Chief Medical Officer Directorate
Pharmacy and Medicines Division

Scottish Government
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IMMEDIATE MESSAGE TO:

1. Directors of Pharmacy
2. Medical Directors NHS Boards

5 June 2019

Dear Healthcare Professional,

DRUG ALERT - PFIZER EPANUTIN (PHENYTOIN) 30MG/5ML ORAL SUSPENSION – SUPPLY DISRUPTION WILL BE OUT OF STOCK FROM 10 JUNE 2019 UNTIL LATE JULY 2019 – IMMEDIATE ACTION

Please see the attached supply disruption notice and accompanying materials for onward transmission as below.

Could all Directors of Pharmacy please forward this alert to:-

Community Pharmacists
Hospital Pharmacists and pharmacies
Primary Care Pharmacist
Chief Pharmacists
Pharmaceutical Advisors

Please could Medical Directors arrange to forward this alert to the relevant departments and healthcare staff as listed below:-

General Practitioners
Accident & Emergency Departments
Directors of Public Health
A & E Departments, Directors, Consultants and Nurses
Intensive care units
Directors of Intensive Care
Intensive care medical staff/paediatrics
Neonatology Departments
Neonatology Directors
Clinical Governance Leads
Clinical Procurement Specialists
Community Hospitals
Community Nurses
District Nurses
Intensive care nursing staff adult and paediatric
Paediatric intensive care units
Paediatric medicines, directors of

Paediatric nurse specialists
Paediatric departments
Paediatric wards
Paediatricians
School nurses
Special care baby units
NHS walk-in centres
Walk-in centres
Chief Executives of NHS Board

Thank you for your co-operation.

Yours sincerely

IRENE FAZAKERLEY
Medicines Policy Team

INVESTOR IN PEOPLE
POSITIVE ABOUT DISABLED PEOPLE

Supply Disruption Alert

SDA/2019/001 Issued: 06 June 2019 at 15:30 Valid until: 31/07/2019

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

Summary

- Epanutin® (phenytoin) 30mg/5ml oral suspension will be out of stock from w/c 10th June for 6-8 weeks.
- The Canadian brand of Epanutin® 'Dilantin-30®' is equivalent to Epanutin® 30mg/5ml oral suspension and supplies are available on an 'unlicensed' basis.
- Different formulations of phenytoin (other than Dilantin® 30mg/5ml oral suspension) are not interchangeable and if patients are switched to anything other than 'Dilantin® (phenytoin) 30mg/5mL oral suspension' careful management of switching and monitoring is required.

Action

Alternative phenytoin formulations (other than Dilantin® 30mg/5ml oral suspension) are not directly interchangeable; switching to alternative formulations may require specialist advice, support, or referral. Health care professionals in primary, secondary or specialist healthcare services who prescribe, dispense or administer Epanutin® oral suspension, should take the following action:

1. 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 they have enough Epanutin® 30mg/5ml oral suspension to last until end of July.
2. If the patient has sufficient supplies to last them until end of July, then no further action is required.
3. If a patient does not have sufficient supplies to last until end of July, the following advice should be followed.
    i. Switch suitable patients to the unlicensed Canadian brand, ***'Dilantin®'*** (phenytoin) 30mg/5ml oral suspension. This can be considered equivalent to the UK brand ***'Epanutin®'*** (phenytoin) 30mg/5ml oral suspension and no dosing adjustments should be required.
    ii. If Dilantin® (phenytoin) 30mg/5ml oral suspension is not considered suitable then General Practitioners should make early contact with secondary care or tertiary care specialists to seek support regarding the most suitable management plan for the patient and monitoring requirements if needed.
    iii. If patients are switched to alternative formulations, other than Dilantin® 30mg/5ml oral suspension, prescribers and pharmacists should work together to ensure the patient receives the correct dose of the alternative product and that monitoring of plasma levels are undertaken.
    iv. Patients should be prescribed a licensed product if available, therefore if it is necessary to switch a patient to an unlicensed preparation they should be switched back to Epanutin® 30mg/5ml oral suspension when supplies are back in stock, which is likely to be by the end of July 2019. Careful management of switching and monitoring may be required when switching back to licensed Epanutin® 30mg/5ml suspension, and prescribers and pharmacists should liaise to ensure this is done safely.

If prescribers have any concerns about switching a patients' medication, or reverting back to Epanutin®, they should consult the patient's specialist prescriber to seek support.

Action, to be taken by

- NHS Regional Offices
- Community pharmacists
- General practitioners
- General practice nurses
- Hospitals in the independent sector
- Independent treatment centres
- Private medical practitioners
- Paediatrics departments
- Paediatric nurse specialists
- Pharmaceutical advisors
- Pharmacists
- Hospital pharmacies
- Hospital pharmacists
- Community nurses
- District nurses

Please also send on to others you feel may need to take actions.

Deadlines for actions

Actions underway:	11/06/2019
Actions completed:	31/07/2019

Product details

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

Problem / background

There is a short-term supply issue affecting Epanutin® suspension due to a manufacturing delay of UK licensed stock. Pfizer are the sole licensed UK supplier of phenytoin 30mg/5ml oral suspension.
It is anticipated that current stock will be depleted week commencing 10th June. Further deliveries are currently anticipated at the end of July, 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 if carbamazepine is ineffective or patients are intolerant to carbamazepine. 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 and monitoring 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:

Prescribing:

- All other available alternative phenytoin oral suspensions are considered unlicensed in the UK.
- Any decision to prescribe an unlicensed medicine must take into account the relevant GMC guidance and NHS Trust or local 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

Switching to Dilantin® 30mg/5ml oral suspension

- Pfizer have obtained permission from the MHRA to import Canadian stock as an unlicensed product, Dilantin® (phenytoin) 30mg/5ml oral suspension.
- Both Epanutin® oral suspension and Dilantin® 30mg/5ml oral suspension contain phenytoin **base** and can be considered equivalent in dosing, therefore changes in dosing should not be required.

