

Package leaflet: Information for the patient
Phenytoin Sodium 50mg/ml Solution for Injection

Read all of this leaflet carefully before you are given 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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- You may have been given Phenytoin Injection as a single dose to control seizures in an emergency (status epilepticus). In this case, you will only be able to read this leaflet after you have had the product given to you. Your doctor will have considered the important safety information in this leaflet, but your urgent need for treatment may have been more important than some of the normal cautions. Check them now, especially if you are going to continue to be given Phenytoin Injection (or any other form of phenytoin).

The name of your medicine is Phenytoin Sodium 50mg/ml Solution for Injection. It will be referred to as Phenytoin Injection for ease hereafter.

What is in this leaflet

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

1. What Phenytoin Injection is and what it is used for

Phenytoin belongs to a group of drugs known as hydantoin. It is called an anticonvulsant because it works by controlling the overactivity in the brain that can cause epilepsy or seizures (fits).

Phenytoin Injection is used to:

- control epileptic fits involving jerking and spasm of the muscles (known as grand mal fits)
- prevent and treat fits resulting from brain surgery or head injury.

You should consult your doctor if you are unsure why you have been given Phenytoin Injection if you do not feel better or if you feel worse.

2. What you need to know before you are given Phenytoin Injection

You must not be given Phenytoin Injection

- if you are allergic to phenytoin sodium or any of the other ingredients of this medicine (listed in section 6) or to any other hydantoin drug (such as ethoin or methoin)
- if you have a slow heart beat or heart problems that interfere with the rate at which your heart beats
- if you are allergic to other medicines for epilepsy
- if you are also taking delavirdine (used for HIV therapy)

- if you suffer from certain conditions that affect the heart rhythm for example a decreased heart rate (sinus bradycardia), heart block (sinoatrial block or A-V block) or Adams-Stokes syndrome.

Make sure your doctor knows if you suffer from any of the above before you are given the injection.

Warnings and precautions

Talk to your doctor or nurse before you are given Phenytoin Injection if you suffer from or have suffered in the past from any of the following conditions:

- low blood pressure or heart failure
- disease of the liver or kidneys
- diabetes
- porphyria (an inherited condition affecting the nervous system and skin, characterised by abdominal pain, vomiting or muscle weakness)
- if you have drunk a large amount of alcohol recently or if you drink large amounts of alcohol regularly or if you have alcohol dependence
- potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported with the use of Phenytoin sodium, 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 Phenytoin sodium, you must not be re-started on Phenytoin sodium at any time
- heart rhythm problems
- if you develop a rash or these skin symptoms, stop taking Phenytoin Injection, seek immediate advice from a doctor and tell that you are taking this medicine. Consult your doctor before discontinuing Phenytoin Injection. If you suddenly stop using this medicine you may have a seizure
- if you are of Taiwanese, Japanese, Malaysian or Thai origin and tests have shown that you carry the genetic variant CYP2C9*3.

The 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 using Phenytoin Injection.

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

If you are taking phenytoin at the same time as you receive radiation therapy to your head and the dose of another medication called corticosteroids is reduced, you may more likely to develop a severe skin rash called erythema multiform or one that causes blistering called Stevens Johnson Syndrome or Toxic Epidermal Necrosis (see Possible Side Effects in section 4).

A small number of people being treated with anti-epileptics such as Phenytoin have had thoughts of harming or killing themselves, if at any time you have these thoughts, immediately contact your doctor.

Tell your doctor if any of these apply to you as special care may be needed. Your doctor will take particular care with this medicine if you are elderly or gravely ill.

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures (two specific types of epilepsy).

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

Other medicines and Phenytoin Injection

Tell your doctor if you are taking, have recently taken or might take any other medicines.

This will allow your doctor to decide whether it is safe for you to be given phenytoin.

