy specialists/allergy teams
- School nursing/medical services
- Emergency Preparedness and Response officer
- Medical directors
- Pharmacists
- Paediatricians
- Paediatrics departments

Please note: CQC and OFSTED do not distribute these alerts. Independent healthcare providers and social care providers can sign up to receive Supply Disruption Alerts directly from the Medicines and Healthcare products Regulatory Agency's Central Alerting System (CAS) by sending an email to: safetyalerts@mhra.gov.uk and requesting this facility.

Enquiries

Send enquiries about this notice to the DH Supply Resilience Team, quoting reference number SDA/2018/002.

Email: supplyresiliencemd@dh.gsi.gov.uk

Addressees may take copies for distribution within their own organisations

PRODUCT MONOGRAPH

PrDILANTIN INFATABS®

(Phenytoin Tablets 50mg, USP)

PrDILANTIN® - 30 SUSPENSION
PrDILANTIN® - 125 SUSPENSION

(Phenytoin Oral Suspension 30mg/5mL & 125mg/5mL, USP)

Anticonvulsant

® Warner-Lambert Company LLC
Pfizer Canada Inc, Licensee
Kirkland, Quebec H9J 2M5

Date of Revision:
July 20, 2018

Submission Control No: **215486**

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PrDILANTIN INFATABS®
(Phenytoin Tablets 50mg, USP)

PrDILANTIN® - 30 SUSPENSION
PrDILANTIN® - 125 SUSPENSION
(Phenytoin Oral Suspension 30mg/5mL & 125mg/5mL, USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Infatabs 50 mg	Alcohol, magnesium stearate, spearmint oil, sugar and talc
	Suspension 30 mg/ 5 ml, 125 mg/5 ml	Alcohol, banana oil, citric acid, glycerin, magnesium aluminium silicate, orange oil, polysorbate 40, Red #2 FD&C (30 mg/5mL suspension only), sodium benzoate, sodium carboxymethylcellulose, sugar, vanillin, yellow #6 FD&C and water
		For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

DILANTIN INFATABS (phenytoin tablets USP) and DILANTIN-30 Suspension / DILANTIN-125 Suspension (phenytoin oral suspension) are indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

Patients who are hypersensitive to phenytoin, other hydantoins, or any of the excipients. For a complete listing of ingredients, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

DILANTIN INFATABS (phenytoin tablets USP) and DILANTIN-30 / DILANTIN-125 Suspension (phenytoin oral suspension) are contraindicated to patients who are hypersensitive to

phenytoin, to other hydantoins or to any of the nonmedicinal ingredients in the formulations (see **WARNINGS AND PRECAUTIONS, Hypersensitivity**).

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

Because of its effect on ventricular automaticity, DILANTIN is contraindicated in patients who currently suffer from sick sinus syndrome, sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular (A-V) block, QT interval prolongation, Adams-Stokes syndrome, or other heart rhythm disorders (see **WARNINGS AND PRECAUTIONS, OVERDOSAGE**).

WARNINGS AND PRECAUTIONS

General

DILANTIN Infatabs (phenytoin tablets USP) or DILANTIN 30 Suspension/DILANTIN-125 Suspension (phenytoin oral suspension USP) should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medication arises, this should be done gradually. However, in the event of an allergic hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant drug which does not belong to the hydantoin chemical class.

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

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

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.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

In patients with renal or hepatic impairment or in those with hypoalbuminemia, there is increased plasma levels of unbound phenytoin. In patients with hyperbilirubinemia, plasma levels of unbound phenytoin may also be elevated. Since unbound phenytoin concentrations may be more useful in these patient populations, it may affect dosing considerations (see **DOSAGE AND ADMINSTRATION, Renal or Hepatic Disease**).

Skin

Serious Dermatological Reactions

Hypersensitivity Syndrome / Drug Reaction with Eosinophilia and Systemic Symptoms

Hypersensitivity Syndrome (HSS) or Drug rash 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, hematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leukocytosis, and eosinophilia. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

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

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported with phenytoin. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of DRESS (see **WARNINGS AND PREACUTIONS, Skin**). In countries with mainly Caucasian populations, these reactions are estimated to occur in 1 to 6 per 10,000 new users, but in some Asian countries (e.g., Taiwan, Malaysia and the Philippines) the risk is estimated to be much higher (see **WARNINGS AND PRECAUTIONS, Skin - Asian Ancestry and Allelic Variation in the HLA-B Genotyping**).