Switching to other formulations

- Different formulations of phenytoin (other than Dilantin® 30mg/5ml oral suspension) are not interchangeable. If patients are switched to anything other than Dilantin® 30mg/5ml oral suspension, careful management of switching and monitoring is required, and the switch should therefore 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.

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]

Dilantin® (phenytoin) 30mg/5ml Oral Suspension

Unlicensed Preparations – Pfizer product imported from Canada

To help mitigate the shortage, Pfizer has obtained approval from the Medicines and Healthcare Regulatory Agency (MHRA) to import stock of phenytoin oral suspension, Dilantin-30®, from Canada. This stock is considered an unlicensed preparation in the UK. Dilantin-30® can be considered equivalent to Epanutin® 30mg/5ml suspension and therefore no dosing adjustments should be required. Pfizer have confirmed they can import sufficient quantities of this stock to support the whole UK market during this period of short supply. Details on Epanutin® and Dilantin-30® are below and copies of the Patient Information Leaflet (PIL), product monograph and Dear Healthcare Professional Letter have been included with this alert on the CAS website. The Dilantin-30® PIL contains different dosing information compared to the Epanutin® PIL. Therefore, patients should be made aware of this and will need to be counselled to always remain on their prescribed regimen and consult their prescriber is they are unsure.

Name	Strength	Presentation	Bottle Size	Excipients	Phenytoin sodium OR base
Epanutin®	30mg/5ml	Oral Suspension	500ml	Carmoisine (E122)	Phenytoin base
*Dilantin-30®	30mg/5ml	Oral Suspension	250ml	Amaranth (E123)	Phenytoin base

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

- Patient consent has been sought for use of an unlicensed preparation.
- Patients are supplied sufficient quantity of a specific unlicensed preparation to cover until Epanutin® returns into stock end of July 2019.

Alternative Phenytoin Preparations

There are a number of alternative licensed and unlicensed phenytoin preparations available. However please note that none of the licensed alternatives are in the form of suspension.

Please be aware that supplies of Epanutin® Infatabs are currently in short supply and patients have been required to switch to unlicensed Canadian stock, Dilantin® 50mg Chewable tablets. As such, **patients should not be switched to Epanutin® Infatabs.**

In the case of the alternative suspensions not being suitable, advice can be sought from pharmacy on emptying out phenytoin 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.

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

- Care Quality Commission (CQC) (headquarters) for information
- Directors of public health
- Health and Safety Executive
- OFSTED (directors of children's services) for information
- Public Health England (for information)
- Social services in England (directors)
- MHRA
- NHS England Patient Safety
- NHS England EPRR
- Chief Medical Officer
- NHS England – National Clinical Director
- NHS Supply Chain

- Wholesalers and Distributors
- Directors of Procurement – Devolved Authorities

If you are responsible for cascading these alerts in your organisation, these are our suggested distribution lists.

Trusts (NHS boards in Scotland)

CAS and SABS (NI) liaison officers for onward distribution to all relevant staff including:

- A&E consultants
- A&E departments
- A&E directors
- A&E nurses
- Chief pharmacists
- Clinical governance leads
- Clinical Procurement Specialists
- Community hospitals
- Community nurses
- District nurses
- Hospital pharmacies
- Hospital pharmacists
- Intensive care medical staff/paediatrics
- Intensive care nursing staff (adult)
- Intensive care nursing staff (paediatric)
- Intensive care units
- Intensive care, directors of
- Medical directors
- Neonatal nurse specialists
- Neonatology departments
- Neonatology directors
- NHS walk-in centres
- Paediatric intensive care units
- Paediatric medicine, directors of
- Paediatric nurse specialists
- Paediatric wards
- Paediatricians
- Paediatrics departments
- Pharmaceutical advisors
- Pharmacists
- School nurses
- Special care baby units
- Walk-in centres

NHS England area teams

CAS liaison officers for onward distribution to all relevant staff including:

- Community pharmacists
- General practitioners
- General practice managers
- General practice nurses

Independent distribution

Establishments registered with the Care Quality Commission (CQC) (England only)

- Care homes providing nursing care (adults)
- Hospitals in the independent sector
- Independent treatment centres
- Private medical practitioners

Establishments registered with OFSTED

- Children's services
- Educational establishments with beds for children
- Residential special schools

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 Medicine and Healthcare Regulatory Agency's Central Alerting System (CAS) by sending an email to: safetyalerts@mhra.gov.uk and requesting this facility.

Enquiries

England
Send enquiries about this notice to the DHSC Supply Resilience Team, quoting reference number SDA/2019/001 or email: supplyresiliencemd@dhsc.gov.uk

Addressees may take copies for distribution within their own organisations

Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Worldwide Biopharmaceutical Businesses

5th June 2019

Dear Healthcare Professional,

Re: Interim supply arrangements for Epanutin® (phenytoin) 30mg/5ml oral suspension to mitigate supply disruption

Pfizer is currently experiencing a supply disruption with Epanutin® (phenytoin) 30mg/5ml oral suspension.

There has been a delay in manufacturing and we anticipate that this will result in an out of stock period for Epanutin® (phenytoin) 30mg/5ml oral suspension from early June 2019, however we are working hard to reduce this supply gap and are exploring all options including bringing in Pfizer stock from other countries.

To help mitigate the shortage Pfizer has obtained approval from the Medicines and Healthcare products Regulatory Agency (MHRA) to import stock of phenytoin oral suspension from Canada.

