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 specific heart rhythm problems (cardiac arrhythmias) when these are caused by the drug digoxin, or when these do not respond well to treatment with other medicines, or when other treatments cannot be used.

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 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.

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.

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.

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).

Other medicines and Epanutin RMP
Tell your doctor if you are taking, have recently taken or might take any other medicines.
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, warfarin and calcium channel blockers including diltiazem and nifedipine)

- Medicines used for epilepsy (e.g. carbamazepine, 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, miconazole)

- Medicines used for tuberculosis and other infections (e.g. chloramphenicol, isoniazid, rifampicin, sulfonamides, sulfadiazine, sulfamethizole, sulfamethoxazole-trimethoprim, sulfaphenazole, sulfisoxazole, doxycycline, 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, tacrolimus)

- Medicines used for cancer (e.g. antineoplastic agents including teniposide, fluorouracil, capecitabine, bleomycin, carboplatin, cisplatin, doxorubicin, 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 food, drink and alcohol
Drinking a lot of alcohol can also affect the concentration of phenytoin in your blood.

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

Epanutin RMP contains ethanol and sodium
This medicinal product contains 8.8% ethanol (alcohol), i.e. up to 440.4 mg per 5 ml ampoule, equivalent to 8.8 ml beer, 3.7 ml wine per dose. It may be harmful if you suffer from alcoholism. It should be taken into account in pregnant or breast-feeding women, children and high risk groups such as patients with liver disease.

This medicine contains up to 1.1 mmol sodium (24.6 mg) per 5 ml ampoule. This should be considered if you are on a sodium-controlled diet.

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) or into your muscle (intramuscularly). When given as an intravenous infusion, Epanutin RMP must be diluted with normal saline. Intramuscular or intravenous Epanutin RMP should not be added to dextrose or dextrose-containing solutions as this could interfere with the dose of this medicine.
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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.

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 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.

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 Epanutin doses.

Use in 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 skin discolouration, 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 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, 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 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:** 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:** 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, phosphates, folic acid and vitamin D. 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.

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 RMP

The storage of Epanutin RMP will not be your responsibility.

The pharmacist will ensure that your medicine is kept out of the sight and reach of children.

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.

Do not throw away any medicine via wastewater. The pharmacist or nurse will throw away any medicine you no longer use. These measures will help protect the environment.

Epanutin RMP is for single use only. Any unused solution should be discarded immediately after initial use.

6. Contents of the pack and other information

What Epanutin RMP 250 mg/5 ml Solution for injection or infusion contains
Each 5 ml ampoule contains 250 mg of the active ingredient phenytoin sodium i.e. 50 mg/ml.

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 packs containing 10 ampoules.

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