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. In any of the above instances, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Treatment recommendations for dermatological reactions
Phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus or SJS or TEN is suspected, use of this drug should not be resumed and alternative therapy should be considered (see **ADVERSE REACTIONS**). 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 use of other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who have shown severe dermatological reactions during phenytoin treatment. If a rash occurs and SJS or TEN is not suspected, the patient should be evaluated for signs and symptoms of DRESS (see **WARNINGS AND PRECAUTIONS, Skin**).

Asian Ancestry and Allelic Variation in the HLA-B Genotyping

HLA-B*1502

In studies that included small samples of patients of Asian ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia[1]. Results of these studies suggest that the presence of the HLA-B *1502 allele may be one of the risk factors for phenytoin-associated SJS/TEN in patients with Asian ancestry. Therefore, physicians should consider HLA-B *1502 genotyping as a screening tool in these patients. Until further information is available, the use of phenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele.

Important Limitations of HLA-B Genotyping

HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with phenytoin will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

In addition, it should be kept in mind that the majority of phenytoin treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration when deciding whether to screen genetically at-risk patients currently on phenytoin.

Should signs and symptoms suggest a severe skin reaction such as SJS or TEN, phenytoin should be withdrawn at once.

Hepatic/Biliary/Pancreatic

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment (see **WARNINGS AND PRECAUTIONS, Skin**). Other common manifestations include arthralgias, rash, jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. 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 liver is the chief site of biotransformation of phenytoin. Patients with impaired liver

[1] The following rates provide a rough estimate of the prevalence of HLA-B*1502 in various populations. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but this may be higher in some groups. HLA-B*1502 is present in <1% of the population in Japan and Korea. HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). The estimated prevalence rates have limitations due to the wide variability in rates that exist within ethnic groups, the difficulties in ascertaining ethnic ancestry and the likelihood of mixed ancestry.

function, elderly patients, or those who are gravely ill may show early signs of toxicity (see **OVERDOSAGE**).

Toxic hepatitis, liver damage, and hypersensitivity syndrome have been reported and may, in rare cases be fatal (see **ADVERSE REACTIONS**).

Immune

Hypersensitivity

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see **CONTRAINDICATIONS**). If there is a history of hypersensitivity reactions to structurally similar drugs, such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these patients or immediate family members, other alternatives should be considered.

Cardiovascular

Cardiac Effects

Cardiac-related adverse events have been reported in association with therapeutic and supratherapeutic levels of phenytoin in patients with or without history of cardiac disease or comorbidities and with or without other medications present. These reactions occurred in all age groups and included bradycardia, ventricular tachycardia, cardiac arrest, and death. In a number of cases, patients recovered following phenytoin dose reduction or discontinuation. Patients with any underlying cardiac conditions should be evaluated on an individual basis, and potential benefits of phenytoin treatment should be assessed against its potential risks (see **CONTRAINDICATIONS, OVERDOSAGE**).

Hematologic

Hematopoietic

Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, 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 generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling DRESS (see **WARNINGS AND PRECAUTIONS, Skin**). 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 anticonvulsant drugs.

While macrocytosis and megaloblastic anemia 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.

Carcinogenesis and Mutagenesis

(See WARNINGS AND PRECAUTIONS, Hematopoietic; WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women)

Endocrine and Metabolism

Porphyria

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.

Hyperglycemia

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

Musculoskeletal

Chronic use of phenytoin by patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, osteomalacia) and bone fractures (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients. Consideration should be given to monitoring with bone-related laboratory and radiological tests and initiating treatment plans, as appropriate.

Neurologic

Central Nervous System

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, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of phenytoin therapy is recommended (see **ACTION AND CLINICAL PHARMACOLOGY; Pharmacokinetics-Absorption WARNINGS AND PRECAUTIONS, General**).

Driving/Operating Machinery

Patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on phenytoin to gauge whether or not it affects their mental and/or motor performance adversely.

Psychiatric

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Special Populations

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

Pregnant Women

Risks to mother: 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 (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Absorption**). However, postpartum restoration of the original dosage will probably be indicated.

Risks to fetus: Phenytoin crosses the placental barrier and 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.

Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), and abnormalities characteristic of fetal hydantoin syndrome, including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits, have been reported among children born to women with epilepsy who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy.

Risk to newborn:
A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

There have been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

Therefore, DILANTIN should be used during pregnancy only if the potential benefit outweighs the potential risks. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus from exposure to phenytoin.