Phenytoin is a Category 1 Anti-epileptic Drug (AED) and therefore there may be clinically relevant differences between different preparations of phenytoin. Any switches to different preparations must be managed under medical supervision and may require monitoring of phenytoin serum levels.

Epanutin (phenytoin) 30mg/5ml oral suspension is indicated for control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Epanutin has also been employed in the treatment of trigeminal neuralgia but it should only be used as a second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

Information on Canadian presentation:

The Canadian phenytoin oral suspension is labelled as Dilantin-30 and is supplied in 250ml bottles containing 30mg/5ml phenytoin. There are small differences in the excipients: Dilantin-30 oral suspension contains Amaranth (E123) whereas Epanutin oral suspension contains Carmoisine (E122). Both suspensions are similar in colour and taste and the concentration of active ingredient (phenytoin), therefore no dosing adjustments should be necessary. The Canadian Patient Information Leaflet (PIL) contains different dosing information compared to the Epanutin PIL, therefore patients may need to be counselled to remain on their prescribed regimen and consult their doctor if they are unsure.

Patient safety is of the utmost priority to Pfizer and we are keenly aware of the importance of the supply of Epanutin® (phenytoin) 30mg/5ml oral suspension to patients. We work very hard to avoid medicines shortages but, despite our best efforts, unexpected delays can occur for which we sincerely apologise.

Normal supply of Epanutin Infatabs are much lower than the oral suspension and are only available to meet normal market demand, furthermore there is an ongoing supply issue with this product. Supplies of unlicensed Canadian Dilantin (phenytoin) Infatabs are available from Pfizer to manage this supply issue. Therefore, **patients should not be switched to Epanutin Infatabs or unlicensed Dilantin Infatabs as this may precipitate a shortage of this presentation. Additionally, Pfizer does not hold bioequivalence data for switches between the two products.**

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

Further Information

When you order Epanutin® (phenytoin) 30mg/5ml oral suspension through the standard PIP code with Alliance Healthcare, you will receive a message to call the Pfizer Customer Contact Centre who will manage your order.

Pfizer does not recommend use of unlicensed product. However if the prescriber/healthcare professional deems it appropriate for their patient to obtain the unlicensed version, then they will need to issue a prescription for the unlicensed product

If you have any questions about this letter, please contact Pfizer Medical Information at the following address:

Medical Information, Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS United Kingdom. Telephone: **01304 616161** or visit https://www.pfizermedicalinformation.co.uk/

Safety Reporting
Suspected adverse drug reactions (ADRs) should be reported to the MHRA by use of a yellow card, which is available electronically via http://www.mhra.gov.uk/yellowcard. Suspected adverse drug reactions should also be reported to Pfizer Medical Information on **01304 616161.**

Yours faithfully,

Shaantanu Donde

UK Medical Director, Upjohn, a Pfizer division, Pfizer LTD

Package Leaflet: Information for the patient

EPANUTIN® 30 mg/ 5ml Oral Suspension
(phenytoin)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Epanutin is and what it is used for
2. What you need to know before you take Epanutin
3. How to take Epanutin
4. Possible side effects
5. How to store Epanutin
6. Contents of the pack and other information

1. What Epanutin is and what it is used for

This medicine contains phenytoin, which is one of a group of medicines called anti-epileptic drugs; these medicines are used to treat epilepsy.

Epanutin can be used to control epilepsy, to control or prevent seizures during or after brain surgery or severe head injury. Epanutin can also be used to treat trigeminal neuralgia (facial nerve pain).

You should consult your doctor if you are unsure why you have been given Epanutin 30mg/5ml Oral Suspension if you do not feel better or if you feel worse.

2. What you need to know before you take Epanutin

Do not take Epanutin

- if you are allergic (hypersensitive) to phenytoin, or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to other medicines for epilepsy
- if you are also taking delavirdine (used for HIV therapy).

Warnings and precautions

Talk to your doctor or pharmacist before you take Epanutin if you suffer from or have suffered in the past from any of the following conditions:

- Liver disease
- Kidney disease
- Porphyria (an inherited disease that affects haemoglobin biosynthesis)
- Alcohol dependence.

Epanutin can cause problems with your heart, including a slow heartbeat. Let your healthcare provider know right away if you have these symptoms.

You should be administered Epanutin with caution if you suffer from kidney or liver problems.

A small number of people being treated with antiepileptics such as phenytoin have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

There is a risk of harm to the unborn child if Epanutin is used during pregnancy. Women of childbearing age should use effective contraception with Epanutin (see Pregnancy, contraception in women, and breast-feeding).

Potentially life-threatening skin rashes (Stevens Johnson syndrome, toxic epidermal necrolysis) have been reported with the use of Epanutin, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). These potentially life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin. The highest risk for occurrence of serious skin reactions is within the first weeks of treatment. If you have developed Stevens-Johnson syndrome or toxic epidermal necrolysis with the use of Epanutin, you must not be re-started on Epanutin at any time.

If you develop a rash or these skin symptoms, stop taking Epanutin, seek urgent advice from a doctor and tell him that you are taking this medicine. Consult your doctor before discontinuing Epanutin. If you suddenly stop taking this medicine you may have a seizure.

This risk of these serious skin side effects may be associated with a variant in genes in a subject with Chinese or Thai origin. If you are of such origin and have been tested previously carrying this genetic variant (HLA-B*1502), discuss this with your doctor before taking Epanutin.

Black patients may be at greater risk of liver problems, serious skin reactions and allergic reactions.