Some medicines can affect the way Phenytoin Injection works, or Phenytoin Injection itself can reduce the effectiveness of other medicines taken at the same time. These include:

- medicines used for epilepsy or fits (e.g. carbamazepine, lamotrigine, phenobarbital, sodium valproate and valproic acid, topiramate, oxcarbazepine, succinimides including ethosuximide and vigabatrin)
- corticosteroids e.g. prednisolone (used in numerous situations to aid the body's healing process)
- medicines used to treat fungal infections (e.g. amphotericin B, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole and miconazole)
- medicines used to treat skin diseases (e.g. methoxsalen)
- medicines used for tuberculosis and other infections (e.g. chloramphenicol, isoniazid, rifampicin, sulphonamides, sulfadiazine, sulfamethizole, sulfamethoxazole-trimethoprim, sulfaphenazole, sulfisoxazole, doxycycline and ciprofloxacin)
- medicines used for asthma and bronchitis (e.g. theophylline)
- medicines used for diabetes (e.g. tolbutamide)
- medicines used for high blood pressure (e.g. calcium channel blockers like diltiazem, felodipine)
- medicines used for pain and inflammation (e.g. phenylbutazone, salicylates, including aspirin and steroids)
- medicines used for stomach ulcers and heartburn (e.g. omeprazole, sucralfate, the medicines known as H₂ antagonists e.g. cimetidine, ranitidine, famotidine and some antacids)
- medicines used for sleeplessness, depression and psychiatric disorders (e.g. chlordiazepoxide, clozapine, diazepam, disulfiram, lithium, methadone, fluoxetine, fluvoxamine, sertraline, haloperidol, levodopa, paroxetine, methylphenidate, phenothiazines, quetiapine, trazodone, reserpine, tricyclic antidepressants and viloxazine)
- medicines used for cancer (e.g. antineoplastic agents like teniposide, fluorouracil, capecitabine, bleomycin, carboplatin, cisplatin, doxorubicin and methotrexate)
- medicines used for organ and tissue transplants, to prevent rejection (e.g. ciclosporin, tacrolimus)
- medicines used for heart and circulation problems (e.g. dicoumarol, amiodarone, digoxin, digoxin, nisoldipine, disopyramide, mexiletine, furosemide and quinidine, reserpine, warfarin and calcium channel blockers including diltiazem and nifedipine)
- hormone replacement therapies (oestrogens) and oral contraceptives (the birth control pill)
- 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)
- medicines used to treat thyroid disorders (e.g. thyroxine)
- some medicines used in operations, e.g. halothane, methadone (an anaesthetic) and neuromuscular blockers (used to relax muscles e.g. pancuronium, vecuronium, rocuronium and cisatracurium)
- some products available without a prescription (e.g. folic acid, vitamin D). Blood test may be necessary every six months to monitor the amount of folic acid in the blood
- the herbal remedy St. John's wort (*Hypericum perforatum*) should not be taken at the same time as this medicine. If you have already taken St. John's wort, consult your doctor before stopping St. John's wort preparations
- anticoagulants, e.g. warfarin (as its effect may be enhanced by phenytoin)
- Phenytoin Injection may also interfere with certain laboratory tests that you may be given
- anticoagulants e.g. rivaroxaban, dabigatran, apixaban, edoxaban
- medicines used for seizures e.g. lacosamide
- medicine used as blood thinner e.g. ticagrelor.

Phenytoin Injection with food, drink and alcohol

Speak to your doctor before being given this medicine if you have recently had a drink of alcohol.

Drinking a lot of alcohol can also affect the concentration of Phenytoin in your blood.

Pregnancy, contraception in women and breast-feeding

Pregnancy

What you should know about the use of antiepileptic drugs in pregnancy

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you are planning to become pregnant you should discuss your epilepsy treatment with your doctor as early as possible before you become pregnant. If you do get pregnant or think you may be pregnant while you are taking Phenytoin Injection, you must tell your doctor straight away and discuss possible risks the epilepsy medicine you are taking might pose to your unborn baby. You should not stop your treatment without discussing this with your doctor. Suddenly stopping may lead to breakthrough seizures which may harm you and your unborn baby. It is important that your epilepsy remains well controlled, but, as with other anti-epilepsy treatments, there is a risk of harm to the foetus.

Taking phenytoin during pregnancy increases the chance that the baby may have a physical birth abnormality.

Studies with women treated with phenytoin for epilepsy during pregnancy have shown that around babies in every 100 will have serious physical birth abnormalities. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.

The most common types of serious physical birth abnormalities (major congenital malformations) reported for phenytoin include abnormalities of the lip and palate, heart, skull, nail and finger disorders and growth abnormalities.

Taking more than one epilepsy medicine at the same time may also increase the risk of physical birth abnormalities. Where possible, your doctor will consider using one epilepsy medicine only to control your epilepsy.