Counsel pregnant women and women of childbearing potential about alternative therapeutic options.Women of childbearing potential who are not planning a pregnancy should be advised regarding the use of effective contraception during treatment. Phenytoin may result in a failure of the therapeutic effect of hormonal contraceptives.(see **DRUG INTERACTIONS, Drug-Drug Interactions**, Table 4).

Nursing Women: Infant breast feeding is not recommended for women taking phenytoin. Phenytoin is secreted into human milk. Limited observations in patients suggest that phenytoin concentration in breast milk is approximately one-third of the corresponding maternal plasma concentration.

Geriatrics (> 65 years of age): Phenytoin clearance is decreased slightly in elderly patients (see **DOSAGE AND ADMINISTRATION, Geriatrics**).

Monitoring and Laboratory Tests
Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Information for Patients and Caregivers
Patients and caregivers should be advised to read the Consumer Information sheet for DILANTIN Infatabs prior to use. Patients receiving DILANTIN Infatabs, and caregivers, should be given the following instructions by the physician and pharmacist:

1. Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing their physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

2. Patients should be advised of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should

be reported even if mild or when occurring after extended use. Patients should also be advised that a history of hypersensitivity reactions with other antiepileptic drugs may be a risk for developing reactions with phenytoin (see **WARNINGS AND PRECAUTIONS, Hematologic; Immune; Skin; Hepatic/Biliary/Pancreatic**).

3. Patients should be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice (see **DRUG INTERACTIONS**).

4. Patients should be instructed to call their physician if skin rash develops.

5. The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

6. Patients, their caregivers, and families should be counseled that antiepileptic drugs, including DILANTIN Infatabs, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers (see **WARNINGS AND PRECAUTIONS, Psychiatric**).

7. Women of child-bearing potential should be warned to consult their physician regarding the discontinuation of the drug due to the potential hazards to themselves and to the fetus if they are pregnant or intend to become pregnant (see **WARNINGS AND PRECAUTIONS, Special Populations – Women of child-bearing potential, Pregnant Women, Nursing Women**).

8. Patients who become pregnant should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients themselves must call the toll free number 1-888-233-2334. Registry information can also be obtained from the Internet at http://www.massgeneral.org/aed/

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following listing of adverse events is based on adverse events reported in clinical trials and/or spontaneous adverse event reports from post-marketing experience. A frequency cannot be estimated from the available data and is therefore classified as 'not known'.

Body as a whole: Anaphylactic reaction and anaphylaxis

Central Nervous System: The most common manifestations encountered with DILANTIN 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 **WARNINGS AND PRECAUTIONS, Neurologic**). Dizziness, vertigo,

insomnia, transient nervousness, motor twitchings, headaches, paresthesia and somnolence have also been observed.

There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

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

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, and Peyronie's Disease.

Gastrointestinal System: Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, constipation (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Hematopoietic System: Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy, including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease has been reported (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Immunologic: Drug rash with eosinophilia and systemic symptoms (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. Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients (see **WARNINGS AND PRECAUTIONS, Skin**).

Investigations: Thyroid function test abnormal

Musculoskeletal System: Bone fractures and osteomalacia have been associated with chronic use of phenytoin by patients with epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcemia, hypophosphatemia and decreased levels of Vitamin D metabolites have also been reported (see **WARNINGS AND PRECAUTIONS, Musculoskeletal**).

Skin: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, and Stevens-Johnson syndrome and toxic epidermal necrolysis (see **WARNINGS AND PRECAUTIONS, Skin**). There have also been reports of hypertrichosis.

Special Senses: Taste perversion

DRUG INTERACTIONS

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

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

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

The most commonly occurring drug interactions are listed below.

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

Table 1. Drugs Which May Increase Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
Analgesic/anti-inflammatory agents	azapropazone phenylbutazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides (e.g. ethosuximide) valproate sodium topiramate[a]
Antifungal agents	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastic agents	capecitabine fluorouracil
Benzodiazepines/psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone phenothiazine viloxazine
Calcium channel blockers/ Cardiovascular agents	amiodarone dicumarol diltiazem nifedipine ticlopidine
H_2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	estrogens
Immunosuppressant drugs	tacrolimus

Drug Classes	Drugs in each Class (such as)
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

[a] Coadministration with topiramate reduces serum topiramate levels by 59%, and has the potential to increase phenytoin levels by 25% in some patients. The addition of topiramate therapy to phenytoin should be guided by clinical outcome.