Other medicines and Epanutin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some medicines can affect the way Epanutin works, or Epanutin itself can reduce the effectiveness of other medicines taken at the same time. These include (Not all medicines are listed here. Talk with your doctor or pharmacist):

- Medicines used for heart and circulation problems (e.g. dicoumarol, digitoxin, digoxin, disopyramide, mexiletine, nisoldipine, amiodarone, furosemide, quinidine, reserpine, warfarin, and calcium channel blockers including diltiazem and nifedipine)
- Medicines used for epilepsy (e.g. carbamazepine, lamotrigine, phenobarbital, sodium valproate and valproic acid, topiramate, oxcarbazepine, succinimides including ethosuximide and vigabatrin)
- Medicines used to treat fungal infections (e.g. amphotericin B, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole and miconazole)

- Medicines used for tuberculosis and other infections (e.g. chloramphenicol, isoniazid, rifampicin, sulfonamides, sulfadiazine, sulfamethiazole, sulfamethoxazole-trimethoprim, sulfaphenazole, sulfisoxazole, doxycycline and ciprofloxacin)
- Medicines used for stomach ulcers (e.g. omeprazole, sucralfate, the medicines known as H_2 antagonists including cimetidine, ranitidine, famotidine and some antacids)
- Medicines used for asthma and bronchitis (e.g. theophylline)
- Medicines used for pain and inflammation (e.g. phenylbutazone, salicylates including aspirin and steroids)
- Medicines used for sleeplessness, depression and psychiatric disorders (e.g. chlordiazepoxide, clozapine, diazepam, disulfiram, fluoxetine, methylphenidate, paroxetine, phenothiazines, quetiapine, trazodone, tricyclic antidepressants, fluvoxamine, sertraline and viloxazine)
- Medicines used for diabetes (e.g. tolbutamide)
- Medicines used for cancer (e.g. antineoplastic agents e.g. teniposide, fluorouracil), capecitabine, bleomycin, carboplatin, cisplatin, doxorubicin and methotrexate
- Some hormone replacement therapies (oestrogens), oral contraceptives (the birth control pill) (see Pregnancy, contraception in women, and breast-feeding)
- Medicines used for organ and tissue transplants, to prevent rejection (e.g. ciclosporin, tacrolimus)
- Medicines used to lower high blood cholesterol and triglycerides (e.g. atorvastatin, fluvastatin, simvastatin)
- Medicines used in the treatment of HIV infection (e.g. delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)
- Medicines used to expel parasitic worms from the body (e.g. albendazole, praziquantel)
- Muscle relaxants used for surgery (neuromuscular blockers), some anaesthetic drugs (e.g. halothane, methadone)
- Some products available without a prescription (e.g. folic acid, vitamin D).

Your doctor may need to test the amount of phenytoin in your blood to help decide if any of these drugs are affecting your treatment.

The herbal preparation St John's wort (*Hypericum perforatum*) should **not** be taken at the same time as this medicine. If you already take St John's wort, consult your doctor before stopping the St John's wort preparation.

If you are being fed by a tube this can affect the concentrations of phenytoin, the active ingredient of Epanutin 30 mg/5 ml Oral Suspension, in your blood. Your doctor or pharmacist will tell you how to take this medicine with your feeds.

Epanutin 30 mg/5 ml Oral Suspension may also interfere with certain laboratory tests that you may be given.

Epanutin with food, drink and alcohol
Epanutin can be taken before or after food and drink.

Drinking a lot of alcohol can also affect the concentration of phenytoin in your blood. Talk to your doctor or pharmacist for advice.

Pregnancy, contraception in women, and breast-feeding

Pregnancy
If you are pregnant, consult your doctor promptly. You should not stop taking your medicine until you have discussed this with your doctor. Stopping your medication without consulting your doctor could cause seizures which could be dangerous to you and the pregnancy. Your doctor may decide to change your treatment. Closer monitoring of your unborn child could also be considered.

Epanutin may cause birth defects. If you take Epanutin during pregnancy your baby has a higher risk of having a birth defect. Birth defects which have been reported include facial, skull, nail, finger and heart abnormalities.

If you are of childbearing age and plan to become pregnant, consult your doctor for a preconceptional visit. You should discuss your treatment options with your doctor.

If you take Epanutin during pregnancy, your baby is also at risk for bleeding problems right after birth. Your doctor may give you and your baby a medicine to prevent this. Moreover, your child should be closely monitored.

Contraception in women
If you are of childbearing age, you should discuss your treatment options and effective methods of birth control with your doctor. Epanutin may result in a failure of hormonal contraceptives, hence you should be counselled regarding the use of other effective contraceptive methods.

Breast-feeding
Epanutin passes into breast milk. You should not take Epanutin if you are breast-feeding.

Driving and using machines
Epanutin may cause dizziness or drowsiness. If you experience these symptoms, do not drive or use any tools or machinery and contact your doctor.

Epanutin contains sucrose, ethanol and the colouring agents sunset yellow (E110) and carmoisine (E122).
This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

Epanutin contains sucrose, a type of sugar. If you have been told that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. This medicine may be harmful to the teeth.

This medicine contains the colouring agents sunset yellow (E110) and carmoisine (E122) that may cause allergic reactions.

3. How to take Epanutin

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Shake the bottle vigorously before you measure your dose. Always use a medicine spoon or measure.

It is best to take Epanutin at the same time each day.

Adults
The amount of Epanutin needed varies from one person to another. Most adults need between 200mg and 500mg a day (between 7 and 17 five-ml spoonfuls of Suspension) either as a single or divided dose. Occasionally higher doses are needed.

Use in Children and adolescents
Infants and children usually start on a dose that depends on their weight (5mg per day for every kg they weigh) and is given as a divided dose, twice a day. The dose is then adjusted up to a maximum of 300mg a day (10 five-ml spoonfuls of Suspension).