Your doctor may advise you to take folic acid if you're planning to become pregnant and while you're pregnant. Your doctor may adjust your epilepsy medicine when you take folic acid.

Some studies observed that taking phenytoin during pregnancy increases the chance that the baby may have problems affecting learning and thinking abilities.

Make sure you are very clear about the risks and benefits of taking Phenytoin Injection.

Do not stop taking Phenytoin Injection until you have seen your doctor as it is important to control your fits. If given during pregnancy phenytoin may affect the baby but your doctor may decide that it is very important that you continue with phenytoin. He or she will explain the risks to you.

Phenytoin Injection can cause major birth defects. If you take Phenytoin Injection during pregnancy your baby has up to 3 times the risk of having a birth defect than women not taking an antiepileptic medication. Major birth defects including growth, skull, facial, nail, finger and heart abnormalities have been reported. Some of these may occur together as part of a fetal hydantoin syndrome.

Problems with neurodevelopment (development of the brain) have been reported in babies born to mothers who used phenytoin during pregnancy. Some studies have shown that phenytoin negatively affects neurodevelopment of children exposed to phenytoin in the womb, while other studies have not found such an effect. The possibility of an effect on neurodevelopment cannot be ruled out.

Breast-feeding

As phenytoin is released into breast milk, you should not breast-feed if you are being given this medicine.

Driving and using machines

Phenytoin Injection may cause dizziness or drowsiness. If you experience these symptoms, do not drive or use any tools or machinery.

Ask your doctor for advice before taking any medicine.

Phenytoin Injection contains propylene glycol and ethanol:

- This medicine contains 2070 mg propylene glycol in each 5 ml which is equivalent to 414 mg/ml. If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol. If you are pregnant, breast-feeding or if you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects. Use this medicine only if recommended by a doctor.
Your doctor may carry out extra checks while you are taking this medicine.
- This medicine contains 404.25 mg of alcohol (ethanol) in each 5 ml which is equivalent to 80.85 mg/ml. The amount in 5 ml of this medicine is equivalent to 10.11 ml beer or 4.04 ml wine. The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy. The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine. If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

Information on sodium content

This medicine contains less than 1 mmol sodium (23 mg) per 5 ml, that is to say essentially ‘sodium-free’.

3. How Phenytoin Injection is given to you

Phenytoin Injection is given by a doctor or nurse. It may be given as an injection slowly into a muscle or a large vein. Alternatively, it may be diluted and given as a drip or infusion into one of your large veins (intravenously). When given as an intravenous infusion, Phenytoin Injection must be diluted with normal saline. Intramuscular or intravenous Phenytoin Injection should not be added to dextrose or dextrose-containing solutions as this could interfere with the dose of this medicine.

The correct dose will be calculated by your doctor according to your body weight and will be written as the equivalent dose of phenytoin sodium (PE). The dose will be as mg per dose if given as an injection or mg per ml of solution if given as an infusion (drip). A repeat injection may be given after 30 minutes if necessary.

During your treatment your doctor may monitor your blood levels of phenytoin by taking regular blood samples. Sometimes it is necessary to give Phenytoin Injection into your muscle if you cannot continue to take it by mouth. This is not normally continued for longer than one week. When switching from oral Phenytoin to intramuscular injection, the dose needs to be increased by approximately 50%. When switching back to oral Phenytoin, the dose should be reduced to half the original oral dose for the same period of time that the intramuscular injection was given. This is because phenytoin continues to be released from your muscles for some time after the injections have been given.

The recommended dose is as follows:

Adults

Severe epileptic seizure or fits (Status Epilepticus)

A dose of 10 to 15 mg per kg of body weight is given intravenously at a rate not exceeding 50 mg per minute in adults. This is followed by more Phenytoin Injection given every 6 to 8 hours either by injection or by mouth.

If Phenytoin Injection does not stop your seizures, other treatments will be tried.

Neurosurgery

A dose of 100 to 200 mg may be given into your muscle (intramuscularly) approximately every 4 hours during surgery and for two to three days afterwards to prevent seizures. This dosage may then be reduced to a maintenance dose of 300 mg daily and adjusted according to your blood levels.

Elderly

Lower or less frequent dosing may be needed in some elderly patients due to decreased clearance of Phenytoin Injection. Your doctor may not need to change your dose, but side effects can occur more often in the elderly.

Kidney or liver problems

Make sure your doctor knows if you have liver or kidney problems as you may need your dose adjusted.