2. **Table 2** summarizes drugs which may decrease phenytoin serum levels.

Table 2. Drugs Which May Decrease Phenytoin Serum Levels

Drug Classes	Drugs in each Class (such as)
Alcohol (chronic intake)	
Antibacterial agents/Fluoroquinolones	ciprofloxacin rifampin
Anticonvulsants	carbamazepine vigabatrin[b]
Antineoplastic agent	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiretrovirals	fosamprenavir nelfinavir ritonavir
Antiulcer agents	sucralfate
Bronchodilators	theophylline
Calcium preparation	molindone hydrochloride
Cardiovascular agents	reserpine
Folic Acid	folic acid
Hyperglycemic agents	diazoxide
Protease Inhibitors	nelfinavir
St. John's Wort	St. John's Wort

[b] Coadministration with vigabatrin reduces serum phenytoin levels by 20 to 30%. This may be clinically significant in some patients and may require dosage adjustment.

Molidone hydrochloride
Molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin.

Calcium Preparations
Ingestion times of phenytoin and antacid calcium preparations, including antacid preparations containing calcium should be staggered to prevent absorption problems.

Nelfinavir
A pharmacokinetic interaction study between nelfinavir (1,250 mg twice a day) and phenytoin (300 mg once a day) administered orally showed that nelfinavir reduced AUC values of phenytoin (total) and free phenytoin by 29% and 28% (n=12), respectively. The plasma concentration of nelfinavir was not changed (n=15). Phenytoin concentration should be monitored during coadministration with nelfinavir, as nelfinavir may reduce phenytoin plasma concentration.

3. **Table 3** summarizes drugs which may either increase or decrease phenytoin serum levels.

Table 3. Drugs Which May Either Decrease or Increase Phenytoin Serum Levels

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

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

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

5. **Table 4** summarizes drugs whose blood serum levels and/or effects may be altered by phenytoin.

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

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

Drug Classes	Drugs in each Class (such as)
	oral contraceptives
Hyperglycemic agents	diazoxide
Immunosuppressant	cyclosporine
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamins	vitamin D
Folic Acid	Folic Acid

[a] Coadministration with lamotrigine doubles the plasma clearance and reduces the elimination half life of lamotrigine by 50%. **This clinically important interaction requires dosage adjustment for lamotrigine.** There is no significant change in phenytoin plasma levels in the presence of lamotrigine.

[b] Coadministration with topiramate reduces serum topiramate levels by 59%, and has the potential to increase phenytoin levels by 25% in some patients. **The addition of topiramate therapy to phenytoin should be guided by clinical outcome.**

Drug-Food Interactions

Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation.

More frequent serum phenytoin level monitoring may be necessary in these patients.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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 increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT). Phenytoin may affect blood calcium and blood sugar metabolism tests.

Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

DILANTIN SUSPENSIONS ARE NOT FOR PARENTERAL USE.

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

DILANTIN extended capsules are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in DILANTIN-30 Suspension and DILANTIN-125 Suspension and DILANTIN Infatabs. Because there is approximately an 8% increase in drug content with the free acid 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.

Recommended Dose and Dosage Adjustment

General
DILANTIN Infatabs (phenytoin tablets, USP) and DILANTIN-30 Suspension/DILANTIN-125 Suspension (phenytoin oral suspension, USP) are not for once-a-day dosing.

Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments. The clinically effective serum level is usually 40-80 micromol/L (10-20 mcg/mL). Serum blood level determinations are especially helpful when possible drug interactions are suspected. With recommended dosage, a period of 7 to 10 days may be required to achieve therapeutic blood levels with DILANTIN and changes in dosage (increase or decrease) should not be carried out at intervals shorter than 7 to 10 days.

Adults
Patients who have received no previous treatment may be started on 2 DILANTIN Infatabs 3 times daily or on 1 teaspoonful (5 mL) of DILANTIN-125 Suspension 3 times daily, and the dose then adjusted to suit individual requirements. For some adults, the satisfactory maintenance dosage will be 8 DILANTIN Infatabs daily; an increase to 12 DILANTIN Infatabs may be made, if necessary. With DILANTIN-125 Suspension, an increase to 5 teaspoonfuls (25 mL) daily may be made if necessary.