Elderly
Due to decreased clearance of Epanutin, lower or less frequent dosing may be needed. The dose of Epanutin for elderly patients who may be taking other medicines may also need careful consideration and adjustment by their doctor.
Kidney or liver problems
Make sure your doctor knows if you have liver or kidney problems as you may need your dose adjusted.

If you take more Epanutin than you should
Epanutin is dangerous in overdose. If you accidentally take too much Epanutin contact your doctor at once or go to the nearest hospital casualty department. Always take the labelled medicine package with you, whether there is any Epanutin left or not.

If you forget to take Epanutin
If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. **Do not take a double dose to make up for a missed dose.**

If you stop taking Epanutin
Do not stop taking Epanutin unless your doctor tells you to. If you suddenly stop taking this medicine you may have a seizure. Your doctor will advise you how to stop taking the medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** if you experience any of the following symptoms after taking this medicine. Although they are very rare, these symptoms can be serious.

- Sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body). There is a higher incidence of this in black patients.
- If you develop potentially life-threatening skin rashes that cause blistering, (this can also affect the mouth and tongue). These may be signs of a condition known as Stevens Johnson syndrome, or toxic epidermal necrolysis (TEN). These have been reported very rarely.
- If you notice bruising, fever, you are looking pale or you have a severe sore throat. These may be the first signs of an abnormality of the blood, including decreases in the number of red cells, white cells or platelets. Your doctor may take regular blood samples to test for these effects.

- Skin rash and fever with swollen glands, particularly in the first two months of treatment, as these may be signs of a hypersensitivity reaction. If these are severe and you also experience pain and inflammation of the joints this could be related to a condition called systemic lupus erythematosus.
- Skin rash, fever, swollen glands, increase in a type of white blood cell (eosinophilia) and inflammation of internal organs (liver, lungs, heart, kidneys and large intestine) as they may be signs of a hypersensitivity reaction (Drug Reaction or rash with Eosinophilia and Systemic Symptoms (DRESS)).
- If you experience confusion or have a severe mental illness, as this may be a sign that you have high amounts of phenytoin in your blood. Your doctor may test your blood to see how much phenytoin is in the blood and may change your dose.

Other side effects that may occur are:

- **Effects on your nervous system:** Unusual eye movements, unsteadiness, difficulty in controlling movements, shaking, abnormal or uncoordinated movements, slurred speech, confusion, pins and needles or numbness, drowsiness, dizziness, vertigo, sleeplessness, nervousness, twitching muscles, headaches and change in taste.
- **Effects on your skin:** skin rash including measles-like reactions which are mild.
- **Effects on your stomach and intestines:** feeling sick, being sick and constipation.
- **Effects on your blood and lymph system:** swelling of the lymph glands.
- **Effects on your liver and kidney:** inflammation of the kidneys and liver, liver damage or liver failure which can lead to death (seen as yellowing of the skin and whites of the eye).
- **Effects on your reproductive system and breasts:** changes in the shape of the penis, painful erection.
- **Effects on your hands, face and body:** changes in the hands with difficulty in straightening the fingers, changes in facial features, enlarged lips or gums, increased or abnormal body or facial hair.
- **Effects on medical tests:** increased levels of blood sugar, or decreased levels of blood calcium, phosphate, folic acid and vitamin D. If you also do not get enough vitamin D in your diet or from exposure to sunlight, you may suffer from bone pain or fractures. Taking Phenytoin may cause abnormal thyroid test results.
- **Effects on your respiratory system:** problems breathing, inflammation of the lining of the lung.
- **Effects on your immune system:** problems with the body's defence against infection, inflammation of the wall of the arteries and immunoglobin abnormalities.
- **Effects on your bones:** there have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Malta
ADR Reporting website: www.medicinesauthority.gov.mt/adrportal

5. How to store Epanutin

Keep this medicine out of the sight and reach of children.

Do not store above 25°C

Do not use this medicine after the expiry date which is printed on the bottle label after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Epanutin 30 mg/5 ml Oral Suspension contains
Each 5 ml dose contains 30 mg of the active ingredient phenytoin.

The other ingredients are aluminium magnesium silicate, sodium benzoate (E211), citric acid monohydrate, carmellose sodium, glycerol, polysorbate 40, sucrose, ethanol (each 5 ml dose contains 0.493% of ethanol), vanillin, banana flavour, orange oil, carmoisine (E122), sunset yellow (E110) and purified water.

What Epanutin looks like and contents of the pack

Epanutin 30 mg/5 ml Oral Suspension is a cherry red liquid and is available in bottles containing 500 ml of suspension.

Marketing Authorisation Holder

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

Manufacturer
Famar Orleans
5 Avenue de Concyr
45071 Orléans
Cedex 02
France

Company Contact Address
For further information on this medicine please contact Medical Information at Pfizer Limited, Walton Oaks, Tadworth, Surrey, KT20 7NS; Tel 01304 616161.

This leaflet was last revised in: 04/2019

Ref: EP 23_1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EPANUTIN 30 MG/5 ML ORAL SUSPENSION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of suspension contains 30 mg phenytoin.

Excipients with known effect
Each 5 ml also contains 1.044 g Sucrose, 24.66 microlitres Ethanol, 0.316 mg Carmoisine (E122), 0.1 mg Sunset Yellow FCF (E110).

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

Viscous cherry red coloured oral suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Epanutin has also been employed in the treatment of trigeminal neuralgia but it should only be used as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

4.2 Posology and method of administration

For oral administration only.

