

**PROPOSED PATIENT INFORMATION LEAFLET (CLEAN COPY) FOR
RIFAFOUR e-275 TABLETS, DATED 12 APRIL 2018**

SCHEDULING STATUS: S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM:

RIFAFOUR e-275 tablets

Rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol hydrochloride 275 mg.

Read all of this leaflet carefully before you start taking RIFAFOUR e-275:

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- RIFAFOUR e-275 has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT RIFAFOUR e-275 CONTAINS:

- The active substances in RIFAFOUR e-275 tablets are rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol hydrochloride 275 mg.
- The other ingredients are croscarmellose sodium, glyceryl behenate, lactose monohydrate, magnesium stearate, maize starch, polyvinylpyrrolidone, sodium lauryl sulphate and sodium ascorbate as anti-oxidant.
- The tablets are film coated with carmine, FD&C blue indigo carmine aluminium lake, iron oxide black, macrogol 3350, polyvinyl alcohol, talc and titanium dioxide.
- Contains sugar (54,66 mg lactose monohydrate per tablet).

WHAT RIFAFOUR e-275 IS USED FOR:

RIFAFOUR e-275 tablets contain four different medicines called isoniazid, rifampicin, pyrazinamide and ethambutol hydrochloride. They all belong to a group of medicines called antituberculosis medicines. They work by killing the bacteria that cause tuberculosis (also known as TB).

BEFORE YOU TAKE RIFAFOUR e-275:

Do not take RIFAFOUR e-275 if:

- You are allergic (hypersensitive) to isoniazid, rifampicin or other rifamycins, pyrazinamide or ethambutol hydrochloride, or to any of the other ingredients of the RIFAFOUR e-275 tablets. Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue (see POSSIBLE SIDE EFFECTS).
- You have yellowing of the skin and eyes (jaundice) or have an active liver disease.
- You are taking both saquinavir and ritonavir for an HIV infection.
- You suffer from porphyria (a hereditary condition causing your skin to blister or darken the colour of your urine).
- You have optical neuritis (inflammation of the nerve of the eye, which may cause pain and vision loss in the eye).
- You are taking ketoconazole (used for fungal infections).
- You are under 13 years old.

Tell your doctor or pharmacist before taking RIFAFOUR e-275 if:

- You have liver problems including hepatitis (inflammation of the liver), especially if you are aged over 35 years or are elderly as your doctor may need to monitor your liver enzymes in your blood more carefully.
- You have kidney problems.
- You have problems with your eyes or eyesight.

- You have weakness, numbness and pain, usually in your hands and feet, but also in other areas of your body (peripheral neuropathy). If you are underweight or malnourished, an alcoholic, pregnant, elderly, have kidney problems, or suffer from HIV infection, you may be at risk to develop peripheral neuropathy. Your doctor may advise that you use pyridoxine (vitamin B6) to prevent or treat this.
- You have or have ever had gout (pain or swelling in the joints) and if you are using medicine to treat gout.
- You have previously had 'fits' or suffer from epilepsy.
- You have or have ever had mental health problems (such as depression, schizophrenia or psychosis).
- You have diabetes. Your diabetes may become more difficult to control while taking this medicine.
- You are using oral contraceptives (birth control tablets). RIFAFour e-275 may make oral contraception ('the Pill') less effective and it is important that you use an alternative barrier method of contraception or the 'coil' whilst taking RIFAFour e-275. If you have any questions or are unsure about this, talk to your doctor, pharmacist or other healthcare professional.
- You are using anticoagulants (medicines to thin your blood e.g. warfarin) (also see: Taking other medicines with RIFAFour e-275).
- You drink alcohol every day or you are an alcoholic.
- You develop or have previously developed thrombocytopenic purpura (easy or excessive bruising and superficial bleeding into the skin causing a rash of pinpoint sized reddish-purple spots) after using RIFAFour e-275 or rifampicin.
- You wear contact lenses. Taking RIFAFour e-275 may permanently stain soft contact lenses (see: Important information about some of the ingredients of RIFAFour e-275).

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking RIFAFour e-275.

