

Rifampicin/Isoniazid/Pyrazinamide
75mg/50mg/150mg Dispersible Tablets
(Macleods Pharmaceuticals Ltd), TB309

WHOPAR part 3

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets ¹
Rifampicin, Isoniazid, Pyrazinamide

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for your child.

- Keep this leaflet; you may need to read it again.
- If you have any further questions, ask your health care provider.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- If your child has any side effects, tell the health care provider. This includes any side effects not listed in this leaflet. See section 4

What is in this leaflet:

1. What Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is and what it is used for
2. What you need to know before you give your child Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets
3. How to give Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets
4. Possible side effects
5. How to store Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets
6. Contents of the pack and other information

1. WHAT RIFAMPICIN/ISONIAZID/PYRAZINAMIDE 75MG/50MG/150MG DISPERSIBLE TABLETS IS AND WHAT IT IS USED FOR

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets, contains rifampicin 75 mg, isoniazid 50 mg and pyrazinamide 150 mg in each tablet.

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets are used for the initial treatment of tuberculosis in children weighing between 4 kg and 24 kg.

Although the product is intended for children, safety information on its use in adults is given.

2. WHAT YOU NEED TO KNOW BEFORE YOU GIVE YOUR CHILD RIFAMPICIN/ISONIAZID/PYRAZINAMIDE 75MG/50MG/150MG DISPERSIBLE TABLETS

Do not use Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets if your child:

- is allergic (hypersensitive) to isoniazid, pyrazinamide, or rifampicin, or to any of the other ingredients of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets

¹ Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the trade/proprietary name is given as an example only.

(see section 6, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets contains);

- has acute liver disease;
- has drug-induced liver disease;
- has liver damage linked to isoniazid, pyrazinamide, or rifampicin before;
- has had severe side effects to isoniazid, pyrazinamide or rifampicin, such as drug fever, chills or inflammation of the joints;
- has inflammation of the joints (arthritis) due to gout;
- is being treated with voriconazole (a medicine for fungal infections) or with some medicine against HIV infection including elvitegravir/cobicistat, etravirine, bictegravir, rilpivirine and others that belong to the class of protease inhibitors, as well as several antiviral medicines for treating chronic hepatitis C.

Take special care with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may cause liver disease (hepatitis). You should watch out for symptoms that might be caused by liver damage, such as unexplained loss of appetite, nausea, vomiting, dark urine, yellow discoloration of the skin (jaundice), persistent fatigue lasting longer than 3 days and abdominal pain and tenderness. If these occur, you should immediately tell your child's health care provider.

People at special risk for developing hepatitis include those:

- older than 35 years;
- who drink alcoholic beverages daily (see "Taking Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with food and drink");
- with chronic liver disorder ;
- who inject drugs (e.g. heroin).

The health care provider will carefully check the liver function of people at special risk.

Furthermore, the following will be carefully monitored:

- those who take any long-term medicines while being treated with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets (see "Taking other medicines");
- those suffering from tingling in the hands and feet (peripheral neuropathy);
- pregnant women;
- those who have HIV infection.

If your child gets flu-like symptoms such as fever, headache and muscle aches, you should report this to your child's health care provider, since Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may be the cause.

If your child has had abnormally high levels of uric acid in the blood or symptoms of gout, the doctor will monitor for signs of deterioration when treated with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Tingling in the hands and feet (peripheral neuropathy) is the most common side effect of isoniazid, one of the active agents in Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets (see “Possible side effects”). You should report tell your child’s healthcare provider of any such symptoms. Your child should be given a certain vitamin, pyridoxine, at a dose of 10 mg every day during treatment with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets, because it largely reduces the risk of your child developing neuropathy.