Dosage:
Dosage should be individualised as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. Epanutin should be introduced in small dosages with gradual increments until control is achieved or until toxic effects appear. In some cases serum level determinations may be necessary for optimal dosage adjustments - the clinically effective level is usually 10 mcg/mL - 20 mcg/mL (40-80 micromoles/l) although some cases of tonic-clonic seizures may be controlled with lower serum levels of phenytoin. With recommended dosage a period of 7 to 10 days may be required to achieve steady state serum levels with Epanutin and changes in dosage should not be carried out at intervals shorter than 7 to 10 days. Maintenance of treatment should be the lowest dose of anticonvulsant consistent with control of seizures.

Epanutin Capsules, Oral Suspension and Infatabs:
Epanutin Capsules contain phenytoin sodium whereas Epanutin Oral Suspension and Epanutin Infatabs contain phenytoin. Although 100 mg of phenytoin sodium is equivalent to 92 mg of phenytoin on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent. Physicians should therefore exercise care in those situations where it is necessary to change the dosage form and serum level monitoring is advised.

Posology
Adult Dosage for Seizures:
Initially 3 to 4 mg/kg/day with subsequent dosage adjustment if necessary. For most adults a satisfactory maintenance dose will be 200 mg to 500 mg daily in single or divided doses. Exceptionally, a daily dose outside this range may be indicated. Dosage should normally be adjusted according to serum levels where assay facilities exist.

Dosing in Special Populations

Patients with Renal or Hepatic Disease:
See section 4.4.

Adult Dosage for Trigeminal Neuralgia:
The clinically effective dose has not been established in clinical trials. In adults, 300-500 mg daily given in divided doses has been reported in the literature. Dosing should be adjusted based on clinical response. Determination of serum phenytoin levels is advised. Levels of total phenytoin should not exceed 20 mcg/ml

Elderly (over 65 years)
Phenytoin clearance may be decreased in elderly patients and lower or less frequent dosing may be required (see section 5.2 – Special Populations – Age). As with adults the dosage of Epanutin should be titrated to the patient's individual requirements using the same guidelines. As older people tend to receive multiple drug therapies, the possibility of drug interactions should be borne in mind.

Paediatric population Dosage for Seizures:
Initially, 5 mg/kg/day in two divided doses, with subsequent dosage individualised to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 mg/kg - 8 mg/kg.

Neonates:
The absorption of phenytoin following oral administration in neonates is unpredictable. Furthermore, the metabolism of phenytoin may be depressed. It is therefore especially important to monitor serum levels in the neonate.

4.3 Contraindications

Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin, or to any of the excipients listed in section 6.1, or other hydantoins.

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

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 seizures are present together, combined drug therapy is needed.

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

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anti-epileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anti-epileptic drug not belonging to the hydantoin chemical class.

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

Acute alcohol intake may increase phenytoin serum levels while chronic alcoholism may decrease serum levels.

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total plasma phenytoin concentrations should be made with caution. Unbound concentration of phenytoin may be elevated in patients with hyperbilirubinemia. Unbound phenytoin concentrations may be more useful in these patient populations.Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking phenytoin due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin (see section 4.5).

Suicide
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for phenytoin.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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

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

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, haematological abnormalities, myocarditis, myositis or pneumonitis. Initial

symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leucocytosis, and eosinophilia. The 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.

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

Serious Skin Reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Epanutin. Although serious skin reactions may occur without warning, patients should be advised of the signs and symptoms of HSS/DRESS (see section 4.4-HSS/DRESS), occurrence of rash and should be monitored closely for skin reactions. Patients should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Epanutin treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Epanutin, Epanutin must not be re-started in this patient at any time.

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 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 human leukocyte antigen HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of drugs associated with SJS/TEN, including phenytoin, in HLA-B*1502 positive patients when alternative therapies are otherwise equally available.

HLA-B* 1502 may be associated with an increased risk of developing SJS in individuals of Thai and Han Chinese Origin when treated with phenytoin. If these patients are known to be positive for HLA-B*1502, the use of phenytoin should only be considered if the benefits are thought to exceed risks.

In the Caucasian and Japanese population, the frequency of HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other ethnicities is currently not available.

Hepatic Injury

Phenytoin is highly protein bound and extensively metabolised by the liver. Reduced dosage to prevent accumulation and toxicity may therefore be required in patients with impaired liver

function. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, the pharmacologically active free drug concentration is unlikely to be altered. Therefore, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range of 10 mcg/mL - 20 mcg/mL (40-80 micromoles/l).

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

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

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

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local and generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without signs and symptoms resembling HSS/DRESS (see section 4.4). 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.

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, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with phenytoin is recommended.

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 D_3. This may lead to vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

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

Phenytoin may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported in association with toxic levels.

Women of Childbearing Potential

~~Phenytoin~~Epanutin may cause foetal 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).

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

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

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

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

Drugs that may increase phenytoin serum levels

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

Table 1 Drugs that may potentially increase phenytoin serum levels

Drug Classes	Drugs in each Class (such as*)
Alcohol (acute intake)	
Analgesic/Anti-inflammatory agents	azapropazone phenylbutazone salicylates
Anesthetics	halothane
Antibacterial agents	chloramphenicol erythromycin isoniazid sulfadiazine, sulfamethizole sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides topiramate
Antifungal agents	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole

Drug Classes	Drugs in each Class (such as*)
Antineoplastic agents	capecitabine fluorouracil
Benzodiazepines/Psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine
Calcium channel blockers/Cardiovascular agents	amiodarone dicoumarol diltiazem nifedipine ticlopidine
H2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	oestrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted.

Drugs that may <u>decrease</u> phenytoin serum levels

Table 2 summarizes the drug classes that may potentially decrease phenytoin plasma levels.