Pediatrics (< 18 years of age)
Initially, 5 mg/kg/day of DILANTIN Infatabs, DILANTIN-30 Suspension or DILANTIN-125 Suspension may be given in 2 or 3 equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years may require the minimum adult dose (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

Geriatrics (> 65 years of age)
Phenytoin clearance is decreased slightly in elderly patients. Lower doses than the doses

recommended for adults may be required when initiating treatment. Phenytoin dosing requirements are highly variable and must be individualized **(see ACTION AND CLINICAL PHARMACOLOGY – Special Populations – Geriatrics)**.

Renal or Hepatic Disease
In patients with renal or hepatic impairment or in those with hypoalbuminemia, plasma levels of unbound phenytoin are elevated. Unbound phenytoin concentrations may be more useful in these patient populations. This finding should be considered during therapeutic monitoring and following phenytoin serum level determinations, which may be necessary for optimal dosage adjustment (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment; **(see WARNINGS AND PRECAUTIONS – General)**

Missed Dose
The patient/caregiver should be advised that if a dose is missed, the missed dose should be taken as soon as it is remembered. If it is almost time for the next dose, the missed dose should not be taken. Instead, take the next scheduled dose. The patient/caregiver should be advised to not to make up for a missed dose by taking a double dose next time.

OVERDOSAGE

For management of suspected drug overdose, contact the regional Poison Control Centre.

The lethal dose of DILANTIN Infatabs (phenytoin tablets USP) and DILANTIN 30 Suspension/DILANTIN 125 Suspension (phenytoin oral suspension USP) in pediatric patients is not known. The lethal dose of phenytoin in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, somnolence, drowsiness, lethargy, slurred speech, blurred vision, nausea, vomiting. The patient may become comatose and hypotensive. Bradycardia and asystole/cardiac arrest have been reported (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Cardiac effects**). Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus on lateral gaze, usually appears at 80 micromol/L (20 mcg/mL), ataxia at 119 micromol/L (30 mcg/mL). Dysarthria and lethargy appear when the serum concentration is > 159 micromol/L (40 mcg/mL), but a concentration as high as 198 micromol/L (50 mcg/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 over >396 micromol/L (100 mcg/mL) with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment and Management

Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DILANTIN Infatabs (phenytoin tablets USP) and DILANTIN-30 Suspension/DILANTIN-125 Suspension (phenytoin oral suspension) are anticonvulsant drugs which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

Pharmacokinetics

Absorption: Phenytoin is a weak acid and has limited hydrosolubility, even in the intestine. The compound undergoes a slow and somewhat variable absorption after oral administration.

Clinical studies using DILANTIN Infatabs have shown an average plasma half-life of 14 hours with a range of 7 to 29 hours. The plasma half-life of phenytoin in man after oral administration of phenytoin oral suspension averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days after initiation of therapy with recommended doses of 300 mg/day.

In most patients maintained at a 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 hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin serum levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

When serum level determinations are necessary, they should be obtained at least 7 - 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. Trough levels obtained just prior to the patient's next scheduled dose provide information about clinically effective serum level range and confirm patient compliance. Peak drug levels, obtained at the time of expected peak concentration, indicate an individual's threshold for emergence of dose-related side effects. For DILANTIN Infatabs, DILANTIN-30 Suspension and DILANTIN-125 Suspension, peak serum levels occur 1½-3 hours after administration.

Clinical studies show that chewed and unchewed DILANTIN Infatabs are bioequivalent, yield approximately equivalent plasma levels, and are more rapidly absorbed than DILANTIN 100-mg capsules (extended phenytoin capsules, USP).

Distribution: Phenytoin is distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile, and breast milk. The concentration of phenytoin in cerebrospinal fluid approximates the level of free phenytoin in plasma.

Metabolism: Phenytoin is biotransformed in the liver by oxidative metabolism. The major pathway involves 4-hydroxylation, which accounts for 80% of all metabolites. Experiments in human liver microsomes have demonstrated that CYP2C9 plays the major role in the metabolism of phenytoin (90% of net intrinsic clearance), while CYP2C19 has a minor involvement in this process (10% of the net intrinsic clearance). In experiments with human liver microsomes, the relative contribution of CYP2C19 to phenytoin metabolism increased with increasing phenytoin concentrations, above the concentrations considered to be in the therapeutic range (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment**).

Pharmacokinetic data on six patients (age range: 22-64 years) receiving phenytoin monotherapy showed that ticlopidine (a CYP2C19 inhibitor), administered for two weeks, decreased plasma clearance of phenytoin.

In a human liver microsome study, phenylbutazone (a CYP2C9 inhibitor) decreased clearance of phenytoin (see **DRUG INTERACTIONS**).