If your child is allergic to ethionamide or niacin (nicotinic acid), you should tell your child’s health care provider, because your child may also be allergic to Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Tell your child’s health care provider if your child:

- has epilepsy or a history of psychiatric disease because this may increase the chances of your child suffering certain side effects with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets;
- has kidney problems, diabetes or porphyria because Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may then be unsuitable;
- is taking cortisone or any cortisone-like drug because the cortisone dose may have to be increased while your child is taking Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

It is normal for Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets to discolour body fluids such as urine, sputum and tears reddish orange. This is due to rifampicin in the medicine and you do not need to tell your child’s health care provider of this. Also, the medicine may discolour contact lenses.

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets can reduce the effects of oral contraceptive pills. Therefore, a different or additional method of contraception (e.g. condoms, intra-uterine device, or pessary) should be used during treatment with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

It is important that your child’s healthcare provider knows about all your child’s symptoms, even when you think they are not related to tuberculosis infection.

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets contains **aspartame**, which is a source of phenylalanine and may be harmful for people with phenylketonuria.

Taking other medicines

It is important that you tell your child’s health care provider if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription. These medicines may affect the action of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets, or Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may affect their action. Side effects of either medicine may become worse or the medicines may become less effective.

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Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should not be taken with:

- voriconazole and itraconazole (medicines used to treat fungal infections);
- HIV medicines called protease inhibitors as well as bictegravir, elvitegravir/cobicistat, etravirine and rilpivirine;
- Many medicines for treating chronic hepatitis C (check with your child's health care provider);
- aluminium hydroxide (medicine used to treat indigestion and other stomach disorders);
- ethionamide (another medicine used for treating tuberculosis).

The active ingredients of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may also interact with a great number of other medicines, including for instance:

- Medicines to treat HIV infection (e.g. efavirenz, nevirapine)
- Medicines to treat fungal infections (e.g. ketoconazole, fluconazole)
- Antibiotics (e.g. clarithromycin, chloramphenicol, doxycycline, levofloxacin, ofloxacin, metronidazole, sulfamethaxazole and trimethoprim)
- Medicines to treat malaria (e.g. amodiaquine, medicines related to artemisinin atovaquone, chloroquine, lumefantrine, mefloquine and quinine)
- Immunosuppressant drugs (e.g. ciclosporin, tacrolimus)
- Medicines to treat heart conditions (e.g. verapamil, digoxin)
- Medicines to treat blood lipids (e.g. simvastatin)
- Some medicines to treat diabetes (e.g. glibenclamide)
- Oral contraceptive pills
- Medicines to treat epilepsy (e.g. carbamazepine, lamotrigine, phenobarbital, phenytoin and valproate)
- Medicines used to help with sleep (benzodiazepines, e.g. diazepam, flurazepam, triazolam, midazolam)
- Medicines for certain psychiatric conditions (amitriptyline and antipsychotics, e.g. chlorpromazine, haloperidol)
- Medicines for preventing blood clots (coumarin or indandione derivatives, e.g. warfarin)
- Medicines used at surgery (opioids and anaesthetics, e.g. alfentanil, enflurane)
- Corticosteroids (e.g. prednisolone, medicines for the treatment of inflammation and other diseases, such as asthma or rheumatoid arthritis)
- Medicines for treating gout (e.g. allopurinol and probenecid)
- Medicines for relieving pain (codeine, morphine and paracetamol)
- Methadone (medicine used for treating opioid addiction)
- Disulfiram (medicine used for the treatment of chronic alcoholism).

Taking any of these together with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may be unsuitable or the dose may need to be changed.

Taking Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with food and drink

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be taken on an empty stomach (at least one hour before or two hours after a meal).

Alcohol should be avoided while taking Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets because it increases the risk of liver damage.

Eating cheese or fish (histamine- or tyramine-rich food) while being treated with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may cause itchiness and redness of the skin, sensation of feeling hot, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, and lightheadedness. Cheese and fish should be avoided if these effects occur while taking Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Pregnancy

If a woman becomes pregnant, or is planning to become pregnant, a health care provider should be contacted to discuss the potential benefits and risks of the tuberculosis therapy for the mother and the child.