Take special care with RIFAFOUR e-275:

- It is very important that you take RIFAFOUR e-275 exactly as your doctor has told you. There is a chance of you developing a severe and dangerous allergic reaction if you do not take RIFAFOUR e-275 each day as you are told. You must keep taking RIFAFOUR e-275 until your doctor tells you to stop.
- While taking RIFAFOUR e-275 you must visit your doctor at least once a month. Tell your doctor if you experience any problems with your RIFAFOUR e-275 treatment.
- Blood tests: Your doctor will need to check your blood before you take RIFAFOUR e-275. This will help your doctor to know if any changes happen to your blood after taking RIFAFOUR e-275. You may also need to have regular blood tests to check how your liver is working especially if you are older than 35 years of age, suffer from chronic liver disease or use drink alcohol regularly.
- Eye tests: Your doctor may suggest that regular eye tests are performed while using RIFAFOUR e-275. Inform your doctor immediately if you experience any visual disturbances.
- RIFAFOUR e-275 may make your teeth and body fluids (urine, sweat, sputum and tears) a yellow, orange, red or brown colour. Do not worry - this is normal and not harmful. Teeth may be stained permanently. (See POSSIBLE SIDE EFFECTS and Important information about some of the ingredients of RIFAFOUR e-275.)

Taking RIFAFOUR e-275 with food or drink:

Do not have cheese, red wine or some fish (e.g. skipjack, tuna or other tropical fish) while you are being treated with RIFAFOUR e-275. This may lead to symptoms such as itching of your skin, rapid or pounding heart, sweating, flushing, headache and low blood pressure (fainting).

Using alcohol while you are being treated with RIFAFOUR e-275 can increase your risk of developing liver disease or problems.

Pregnancy and breastfeeding:

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking RIFAFOUR e-275.

Also tell your doctor before taking RIFAFOUR e-275 if you plan to get pregnant or think you are pregnant.

The safety of RIFAFOUR e-275 in pregnant and breastfeeding women has not been established.

You should not breastfeed if you are taking RIFAFOUR e-275. This is because small amounts may pass into the mothers' milk. If you are breastfeeding or planning to breastfeed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machinery:

RIFAFOUR e-275 may cause side effects such as dizziness, vertigo (spinning feeling) or have vision problems or have other side effects that could affect your ability to drive while taking RIFAFOUR e-275. If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of RIFAFOUR e-275:

RIFAFOUR e-275 tablets contain lactose monohydrate which may have an effect on the control of your blood sugar if you have diabetes mellitus.

Patients with the rare hereditary conditions of lactose or galactose intolerance should not take RIFAFOUR e-275.

The active ingredient in RIFAFOUR e-275 may produce a discolouration (yellow, orange, red, brown) of your urine, sweat, sputum or tears and permanently stain your teeth and soft contact lenses (see: Take special care with RIFAFOUR e-275).

Taking other medicines with RIFAFOUR e-275:

Always tell your doctor, pharmacist or healthcare professional if you are taking any other medicines (including complementary or traditional medicine). This is because RIFAFOUR e-275 can affect the way some other medicines work. Also, some medicines can affect the way RIFAFOUR e-275 works.

Do not take RIFAFOUR e-275 if you are taking:

- A combination of saquinavir and ritonavir (used for HIV infection and Aids). (See above: Do not take RIFAFOUR e-275 if.)

The following medicines can make RIFAFOUR e-275 work less well:

- Antacids used for indigestion. Take RIFAFOUR e-275 at least 1 hour before or 2 hours after taking antacids.

Tell your doctor if you are taking any of the following medicines:**Heart and blood medicines:**

- Medicines for high blood pressure: calcium channel blockers (e.g. diltiazem, nifedipine, verapamil), losartan, enalapril.
- Medicines for heart problems or to control your heartbeat (e.g. disopyramide, quinidine, flecainide, propafenone) or other heart medicines such as beta-blockers or cardiac glycosides (e.g. digoxin).
- Medicines used to thin the blood such as warfarin.
- Medicines used to lower cholesterol (clofibrate or statins such as atorvastatin, simvastatin).

Mental health, epilepsy and motor neuron medicines:

- Medicines for thought disorders known as 'antipsychotics' such as haloperidol.

