Package leaflet: Information for the patient

Epanutin® RMP (Ready Mixed Parenteral) 250 mg/5 ml Solution for Injection or Infusion
phenytoin sodium

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, pharmacist or nurse.
- 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.
- You may have been given Epanutin RMP 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 Epanutin RMP (or any other form of phenytoin).

What is in this leaflet

1. What Epanutin RMP is and what it is used for

This medicine is a solution for injection or infusion containing phenytoin which belongs to a group of medicines called antiepileptic drugs.

Epanutin RMP can be used to treat severe epileptic seizures or fits (status epilepticus). It can also be used to control or prevent seizures during or after brain surgery and/or severe head injury. Epanutin RMP is also used to control or prevent seizures for short periods of time when antiepileptic drugs cannot be taken by mouth.

Epanutin RMP can also be used to treat heart rhythm problems (cardiac arrhythmias), when these are caused by the drug digoxin, when they are serious cardiac arrhythmias that did not respond well to treatment with other medicines, or when other treatments cannot be tolerated.

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

2. What you need to know before you are given Epanutin RMP

Do not take Epanutin RMP
- 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 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-Stoke syndrome.
- If you are taking medicines for HIV infection such as delavridine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Epanutin RMP if you suffer from or have suffered in the past from any of the following conditions:
- Low blood pressure or heart failure
- Liver disease where the dosage may need to be adjusted
- Kidney disease
- Diabetes
- Porphyria (an inherited disease that affects haemoglobin biosynthesis)
- Heart rhythm problems (Epanutin RMP can treat some rhythm problems, but can make others worse)
- Alcohol dependence.
- If you are of Taiwanese, Japanese, Malaysian or Thai origin and tests have shown that you carry the genetic variant CYP2C9*3.

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

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

Potentially life-threatening skin rashes (for example 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, seek urgent advice from a doctor and tell him that you are taking this medicine. Consult your doctor before discontinuing Epanutin.

Cases of swelling of the face, mouth (lip, gum, tongue) and neck that can lead to life-threatening breathing difficulty have been reported in people being treated with phenytoin. If at any time you have these signs or symptoms 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 during treatment with Epanutin (see Pregnancy, contraception in women, and breast-feeding).

Other medicines and Epanutin RMP
Tell your doctor 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 RMP works, or Epanutin RMP 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, amiodarone, reserpine, digitoxin, digoxin, disopyramide, mexiletine, nisoldipine, furosemide, quinidine and calcium channel blockers including diltiazem and nifedipine)

- Medicines used to prevent blood clots, anticoagulants (e.g. apixaban, dabigatran, edoxaban, rivaroxaban, warfarin) and antiplatelets (e.g. ticagrelor)

- Medicines used for epilepsy (e.g. carbamazepine, lacosamide, lamotrigine, phenobarbital, sodium valproate, valproic acid, oxcarbazepine, topiramate, 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, sulfamethizole, sulfamethoxazole-trimethoprim, sulfaphenazole, sulfisoxazole, doxycycline and ciprofloxacin)

- Medicines used for stomach ulcers (e.g. omeprazole, sucralfate and 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)

- 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 and tacrolimus)

- Medicines used for cancer (e.g. antineoplastic agents including teniposide, fluorouracil, capecitabine, bleomycin, carboplatin, cisplatin, doxorubicin and methotrexate)

- 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 medicines (halothane) and methadone

- Some products available without a prescription (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.

Epanutin RMP may also interfere with certain laboratory tests that you may be given.

Epanutin RMP with drinking alcohol
Drinking a lot of alcohol can also affect the concentration of phenytoin in your blood.

Pregnancy, contraception in women, and breast-feeding

Pregnancy

Epanutin can cause major birth defects. If you take Epanutin 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. Your unborn baby should be closely monitored if you have taken Epanutin while pregnant. Epanutin should not be used during pregnancy unless nothing else works for you.

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.

There have been isolated reports of tumours, including tumours affecting nerve tissue, in children whose mothers received phenytoin during pregnancy.

If you take Epanutin during pregnancy, your baby is 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 a woman of childbearing age and are not planning a pregnancy, you should use effective contraception during treatment with Epanutin. Epanutin may affect how hormonal contraceptives, such as the contraceptive (birth control) pill, work and make them less effective at preventing pregnancy. Talk to your doctor, who will discuss with you the most suitable type of contraception to use while you are taking Epanutin.

If you are a woman of childbearing age and are planning a pregnancy, talk to your doctor before you stop contraception and before you become pregnant about switching to other suitable treatments in order to avoid exposing the unborn baby to phenytoin.

If you are or think you might be pregnant, tell your doctor straight away. 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 your unborn child. Your doctor may decide to change your treatment. Closer monitoring of your unborn child is also recommended.

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

Driving and using machines
Epanutin RMP may cause dizziness or drowsiness therefore do not drive or use any tools or machines until instructed by the doctor.