Excretion: Most of the drug is eliminated in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine partly with glomerular filtration but more importantly by tubular secretion. Less than 5% of phenytoin is excreted as the parent compound. Because phenytoin is hydroxylated in the liver by a cytochrome system which is saturable at high serum levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels when these are in or above the upper therapeutic range. The steady state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Special Populations

Geriatrics (>65 years of age)

Phenytoin clearance is decreased slightly in elderly patients (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Lower doses than the doses recommended for adults may be required when initiating treatment. Phenytoin dosing requirements are highly variable and must be individualized. (see **DOSAGE AND ADMINISTRATION, Geriatrics**).

STORAGE AND STABILITY

DILANTIN INFATABS: Store at controlled room temperature 15-30°C. Protect from light and moisture.

DILANTIN-30 Suspension and DILANTIN-125 Suspension: Store at controlled room temperature 15 - 30°C. Protect from freezing and light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DILANTIN INFATABS (phenytoin tablets USP): Each 50-mg flavoured, triangular shaped, grooved tablet contains: 50 mg phenytoin (free acid form). The tablet also contains the following non-medicinal ingredients: alcohol, magnesium stearate, spearmint oil, sugar, and talc. Bottles of 100.

DILANTIN-30 Suspension (phenytoin oral suspension USP): Each 5 mL of flavoured,and coloured (red) DILANTIN-30 suspension contains: 30 mg phenytoin (free acid form). The suspension also contains the following non-medicinal ingredients: alcohol, banana oil, citric acid, glycerin, magnesium aluminum silicate, orange oil, polysorbate 40, Red #2 FD&C, sodium benzoate, sodium carboxymethylcellulose, sugar, vanillin, and yellow #6 FD&C. Bottles of 250 mL.

DILANTIN-125 Suspension (phenytoin oral suspension USP): Each 5 mL of flavoured and coloured (orange) DILANTIN-125 Suspension contains 125 mg phenytoin (free acid form). The suspension also contains the following non-medicinal ingredients: alcohol, banana oil, citric acid, glycerin, magnesium aluminum silicate, orange oil, polysorbate 40, sodium benzoate, sodium carboxymethylcellulose, sugar, vanillin, and yellow #6 FD&C. Bottles of 250 mL.

Also available as:

DILANTIN CAPSULES: (extended phenytoin sodium capsules USP): are available in dosage strengths of 30- and 100-mg capsules.

30 mg: A size 4 hemispherical Coni Snap capsule with a white opaque body and pale pink opaque cap containing a white powder. Capsule is imprinted with black rectified radial print, "PD" on cap and "DILANTIN 30 mg" on body. Bottles of 100.

100 mg: No. 3 Coni-Snap white capsule with orange cap, imprinted Parke-Davis and P-D 100 in black ink. Bottles of 100 and 1000.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

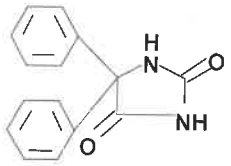
Drug Substance

Proper name: phenytoin

Chemical name: 5,5-diphenyl-2,4-imidazolidinedione

Molecular formula and molecular mass: $C_{15}H_{12}N_2O_2$, 252.27

Structural formula:



Physicochemical properties: phenytoin is related to the barbiturates in chemical structure, but has a 5-membered ring.

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PART III: CONSUMER INFORMATION

DILANTIN® INFATABS®
Phenytoin Tablets USP

DILANTIN®-30 SUSPENSION /DILANTIN®-125 SUSPENSION
Phenytoin Oral Suspension USP

This leaflet is part III of a three-part "Product Monograph" published when DILANTIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DILANTIN.

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DILANTIN has been prescribed to you by our doctor to control seizures. It is specifically used for the control of generalized tonic-clonic seizures, and psychomotor seizures.

What it does:
DILANTIN Infatabs and DILANTIN-30 Suspension/DILANTIN-125 Suspension belong to the family of medicines called anticonvulsant. It acts in the brain to block the spread of seizure activity.

When it should not be used:
- If you are allergic to phenytoin or other medicines of the hydantoin family, including fosphenytoin (CEREBRYX), or to any of the nonmedicinal ingredients in the formulations (see what the nonmedicinal ingredients are).
- If you take Delavirdine (drug used to treat HIV infection).
- If you have slow heart rate (bradycardia), heart block, or other heart problems.