- Medicines to calm or reduce anxiety (hypnotics, anxiolytics) including benzodiazepines and related medicine (e.g. diazepam, zopiclone, zolpidem, triazolam).
- Medicines to help you sleep (barbiturates, e.g. hexobarbitone).
- Medicines used for fits or epilepsy such as phenytoin, carbamazepine, ethosuximide and primidone.
- Some medicines used for depression such as amitriptyline and nortriptyline.
- Riluzole, used for motor neurone disease.

Medicines for infections and the immune system:

- Some medicines used for an HIV infection such as zidovudine, saquinavir, indinavir, efavirenz, atazanavir, lopinavir and nevirapine.
- Medicines used for fungal infections (e.g. fluconazole, itraconazole, ketoconazole voriconazole).
- Medicines used for bacterial infections (antibiotics) (e.g. chloramphenicol, clarithromycin, telithromycin, doxycycline, dapsone, ciprofloxacin, levofloxacin, sulfasalazine).
- Other antituberculosis medicines (e.g. cycloserine, *p*-aminosalicylic acid (PAS)).
- Medicines used for lowering your immune system such as ciclosporin, azathioprine, sirolimus and tacrolimus.
- Praziquantel – used for tapeworm infections.
- Atovaquone – used for pneumonia.

Hormone and cancer medicines:

- Some hormone medicines (oestrogens, progestins, systemic hormones) used for contraception or some types of cancer, such as ethinylestradiol, levonorgestrel or dydrogesterone.
- Some hormone medicines (antioestrogens) used for breast cancer or endometriosis, such as tamoxifen, toremifene and gestrinone.

- Levothyroxine (thyroid hormone) used for thyroid problems.
- Irinotecan - used for cancer.

Pain, inflammation and gout medicines:

- Medicines used for pain such as codeine, morphine, fentanyl, alfentanil or pethidine.
- Corticosteroids used for inflammation such as hydrocortisone, betamethasone and prednisolone.
- Methadone - used for heroin withdrawal.
- Sulfinpyrazone, allopurinol, colchicine, probenecid - used for gout.

Other medicines:

- Medicines used for diabetes (sulfonylureas such as glibenclamide, gliclazide, glipizide, glimepiride or thiazolidinediones such as pioglitazone).
- Cimetidine used to reduce excess stomach acid to treat stomach ulcers.
- Medicines used to relax muscles before surgery (anaesthetics) such as halothane.
- Some medicines used for feeling sick (nausea) or being sick (vomiting) such as ondansetron.
- Quinine - used for malaria.
- Theophylline - used for wheezing or difficulty in breathing.
- Disulfiram (used in alcohol dependence).
- Alcohol and medicines which may increase your risk of developing liver disease or problems while using RIFAFOUR e-275, e.g. paracetamol (for pain).

Make sure to inform your doctor if you are using any of the above medicines before you start treatment with RIFAFOUR e-275. Your doctor may want to adjust the dose of your medicine, if needed.

RIFAFOUR e-275 may make oral contraception ('the Pill') less effective. If you are using 'the Pill' it is important that you use an alternative barrier method of contraception or the 'coil' whilst taking RIFAFOUR e-275. If you have any questions or are unsure about this, talk to your doctor, pharmacist or other healthcare professional.

If you are using anticoagulants (medicines to thin your blood, e.g. warfarin), RIFAFOUR e-275 may cause your blood to clot more easily. You may need more frequent monitoring of your anticoagulant dosage.

Laboratory tests: Taking RIFAFOUR e-275 may affect the results of some blood tests. In particular, tests for folate and vitamin B12 and copper sulphate urine glucose test. If you are going to have a blood test, it is important to tell your doctor that you are taking RIFAFOUR e-275.

RIFAFOUR e-275 may influence contrast media used for gallbladder tests, therefore, these tests should be performed before the morning dose of RIFAFOUR e-275.

HOW TO TAKE RIFAFOUR e-275:

Do not share medicines prescribed for you with others.