Use in children and adolescents

No dosage adjustment is required, but children tend to breakdown the medicine faster than adults and this may mean that your doctor has to change the number or timing of the Phenytoin Injection doses.

Use in neonates (Very young babies)

The starting dose is usually 15 to 20 mg per kg of baby weight. Intravenous Phenytoin Injection should not be given to neonates at a rate faster than 1 to 3 mg per kg body weight per minute. Intravenous Phenytoin Injection is more reliably absorbed than oral Phenytoin in very young babies.

If you think you have been given more Phenytoin Injection than you should have

Tell your doctor immediately.

Phenytoin Injection is dangerous in overdose. The initial signs are nystagmus (condition of involuntary eye movement), diplopia (double vision), ataxia (the loss of full control of bodily movements) and dysarthria (motor speech disorder). Other signs are tremor, hyperflexia (muscle spasms), lethargy, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

If you think you have missed a dose of Phenytoin Injection

If you think that you may have missed a dose, tell your doctor immediately.

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

4. Possible side effects

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

Important: If you experience any of the following serious side effects contact your doctor immediately.

- 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 experience skin discoloration, swelling and pain where the injection was given which then starts to spread down your arm to your hands and fingers. This may mean you have a condition known as Purple Glove Syndrome. In most cases this will improve on its own but in some cases it can be serious and require urgent medical treatment
- if you develop potentially life-threatening skin rashes that causes blistering (this can 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 decrease in the number of red blood cells, white cells or platelets. Your doctor may take regular blood samples to test for these effects

- 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), you may also experience pain and inflammation of the joints, these may be signs of a hypersensitivity reaction (e.g. drug reaction or rash with Eosinophilia and Systemic Symptoms (DRESS)) or be related to a condition called systemic lupus erythematosus (SLE)
- 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. On rare occasions, when the amount of the phenytoin in the blood remains high, irreversible brain injury has occurred. 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 as below:

Rare: may affect up to 1 in 1,000 people:

- difficulty in controlling movements, shaking, abnormal or uncoordinated movements

Not known: frequency cannot be estimated from the available data

- **effects on your nervous system:** unusual eye movements, unsteadiness, 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 rash which is usually mild
- **effects on your stomach and intestines:** feeling sick, being sick and constipation
- **effects on your blood and lymph system:** a decrease in the number of a type of red blood cell (pure red cell aplasia), 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), abnormal liver function
- **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:** abnormal thyroid function tests
- **effects on your respiratory system:** problems breathing including complete stopping of breathing, inflammation of the lining of the lung
- **effects on your immune system:** problems with the body's defense against infection, inflammation of the wall of the arteries
- **effect on your heart and circulation:** low blood pressure, enlargement of blood vessels. Your blood pressure may also be lowered and experience heart rhythm problems when Phenytoin Injection is injected into your vein too quickly
- **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 if you are on long-term antiepileptic medication, have a history of osteoporosis or take steroids
- **effects on injection site:** Intramuscular phenytoin administration may cause pain, tenderness, dying or sloughing of skin cells, and formation of an infection at the injection site.

Please see your doctor if you notice any of these side effects and they cause you concern, or if you notice any side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Phenytoin Injection

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

Do not use this medicine after the expiry date which is stated on the ampoule (a small bottle) label and carton, after 'EXP'. The expiry date refers to the last day of that month.

Do not store above 30°C. Keep the ampoule in the outer carton in order to protect from light.

If only part of the contents of an ampoule is used, the remaining solution should be discarded.

Do not use this medicine if you notice a haziness or precipitate.

The solution should not be mixed with any other drugs.

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 Phenytoin Injection contains

- The active substance is phenytoin sodium. Each 1ml of this solution contains 50mg of phenytoin sodium.
- The other ingredients are propylene glycol, ethanol 96% w/v and sodium hydroxide solution 10% w/v in water for injections.

What Phenytoin Injection looks like and contents of the pack

Phenytoin Injection is a clear, colourless, particle-free solution. Each carton contains ten 5ml ampoules of Phenytoin Injection.

Marketing Authorisation Holder

Mercury Pharmaceuticals Ltd, Dashwood House, 69 Old Broad Street, London, EC2M 1QS, United Kingdom

Manufacturer

Delpharm Tours, Rue Paul Langevin, 37170 Chambray Les Tours, France.

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