Breast-feeding

Isoniazid and rifampicin appear in breast milk. No adverse effects have been reported in breast-fed infants whose mothers were receiving isoniazid, pyrazinamide and rifampicin. The amount of these drugs in breast milk is too low to protect the breast-fed infant against tuberculosis.

Driving and using machines

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may cause visual disturbances, dizziness and other side effects of the nervous system that can impair the ability to drive and to use machines.

3. HOW TO TAKE RIFAMPICIN/ISONIAZID/PYRAZINAMIDE 75MG/50MG/150MG DISPERSIBLE TABLETS

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should always be taken exactly as described by the health care provider. You should check with your child's health care provider if you are not sure.

The dose of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets depends on the weight of your child.

Recommended Dose based on weight of the children

Weight range	Dose
4 to 7 kg	1 tablet daily
8 to 11 kg	2 tablets daily
12 to 15 kg	3 tablets daily
16 to 24 kg	4 tablets daily

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Disperse the required dose of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets in about 50 ml water and make sure that the child drinks all the fluid. Once the dose has been added to water it should be drunk within 10 minutes. .

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be taken on an empty stomach (at least one hour before or two hours after a meal).

If your child has a kidney disease, your child's doctor may prescribe rifampicin, isoniazid and pyrazinamide separately rather than in a single tablet.

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is not recommended for adults or children who weight more than 25 kg.

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is usually given for the first two months of tuberculosis treatment. Your child's health care provider will decide on the duration of treatment for your child.

If your child takes too many Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets

Taking too many Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may cause vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurring of speech, hallucinations and visual disturbances. The skin may become discolored reddish-orange and there may be facial swelling and itching. You should immediately contact a health care provider or the nearest hospital emergency department for further advice.

If a dose of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is missed

If a dose is missed, a dose should be taken as soon as possible, unless the next scheduled dose is due within 6 hours. Skip the missed dose if it is almost time for the next regular dose.

A dose should not be doubled to make up for a missed dose.

If your child stops taking Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets

Your child should keep taking the medicine for as long as the health care provider has ordered, even if feeling better. If the medicine is stopped too soon, the infection may not be completely cured. Treatment should not be stopped unless the health care provider says so.

If you have any further questions on the use of this product, ask the health care provider.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets can cause side effects, but not everybody gets them. When treating tuberculosis, it is not always possible to differentiate between unwanted from Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and those caused by any other medicines your child may be taking at the same time. For this reason, it is important that you inform the health care provider of any change in your child's health.

The following side effects have occurred in patients treated with medicines containing the same active ingredients as Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets (rifampicin, isoniazid and pyrazinamide):

The most important side effects of isoniazid pyrazinamide and rifampicin are nerve injuries (see below) and severe and sometimes fatal inflammation of the liver (hepatitis).

The *most commonly* reported side effects (greater than 1 in every 10 patients treated) include sensations of tingling, pricking, or numbness of the skin, especially in the feet and hands (peripheral neuropathy). The doctor or health care provider will prescribe a vitamin called pyridoxine to counteract this effect (see above, “Take special care with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets”). Also, increased liver enzymes, as measured in blood samples, occur very commonly (see above, “Take special care with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets”), as do increases in uric acid in the blood. Usually, liver enzyme increases during the first 1–3 months of therapy and returns to normal as treatment continues. When the values rise above a certain level the doctor or health care provider may decide to stop treatment with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets. Flushing may also occur after taking Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Side effects that are *common* (greater than 1 in every 100 patients treated) include a reddish discoloration of body fluids such as urine, sputum, tears, saliva and sweat. Further common side effects are diarrhoea, abdominal pain, loss of appetite, nausea and vomiting, as well as skin reactions with rash and itching, and disturbances of the menstrual cycle.