What the medicinal ingredient is:
Phenytoin

What the nonmedicinal ingredients are:
DILANTIN Infatab: alcohol, magnesium stearate spearmint oil, talc and sugar.

DILANTIN-30 and 125 Suspensions: alcohol, banana oil, citric acid, glycerin, magnesium aluminium silicate, orange oil, polysorbate 40, Red #2 FD&C (30 mg/5mL suspension only), sodium benzoate, sodium carboxymethylcellulose sugar, vanillin, yellow #6 FD&C and water.

What dosage forms it comes in:
DILANTIN Infatab: 50 mg phenytoin tablet (free acid form).

DILANTIN-30 Suspension: Each 5 mL of flavoured, red suspension contains 30 mg phenytoin (free acid form).

DILANTIN-125 Suspension: Each 5 mL of flavoured, orange suspension contains 125 mg phenytoin (free acid form).
DILANTIN is also available as extended phenytoin sodium 30 mg and 100 mg capsules.

WARNINGS AND PRECAUTIONS

Do not stop your treatment with DILANTIN without first checking with your doctor as that could cause sudden worsening of your seizure. If you/your child are experiencing any side effects please see "Side Effects and What To Do About Them" section for guidance.

BEFORE you use DILANTIN talk to your doctor or pharmacist if:
- You/your child are diabetic,
- You/your child are anemic.
- You/your child have low bone density,
- You/your child have or have had any kidney or liver disease or blood disorders (including porphyria),
- You/your child have had an allergy to this drug, or other drugs used to treat your condition,
- You/your child have slow heart rate (bradycardia), fast heart rate (tachycardia), heart block, or a history of cardiac arrest (asystole). Regardless of your cardiac history, tell your doctor if you experience any of the adverse events listed above when taking DILANTIN,
- You are pregnant or thinking about becoming pregnant. If you take DILANTIN during pregnancy your baby is at risk for serious birth defects, such as cleft lip or cleft palate. Birth defects may happen even in children born to women who are not taking any medicines and do not have any other risk factors. All women of child-bearing age who are being treated for epilepsy should talk to their healthcare providers about using other possible treatments instead of DILANTIN. If the decision is made to use DILANTIN, you should use effective birth control (contraception) unless you are planning to become pregnant. You should talk to your doctor about the best kind of birth control to use while you are taking DILANTIN.
- You are breast-feeding.
- You/your child are taking other drugs (prescription and over-the-counter medicines), dietary or herbal supplements.
- You consume alcohol on a regular or occasional basis.
- Certain individuals of Asian and /or of black origin may be at an increased risk of developing serious skin reactions during treatment with DILANTIN.
- You/your child have experienced in the past or have a family history of anticonvulsant hypersensitivity syndrome. This may occur rarely in patients treated with anticonvulsant medications and includes symptoms such as fever, rash, hepatitis (such as yellowing of skin and eyes) and lymph node swelling, among other symptoms.

- You/your child are currently being treated with cranial irradiation and corticosteroids.
- You/your child suffer from absence seizures (petit mal) or seizures caused by low blood sugar (hypoglycemia) or other metabolic causes, as DILANTIN is not effective in controlling these types of seizures.
- You/your child have or have had depression, mood problems, or suicidal thoughts or behavior.

When taking DILANTIN:

- Always take DILANTIN as your doctor has prescribed. If it is not possible for you to take DILANTIN as prescribed, tell your doctor.
- Tell your doctor if you develop a skin rash while taking DILANTIN.
- Tell your doctor right away if you develop serious skin reactions such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling that may be accompanied by fever. These reactions may be more frequent in patients of Asian origin. Reports of these reactions have been highest in patients from Taiwan, Malaysia and the Philippines.
- Tell your doctor if you become pregnant while taking DILANTIN. You and your doctor should decide if you will continue to take DILANTIN while you are pregnant. If you become pregnant while taking DILANTIN, talk to your doctor about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicines during pregnancy. Information about the registry can also be found at the website: http://www.aedpregnancyregistry.org/.
- Talk to your doctor about the best way to care for your teeth, gums, and mouth during your treatment with DILANTIN. It is very important that you care for your mouth properly to decrease the risk of gum damage.
- It is recommended that you **do not** drink alcohol while taking DILANTIN, without first talking to your doctor. Drinking alcohol while taking DILANTIN may change your blood levels of DILANTIN, which can cause serious problems.
- Do not drive, operate heavy machinery or do other dangerous activities until you know how DILANTIN affects you. DILANTIN can slow your thinking and motor skills.