Always take RIFAFOUR e-275 exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Dosage: Your doctor or pharmacist will tell you how many tablets to take. The usual dose for adults and children older than 13 years is 2 to 5 tablets depending on your weight. In elderly patients your doctor may monitor your dose more closely, especially if you show signs of liver dysfunction.

RIFAFOUR e-275 is unsuitable for children under 13 years.

Your daily dose of RIFAFOUR e-275 should preferably be taken with a full glass of water, at least 1 hour before a meal or 2 hours after a meal. However, if it irritates your stomach, you may take the tablets with food.

If you are taking antacids (used for indigestion) while you are being treated with RIFAFOUR e-275, take RIFAFOUR e-275 at least 1 hour before taking antacids.

You should usually take all the day's tablets at the same time each day and only stop taking them if your doctor tells you to. It is essential to take the tablets every day and not to stop and start them, as this could cause more serious side effects. You will usually take RIFAFOUR e-275 for about 2 months.

If you take more RIFAFOUR e-275 than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre. Take the medicine pack with you.

If you forget to take RIFAFOUR e-275:

If you forget to take your tablets, take them as soon as you remember on the same day. If it is nearly time for the next dose, then take the next dose as usual. Do not take a double dose to make up for the forgotten tablets.

Effect when treatment with RIFAFOUR e-275 is stopped:

You must take the tablets each day for the whole time the doctor has told you to take them. Do not stop and start taking the tablets. This may increase the risk of side effects and your infection will not be treated properly.

POSSIBLE SIDE EFFECTS:

RIFAFOUR e-275 can have side effects.

Not all side effects reported for RIFAFOUR e-275 are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking RIFAFOUR e-275, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking RIFAFOUR e-275 and tell your doctor or pharmacist immediately or go to the casualty department of your nearest hospital:

Frequency unknown:

- Serious allergic reactions. Signs may be: a rash, swelling of your lips, face, throat or tongue which may cause swallowing or breathing problems, wheezing or collapse.
- You have a fever and yellowing of the skin or whites of the eyes, feel tired, weak or generally unwell, loss of appetite (anorexia), feel sick (nausea), being sick (vomiting). These may be early signs of liver problems.
- Blistering, peeling, bleeding, scaling or fluid-filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may have a serious skin problem (pemphigoid).
- Severe extensive skin damage, e.g. separation of the epidermis and superficial mucous membranes (known as toxic epidermal necrolysis).
- Fever, unexplained tiredness or shortness of breath, cough, swollen glands, muscle pains, diarrhoea, a full feeling quickly while eating or a rash or itching, or liver problems (these may be symptoms of 'DRESS syndrome', a medicine hypersensitivity reaction which affects your internal organs, and increase the white cells in your blood).
- Blistering of the skin, mouth, eyes and genital area, red/purple rash, fever, headache, cough and joint pain (Stevens-Johnson syndrome).
- Blood in your urine or an increase or decrease in the amount of urine you produce. You may also get swelling, especially of the legs, ankles or feet, but also in any area of the body. This may be caused by serious kidney problems.

- A sudden severe headache. This could be a sign of bleeding in the brain.
- Shortness of breath and wheezing.
- You get confused, sleepy, cold clammy skin, shallow or difficult breathing, a racing heartbeat or your skin is paler than normal. These could be signs of shock.
- Abnormal blood clotting (signs may be chest pains, shortness of breath, leg pains or problems speaking) or bleeding from your nose, ear, gums, throat, skin or stomach (signs may include a feeling of tenderness and swelling in your stomach, purple spots on your skin and black or tar-like stools).

Less frequent:

- Inflammation of the pancreas, which causes severe pain in the abdomen and back (pancreatitis).

These are all very serious side effects. If you have them, you may have had a serious allergic reaction or side effect to RIFAFOUR e-275. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Frequent:

- Bruising more easily than usual or you may have a rash of dark red spots under the skin which do not go away when you press on them (purpura). These may be signs of blood disorders (e.g. thrombocytopenia) which are determined by blood tests.
- Weakness, numbness, pricking, tingling or pain, usually in your hands and feet, but also in other areas of your body (peripheral neuropathy). Your doctor may advise that you use pyridoxine (vitamin B6) supplement to prevent or treat this (see: Tell your doctor or pharmacist before taking RIFAFOUR e-275).