Table 2 Drugs that may decrease phenytoin plasma levels

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

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted

Serum levels of phenytoin can be reduced by concomitant use of the herbal preparations containing St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St. John's wort. Herbal preparations containing St. John's wort should therefore not be combined with phenytoin. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St. John's wort check the anticonvulsant levels and stop St. John's wort. Anticonvulsant levels may increase on stopping St. John's wort. The dose of anticonvulsant may need adjusting.

Drugs that may either increase or decrease phenytoin serum levels

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

Table 3 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	
Psychotropic agents	chlordiazepoxide diazepam phenothiazines

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted.

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

Error! Reference source not found. Table 4 summarizes the drug classes whose serum levels and/or effects may be altered by phenytoin.

Table 4 Drugs whose serum levels and/or effects may be altered by phenytoin

Drug Classes	Drugs in each Class (such as*)
Antibacterial agents	doxycycline rifampicin tetracycline
Anticonvulsants	carbamazepine lamotrigine phenobarbital sodium valproate valproic acid
Antifungal agents	azoles posaconazole voriconazole
Antihelminthics	albendazole praziquantel
Antineoplastic agents	teniposide
Antiretrovirals	delavirdine efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin

Drug Classes	Drugs in each Class (such as*)
	disopyramide mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporine	
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	oestrogens oral contraceptives
Hyperglycemic agents	diazoxide
Immunosuppressant drugs	
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine paroxetine quetiapine sertraline
Vitamin D	vitamin D

* This list is not intended to be inclusive or comprehensive. Individual product information should be consulted.

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

Drug-Enteral Feeding/Nutritional Preparations Interaction
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 should not be administered concomitantly with an enteral feeding preparation.

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

There is some evidence that this effect is reduced if continuous feeding is stopped 2 hours before, and for 2 hours after, phenytoin oral suspension administration. However, it may still be necessary to monitor the serum phenytoin level and increase the dose of phenytoin.

Drug/Laboratory Test Interactions

Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result of enhanced peripheral metabolism. These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hypothyroidism. It may, however, produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general
When possible, medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant. 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. As a general principle, monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Risk related to phenytoin
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 2 to 3 times higher than that of the general population, which has a frequency of 2-3%. Malformations such as orofacial clefts, cardiac defects, dysmorphic facial features, nail and digit hypoplasia, and growth abnormalities (including microcephaly) have been reported 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 took 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. 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.

Epanutin should not be used in women of childbearing potential, women planning pregnancy, and pregnant women, except where there is a clinical need and when possible, the woman is made aware of the risks of taking phenytoin during pregnancy.

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of

dosage (see section 4.2). However, postpartum restoration of the original dosage will probably be indicated.

In women of childbearing potential
Epanutin should not be used in women of childbearing potential unless other antiepileptic drugs are ineffective or not tolerated and when possible, the woman is made aware of the risk of potential harm to the foetus and the importance of planning pregnancy. Women of childbearing potential should use effective contraception during treatment. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with Epanutin.

Epanutin may result in a failure of hormonal contraceptives, hence women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see section 4.5).

Women planning to become pregnant and in pregnant women
In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible. Epanutin should not be discontinued prior to reassessment of the treatment. When possible, patients should be informed of the potential harm to the foetus. If based on a careful evaluation of the risks and the benefits, Epanutin treatment is continued during the pregnancy, it is recommended to use the lowest effective dose and to institute specialized prenatal monitoring, oriented on the possible occurrence of the described malformations.

In neonates
Haemorrhagic syndrome has been reported in neonates born from epileptic mothers receiving phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother during the last gestational month and to the neonate after birth.

Post-natal monitoring/children
In case of exposure during pregnancy, children should be closely monitored in relation to neurodevelopmental disorders in order to provide specialized care as soon as possible, if necessary.

Breast-feeding

Following administration of oral phenytoin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast feeding is not recommended for women receiving Epanutin.

Phenytoin is teratogenic in rats, mice and rabbits.

Fertility

In animal studies, phenytoin had no direct effect on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In the table below all adverse reactions with phenytoin are listed by class and frequency Not Known (cannot be estimated from available data).

MedDRA System organ class	Frequency	Undesirable Effects
Blood and lymphatic system disorders	Not Known	Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local and generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease (see section 4.4). Frequent blood counts should be carried out during treatment with phenytoin.
Immune system disorders	Not Known	Anaphylactoid reaction, anaphylactic reaction, immunoglobulin abnormalities may occur.
Metabolism and nutrition disorders	Not Known	Hypocalcaemia, hypophosphataemia in chronically treated epileptic patients.
Psychiatric disorders	Not Known	Insomnia, transient nervousness.

Nervous system disorders	Not Known	Adverse reactions in this body system are common and are usually dose-related. Reactions include nystagmus, ataxia, dysarthria, 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). Dizziness, motor twitchings, headache, paraesthesia, somnolence and dysgeusia have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdosage. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.
Ear and labyrinth disorders	Not Known	Vertigo
Vascular disorders	Not Known	Polyarteritis nodosa may occur.
Respiratory, thoracic and mediastinal disorders	Not Known	Pneumonitis.
Gastrointestinal disorders	Not Known	Vomiting, nausea, gingival hyperplasia constipation (see section 4.4).
Hepatobiliary disorders	Not Known	Acute hepatic failure, hepatitis toxic, liver injury.
Skin and subcutaneous tissue disorders	Not Known	Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or

		morbilliform rashes. A morbilliform rash is the most common; dermatitis is seen more rarely. Other more serious and rare forms have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely, coarsening of the facial features, enlargement of the lips, Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported very rarely (see section 4.4). Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4) has been reported and may in rare cases be fatal (the syndrome may include, but is not limited to, symptoms such as arthralgia, eosinophilia, pyrexia, hepatic function abnormal, lymphadenopathy or rash). 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.
Musculoskeletal and connective tissue disorders	Not Known	Systemic lupus erythematosus, arthropathy. There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenytoin. The mechanism by which phenytoin affects bone metabolism has not been identified. However, phenytoin has been shown to induce the CYP450 enzyme, which can affect bone

		mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to vitamin D deficiency and heightened risk of osteomalacia, osteoporosis.
Renal and urinary disorders	Not Known	Tubulointerstitial nephritis.
Injury, poisoning and procedural complications	Not Known	Fractures.
Investigations	Not Known	Thyroid function test abnormal.