Epanutin RMP contains ethanol, propylene glycol and sodium
This medicine contains 400.0 mg of alcohol (ethanol, 96%) in each 5 ml solution which is equivalent to 10%. The amount in 5 ml of this medicine is equivalent to 11 ml beer or 4.5 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

This medicinal product also contains 2.072 g propylene glycol in each 5 ml solution of phenytoin, which is equivalent to 414.0 mg of propylene glycol per 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 are being given other medicines that contain propylene glycol or alcohol.

If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.

If you suffer from liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks if you need to receive Epanutin for more than 24 hours.

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 less than 1 mmol sodium (23 mg) per 5 ml solution, this is to say essentially ‘sodium-free’.

3. How Epanutin RMP is given

You will be in hospital when you are given Epanutin RMP.

Epanutin RMP will be either injected into one of your large veins (intravenously, IV) or into your muscle (intramuscularly, IM). When given intravenously, Epanutin RMP must be diluted with normal saline. Intramuscular or intravenous Epanutin should not be added to dextrose or dextrose-containing solutions as this could interfere with the dose of this medicine.

The dose and concentration of the solution of Epanutin RMP you are given will be decided by your doctor 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).

Sometimes it is necessary to give Epanutin RMP 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 Epanutin to intramuscular injection, the dose needs to be increased by approximately 50%. When switching back to oral Epanutin, 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.

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 Epanutin given every 6 to 8 hours either by injection or by mouth.

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

Cardiac arrhythmias (variations to normal heartbeat)

A dose of 3.5 to 5 mg per kg of body weight is given intravenously, at a rate not exceeding 50 mg per minute. This may be repeated a second time.

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 Epanutin RMP. 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.

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 Epanutin doses.

The drug should be injected slowly intravenously at a rate of 1 to 3 mg/kg/minute or 50 mg/minute, whichever is slower.

Neonates (Very young babies)

The starting dose is usually 15 to 20 mg per kg of baby weight. Intravenous Epanutin RMP should not be given to neonates at a rate faster than 1 to 3 mg per kg body weight per minute.

Intravenous Epanutin is more reliably absorbed than oral Epanutin in very young babies.

If you are given more Epanutin RMP than you should

Epanutin is dangerous in overdose. If you think you have been given too much Epanutin RMP, contact your doctor immediately.

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

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 being given this medicine.

- 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 irritation, inflammation, tenderness, dying or sloughing of skin cells at the site where Epanutin RMP is injected, or if you experience discolouration, pain or swelling on the skin away from the site of injection. These may be minor, but can also be serious. These may be signs of a condition known as purple glove syndrome (PGS).
- If you develop potentially life-threatening skin rashes that cause 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 decreases 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 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)).
- Areas of red skin with small elevated sterile pustules (small blisters filled with white/yellow fluid). There tends to be more disease in skin folds. Swelling off the face can occur as well (Acute Generalized Exanthematous Pustulosis (AGEP)).
- 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 occassions, 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:

- **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:** life-threatening skin rashes that cause blistering (this can affect the mouth and tongue), skin rash including measles-like rash which is usually mild, hives.
- **Effects on your stomach and intestines:** Feeling sick, being sick and constipation.
- **Effects on your blood and lymph system:** swelling of the lymph glands, a decrease in the number of a type of red blood cell (pure red cell aplasia).
- **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, phosphates, 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 including complete stopping of 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.
- **Effect on your heart and circulation:** low blood pressure, enlargement of blood vessels. Your blood pressure may also be lowered and experience heart problems when Epanutin 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 or pharmacist 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, dying or sloughing of skin cells, and formation of an infection at the injection site.

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

Ireland
HPRA Pharmacovigilance.
Website: www.hpra.ie

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

5. How to store Epanutin RMP

Keep out of the sight and reach of children.

The storage of Epanutin RMP will not be your responsibility.

The pharmacist will ensure that your medicine is not stored above 25°C, and not used after the expiry date which is stamped on the pack after EXP. The expiry date refers to the last day of that month. The pharmacist will also ensure that Epanutin RMP is kept in the original package.

Keep the vial in the outer carton in order to protect from light.

The product should be used immediately after opening the vial. Epanutin RMP is for single use only. Any unused solution should be discarded immediately after initial use.

Do not use Epanutin RMP if the solution is not clear or contains particulate matter.

When stored in the refrigerator, there may be a precipitate in the solution which will disappear when the vial is left at room temperature. The solution may then be used.

The solution may at times appear pale yellow but this does not impact on the potency.

6. Contents of the pack and other information

What Epanutin RMP 250 mg/5 ml Solution for injection or infusion contains
The active substance is phenytoin sodium. Each 5 ml solution contains 250 mg of the active substance.

The other ingredients are propylene glycol, ethanol (alcohol), sodium hydroxide and water for injection.

What Epanutin RMP looks like and contents of the pack
Epanutin RMP 250 mg/5 ml Solution is available in a 6 ml colourless, glass vial containing 5ml of clear, colourless solution and is supplied in packs containing 10 vials.

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