Frequency unknown:

- The following symptoms of blood disorders which your doctor may determine with blood tests:

- Getting infections more easily than normal, fever, sore throat, mouth ulcers or tiredness (low or abnormal number of white blood cells in your blood).
- Chills, tiredness, unusually pale skin colour, shortness of breath, fast heartbeat or dark coloured urine (low number of certain blood cells, e.g. red blood cells).
- Weight loss, night sweats and fever (eosinophilia).
- Immune system problems with symptoms that include tiredness, joint pain and skin rashes (called lupus-like syndrome).
- Mental problems with unusual thoughts and strange visions (hallucinations).
- Your stomach ulcer gets worse.
- Severe watery diarrhoea that will not stop and you are feeling weak and have a fever (called pseudomembranous colitis).
- Your fits get worse or you start to have fits.
- Flu-like symptoms including chills, fever and bone pains, including shortness of breath and wheezing.
- Vision problems such as loss of eyesight, distorted or reduced eyesight.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you have any of the following:

Frequent:

- feeling sick (nausea) or being sick (vomiting)
- fever or chills
- diarrhoea.

Less frequent:

- eye irritation or disturbances in your vision
- swollen glands.

Frequency unknown:

- headache
- dizziness

- feeling drowsy or sleepy
- movement problems such as loss of full control of bodily movements and may affect your manner of walking (ataxia)
- confusion or disorientation
- loss of feeling (numbness)
- unusual skin sensations such as feeling numb, tingling, pricking, burning or creeping on the skin (paraesthesia)
- memory loss
- vertigo (feeling off balance or as if your head is spinning)
- memory problems, diarrhoea, scaly skin rash - this may be due to vitamin B3 deficiency (pellagra)
- inflammation in your blood vessels (vasculitis)
- loss of appetite
- blurred vision
- skin flushing
- skin rash or itching
- blotchy red skin rash (erythema multiforme)
- skin conditions (including acne, lumpy red rash, hives, red/purple skin discolouration (purpura), itching and skin scaling)
- sensitivity of your eyes or skin to sunlight (photosensitivity)
- hair loss
- a yellow, orange, red or brown discolouration of your teeth, urine, sweat, phlegm (sputum), saliva or tears. This is quite common and you need not worry. However, the red colour may permanently stain soft contact lenses. The red colour in tears may last for some time after you have stopped having RIFAFOUR e-275, while the discolouration of the teeth may be permanent.
- chronic or recurrent stomach pain (which may sometimes be alleviated by food)
- dry mouth

- metallic taste
- constipation
- muscle weakness or pain, loss of muscle reflexes, bone pain
- general feeling of discomfort or illness (malaise)
- irregular periods
- breast enlargement in men
- water retention (oedema) which may cause swollen face, stomach, arms or legs, fingers, toes or ankles
- lowering of blood pressure (which may make you feel lightheaded and faint, especially when you stand or sit up quickly)
- blood tests may show changes in the way your liver or kidneys are working
- feeling very tired and weak
- joint pains
- gout (inflammation of the joints caused by high levels of uric acid crystals). Symptoms include: red, tender, hot, swollen and painful joints (inflamed joints). The big toe is often involved, but other joints may also be involved.
- pain or discomfort when passing urine or unable to pass urine
- increased thirst, urgency to pass water more often, feeling tired. Your blood sugar may be high.

If you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF RIFAFOUR e-275:

Store in a cool place, at or below 25 °C in well-closed containers, protected from light.

Do not use your tablets after the expiry date shown on the container.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

If your doctor or clinic decides to stop your treatment, return all left-over medicine to your pharmacist or clinic.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION OF RIFAFOUR e-275:

Packs of 20, 28, 40, 56, 60, 80, 84, 100, 112 and 500 tablets in foil-foil blisters or white polypropylene securitainers.

IDENTIFICATION OF RIFAFOUR e-275 TABLETS:

Purple, smooth, round tablets with a film coating.

REGISTRATION NUMBER:

34/20.2.3/0187

NAME AND BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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