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

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The lethal dose in children is not known. The mean lethal dose for adults is estimated to be 2g to 5 g. The initial symptoms are nystagmus, ataxia and dysarthria. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea. Bradycardia and asystole/cardiac arrest have been reported (see Section 4.4). Death is due to respiratory and circulatory depression.

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

As much as 25 times therapeutic dose has been taken to result in serum concentration over 100 mg/l (400 micromoles/l) with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment:
Treatment is non-specific since there is no known antidote. If ingested within the previous 4 hours the stomach should be emptied. If the gag reflex is absent, the airway should be supported. Oxygen, and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular depression. Haemodialysis can be considered since phenytoin

is not completely bound to plasma proteins. Total exchange transfusion has been utilised in the treatment of severe intoxication in children.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AB02.

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

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

The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated however, possible contributory effects include:

1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation
2. Post-synaptic action to enhance GABA-mediated inhibition and reduce excitatory synaptic transmission
3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter

5.2 Pharmacokinetic properties

Absorption
Phenytoin is absorbed from the small intestine after oral administration. Various formulation factors may affect the bioavailability of phenytoin, however, non-linear techniques have estimated absorption to be essentially complete. After absorption it is distributed into body fluid including the cerebrospinal fluid (CSF). Its volume of distribution has been estimated to be between 0.52 and 1.19 litres/kg, and it is highly protein bound (usually 90% in adults).

Distribution
The plasma half-life of phenytoin in man averages 22 hours with a range of 7 to 42 hours. Steady state therapeutic drug levels are achieved at least 7 to 10 days after initiation of therapy.

Biotransformation
Phenytoin is hydroxylated in the liver by an enzyme system which is saturable. Small incremental doses may produce very substantial increases in serum levels when these are in the upper range of therapeutic concentrations.

Elimination
The parameters controlling elimination are also subject to wide inter-patient variation. The serum level achieved by a given dose is therefore also subject to wide variation.

Special Populations

Patients with Renal or Hepatic Disease: see section 4.4

Age: Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see section 4.2 -Dosing in Special Populations – Elderly).

5.3 Preclinical safety data

Phenytoin causes embryofetal death and growth retardation in rats, mice, and rabbits. Phenytoin is teratogenic in rats (craniofacial defects including cleft palate, cardiovascular malformations, neural and renal defects, and limb abnormalities), mice (cleft lip, cleft palate, neural and renal defects, limb abnormalities, and digital and ocular abnormalities) and rabbits (cleft palate, limb abnormalities, and digital and ocular abnormalities). The defects produced are similar to major malformations observed in humans and abnormalities described for fetal hydantoin syndrome. The teratogenic effects of phenytoin in animals occur at therapeutic exposures, and therefore a risk to the patients cannot be ruled out.

Carcinogenesis:
Two-year carcinogenicity studies in mice and rats showed an increased number of hepatocellular adenomas in mice, but not rats, at plasma concentrations relevant for humans. The clinical significance of these rodent tumours is unknown.

Genetic toxicity studies showed that phenytoin was not mutagenic in bacteria or in mammalian cells in vitro. It is clastogenic *in vitro* but not *in vivo*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium magnesium silicate
Sodium benzoate (E211)
Citric acid monohydrate
Carmellose sodium
Glycerol
Polysorbate 40
Sucrose
Ethanol
Vanillin
Banana flavour
Orange oil
Carmoisine (E122)
Sunset yellow (E110)
Water

6.2 Incompatibilities

Refer to Enteral feeding/Nutritional Preparations Interaction in section 4.5.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottle with 3 piece tamper evident child resistant closure fitted with a polyethylene faced liner containing 125 ml or 500 ml. Finished pack will either have a label/leaflet or be enclosed in a carton with a separate PIL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Shake well before use.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00057/0528.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of latest renewal: 1 April 2003.

10. DATE OF REVISION OF THE TEXT

05/2019

Ref: EP 33_3

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

This leaflet was prepared by Pfizer Canada ULC

Last revised: January 23, 2019

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.
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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.
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- 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.

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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

This leaflet was prepared by Pfizer Canada ULC

Last revised: January 23, 2019

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 ULC, Licensee
Kirkland, Quebec H9J 2M5

Date of Revision:
January 23, 2019

Submission Control No: **222374**

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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

Phenytoin can cause rare, severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis, Steven-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the occurrence of rash and other symptoms of hypersensitivity syndrome (HSS)/DRESS.

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, Acute Generalized Exanthematous Pustulosis and Toxic Epidermal Necrolysis

Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) Acute Generalized Exanthematous Pustulosis (AGEP) 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.

[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.

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.

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 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. Angioedema has been reported. 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. Urticaria has been reported. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, acute generalized exanthematous pustulosis, 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

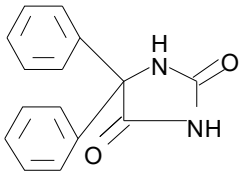
Drug Substance

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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