Uncommon side effects (greater than 1 in every 1000 patients treated but less than 1 in 100) are inflammation of the liver (hepatitis), epileptic seizures, headache, inflammation of the brain, personality changes and memory impairment. If you notice signs and symptoms suggestive of liver damage (see “Take special care with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets”), you should inform your child’s healthcare provider immediately.

Rare side effects (less than 1 in every 1000 patients treated) include gastritis, bowel infection, inflammation of the kidney (nephritis), photosensitivity reactions (skin sensitivity to light) and conjunctivitis.

The following side effects have been reported in patients treated with medicines containing the same active ingredients as Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets (isoniazid, pyrazinamide and rifampicin). However, it is not known how frequently they occur:

- allergic reactions with fever, muscle aches, and cough
- severe skin reactions with fever, blisters and involving the mucous membranes, life-threatening anaphylactic reactions
- dizziness, drowsiness
- confusion, disorientation, hallucination
- inflammation of the lungs (pneumonitis)
- inflammation of the optic nerve
- gout, build up of acid in the body (metabolic acidosis), increased glucose in the blood, a vitamin deficiency syndrome called pellagra (with e.g. dementia, loose stools and skin

inflammation)

- metallic taste, dry mouth, flatulence, constipation
- difficulty in passing urine
- changes in the white blood cell count (leucopenia, neutropenia, eosinophilia, agranulocytosis), possibly resulting in an increased risk of infection
- decreased red blood cell counts (anaemia), possibly leading to fatigue, weakness and shortness of breath
- decreased platelet count, which may result in an increased risk of bruising and bleeding.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your child's doctor, healthcare provider or pharmacist as soon as possible.

5. HOW TO STORE RIFAMPICIN/ISONIAZID/PYRAZINAMIDE 75MG/50MG/150MG DISPERSIBLE TABLETS

Keep out of the reach and sight of children.

Do not store above 25°C. Store in a dry place. Protect from light.

Once dispersed in water, the fluid should be used within 10 minutes.

Once the bottle is opened, use within 120 days.

Medicines should not be disposed of in wastewater or household waste. Ask the pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets contain

The active ingredients of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets are rifampicin 75 mg, isoniazid 50 mg and pyrazinamide 150 mg.

The other ingredients are: microcrystalline cellulose, crospovidone, povidone, bleached shellac, croscarmellose sodium, aspartame, strawberry flavour, and magnesium stearate.

What Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets look like and contents of the pack

Brick-red, mottled, circular, uncoated biconvex tablets having a deep score on one side and a plain surface on the other side.

The score-line is only to facilitate breaking for ease of swallowing and **not** to divide the tablet into equal doses.

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Bottle packs

100 tablets packed in self-sealing LDPE bag, plain triple laminated (LDPE/AL/PET) sachet and then to round wide mouth opaque milky white HDPE container with HDPE screw thread cap along with the leaflet.

Strip packs

Alu/Alu strip pack of 10 tablets, such 10 strips are packed in a carton along with the package insert.

Alu/Alu strip pack of 28 tablets, such 3 strips are packed in a carton along with the package insert.

Supplier

Macleods Pharmaceuticals Ltd
304 Atlanta Arcade
Marol Church Road
Andheri (East)
Mumbai 400 059
India
Tel + 91 22 66762800
Fax + 91 22 28216599
Email: vijay@macleodspharma.com
sjadhav@macleodspharma.com

Manufacturer

Macleods Pharmaceuticals Ltd
Unit 2, Plot No 25-27, Survey No 366
Premier Industrial Estate
Kachigam,
Daman 396 210
India
Tel: +91-0260 2244337
Fax: +91-0260 2241565+ 91-1795 661452

Oxalis Labs
Village Theda
P.O. Lodhimajra,
Baddi, Dist.: Solan,
Himachal Pradesh,
India.

This leaflet was last approved in April 2018. Section 6 updated in June 2018.

Detailed information on this medicine is available on the World Health Organization (WHO) web site: <https://extranet.who.int/prequal/>