INTERACTIONS WITH THIS MEDICATION

There are many drugs that may increase or decrease phenytoin levels. DILANTIN may affect the levels of many drugs. Therefore, tell your doctor or pharmacist about all other prescription and non-prescriptions medication you are talking, as well as dietary and herbal supplements, enteral feeding preparations or nutritional drinks, as there may be a need to adjust your medication or monitor you more carefully.

PROPER USE OF THIS MEDICATION

It is very important that you take these medicines exactly as your doctor has prescribed. Never increase or decrease the dose yourself. Do not stop taking it abruptly unless directed by your doctor as your seizures may increase. Tell your doctor if you cannot take the drug as prescribed, for example if you will be having surgery. You should always check that you have an adequate supply of DILANTIN.

DILANTIN Infatabs and oral suspension are not for once-a-day dosing. These medications must be taken 2 or 3 times per day.

DILANTIN is also available as Extended Phenytoin Sodium Capsules which can be taken once daily. Dosage adjustments are required when switching from DILANTIN Infatabs/oral suspension to the extended phenytoin sodium capsules.

Usual dose:
The dose is adjusted to suit your/your child's response to treatment. In some cases, blood level assessment may be necessary to adjust the dose optimally.

DILANTIN Infatabs

Adult: ***Starting dose***: 2 Infatabs 3 times daily.
Maintenance dose: 8 to 12 Infatabs daily.

Pediatric: ***Starting dose***: 5 mg/kg/day in 2 or 3 equally divided doses.
Maintenance dose: 4 to 8 mg/kg in 2 or 3 divided doses.

DILANTIN-30 Suspension and DILANTIN-125 Suspension
It is important to use an accurate measuring device when using the oral suspension formulation.

Adult: ***Starting dose***: 1 teaspoonful (5 mL) DILANTIN **-125** Suspension 3 times daily.
Maintenance dose: Up to 5 teaspoonfuls (25 mL) DILANTIN **-125** Suspension daily.

Pediatric: ***Starting dose***: 5 mg/kg/day, of DILANTIN Infatabs, DILANTIN-**30** Suspension or DILANTIN-**125** Suspension in 2 or 3 equally divided doses.
Maintenance dose: 4 to 8 mg/kg/day.

The maximum dose recommended for children is 300 mg/day. Children over 6 years old may require the minimum adult dose (300 mg/day).

If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.

Overdose:
Very high doses can cause toxicity or death.

In case of drug overdose, contact the regional Poison Control Centre and talk to a health care practitioner right away, or go to a hospital emergency department even if there are no symptoms. Take your medicine bottle with you to show the doctor.

Missed Dose:
If you/your child miss/misses a dose, take it as soon as you remember. If it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose. Do not try to make up for the missed dose by taking a double dose next time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DILANTIN Infatabs and DILANTIN-30 Suspension/ DILANTIN-125 Suspension can cause side effects, although not everybody gets them.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Get immediate medical help
		Only if severe	In all cases	
Uncommon	Severe skin reactions (rashes, eruptions, skin blistering)			√
	Skin rash and fever with swollen glands, particularly in the first two months of therapy			√
	Sudden wheeziness, difficulty breathing, swelling of eyelids, face or lips, rash or itching			√
	Bruising, fever, looking pale or severe sore throat		√	
	Seizures or fits		√	√
	Suicidal thoughts, self injury, confusion or disorientation		√	
	Gum disorders (red or bleeding gums)		√	
	Liver failure or disorders (jaundice, yellowing of skin and eyes)		√	√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Get immediate medical
Unknown	Softening of the bones (bone pain, broken bones)		√	

Other Side Effects:
If you experience any side effects such as unusual eye movement, changes in muscle movements or co-ordination, slurred speech, confusion, dizziness, vertigo, trouble sleeping (insomnia), lymph node swelling, changes to facial skin or gums, rash, headache, nausea or vomiting, consult your doctor.

This is not a complete list of side effects. For any unexpected effects, or effects that worry you while taking DILANTIN Infatabs or DILANTIN-30 Suspension/ DILANTIN-125 Suspension, contact your doctor or pharmacist.

HOW TO STORE IT

DILANTIN Infatabs: Store at controlled room temperature 15-30°C. Protect from light and moisture.

DILANTIN-30 Suspension and DILANTIN-125 Suspension: Store at controlled room temperature 15 - 30°C. Protect from freezing and light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at** https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada, at:
1-800-463-6001

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