

WHO-PQ RECOMMENDED PATIENT INFORMATION LEAFLET

*This patient information leaflet focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.**

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

* https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

Information for the patient

[TB369 trade name][†]

Isoniazid/rifapentine

The warnings and instructions in this leaflet are intended for the person taking the medicine. If you are a parent or carer responsible for giving the medicine to someone else such as a child, you will need to apply the instructions accordingly.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have questions about the medicine, ask your health care provider.
- This medicine is for you only. Do not pass it on to others. It may harm them, even if their illness seems to be the same as yours.
- If you are concerned about any side effects, talk to your health care provider. This includes unwanted effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [TB369 trade name] is and what it is used for
2. What you need to know before you take [TB369 trade name]
3. How to take [TB369 trade name]
4. Possible side effects
5. How to store [TB369 trade name]
6. Contents of the pack and other information

1. What [TB369 trade name] is and what it is used for

[TB369 trade name] is used on its own for preventing tuberculosis (TB), an infection caused by bacteria called *Mycobacterium tuberculosis*, if you are at high risk of infection.

[TB369 trade name] is a combination of two antimycobacterial agents, rifapentine and isoniazid, that act against the bacteria that cause TB.

2. What you need to know before you take [TB369 trade name]

Do not take [TB369 trade name] if you:

- are hypersensitive (allergic) to isoniazid or rifapentine, or any of the other ingredients of [TB369 trade name] (see section 6, What [TB369 trade name] contains)
- have any sort of acute liver disease
- have ever had liver problems after taking isoniazid, rifapentine or any other medicine
- have had other severe side effects with isoniazid or rifapentine, such as drug fever or chills
- are taking certain medicines:
 - **chronic hepatitis C medicines:** daclatasvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, sofosbuvir
 - **HIV infection medicines:** atazanavir, darunavir, doravirine, elvitegravir/cobicistat, etravirine, fosamprenavir, lopinavir, nevirapine, rilpivirine, ritonavir, tipranavir

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

- **malaria medicines:** artemisinin and its derivatives (artemether, artemotil, artesunate, dihydroartemisinin)

Check with your health care provider if you are not sure.

Warnings and precautions

[TB369 trade name] may cause **liver disease** (hepatitis). When taking [TB369 trade name], your health care provider will monitor you regularly to check for any problems with your liver.

You should watch out for symptoms of liver damage, such as unexplained lack of appetite, nausea, vomiting, dark urine, yellow discolouration of the skin and the eyes (jaundice), rash, tingling in the hands and feet, persistent tiredness, weakness lasting longer than 3 days and abdominal (belly) pain and tenderness. If these occur, you should immediately tell your health care provider.

You may be at special risk for developing hepatitis:

- if you are older than 35 years,
- if you drink alcoholic beverages daily (see '*TB369 trade name* with food and drink')
- if you have a long-term liver disorder
- if you are a user of injection drugs (e. g. heroin).

If you are in one of these groups, your health care provider will check your liver function more often.

Furthermore, you will be carefully monitored:

- if you are on another long-term medication (see '*Other medicines and TB369 trade name*')
- if you suffer from tingling in the hands and feet (peripheral neuropathy)
- if you are pregnant
- if you are HIV infected.

If you get **flu-like symptoms** such as fever, headache and muscle aches, you should tell your health care provider, since [TB369 trade name] may be the cause.

Tingling in the hands and feet (peripheral neuropathy) is the most common side effect of isoniazid, one of the active substances in [TB369 trade name] (see '*Possible side effects*'). You should tell your health care provider of any such side effect. You should take vitamin B6, also called pyridoxine, routinely at doses of 10 mg per day during treatment with [TB369 trade name], since it can reduce the risk of developing neuropathy.

You should also tell your health care provider:

- If you have epilepsy or you have ever had psychiatric disease, since it may affect your ability to tolerate [TB369 trade name].
- If you have kidney problems, diabetes or porphyria, since [TB369 trade name] may then be unsuitable for you.
- If you are taking a corticosteroid (such as cortisone), since the corticosteroid dose may have to be increased while taking [TB369 trade name].
- If you are allergic to ethionamide, pyrazinamide or niacin (nicotinic acid), because you may also be hypersensitive to [TB369 trade name].

[TB369 trade name] may cause a **reddish orange discolouration of body fluids** such as urine, sputum and tears. This is due to rifapentine, and does not require medical attention. Also, contact lenses or dentures may become permanently stained due to [TB369 trade name].

[TB369 trade name] may **lower the effects of oral contraceptive pills**. Therefore, a different or additional method of contraception (e.g. condoms, intra-uterine device, pessary) should be used during treatment with [TB369 trade name].

Other medicines and [TB369 trade name]

Tell your health care provider if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Medicines you must not take with [TB369 trade name]

- **You must not take [TB369 trade name] with** certain medicines for chronic hepatitis C infection, HIV infection and malaria. This is because [TB369 trade name] may significantly decrease the amount of these medicines in your blood, preventing them from working well enough. See the full list of these medicines above, under ‘Do not take [TB369 trade name] if you’.

Check with your health care provider if you are not sure.

Other medicines that can interfere with [TB369 trade name]

Where possible, you should not take [TB369 trade name] with other medicines that can cause damage to the liver or the nerves, since their side effects may add up. Your health care provider will be able to advise you about any changes that may be needed to your treatment.

You should not take [TB369 trade name] with antacids (medicines for indigestion) especially those that contain aluminium hydroxide, as they lower the dose of isoniazid that your body absorbs and so reduce how well it works.

[TB369 trade name] may also interfere with a great number of other medicines, including for instance:

- medicines to treat fungal infections (e.g. ketoconazole, fluconazole)
- antibiotics (e.g. clarithromycin)
- medicines to treat malaria (e.g. quinine)
- immunosuppressant medicines (e.g. cyclosporine, tacrolimus)
- medicines to treat heart conditions (e.g. digoxin, verapamil)
- medicines used to treat high blood pressure and some heart conditions (calcium channel blockers, e.g. nifedipine)
- medicines to treat high cholesterol (atorvastatin, simvastatin)
- some medicines to treat diabetes (e.g. glibenclamide)
- oral contraceptive pills
- medicines to treat epilepsy (e.g. carbamazepine, phenytoin, valproate)
- medicines used to help you sleep (benzodiazepines, e.g. diazepam, flurazepam, midazolam, triazolam)
- medicines for the treatment of certain psychiatric conditions (e.g. haloperidol)
- medicines for preventing blood clots (e.g. phenindione, warfarin)
- corticosteroids (medicines for the treatment of inflammations and other diseases, such as asthma or rheumatoid arthritis, e.g. prednisolone)
- disulfiram (medicine used for treating of chronic alcoholism)
- sildenafil (medicine used to treat erectile dysfunction).
- medicines used to treat pain (codeine, morphine, paracetamol)

Taking any of these drugs together with [TB369 trade name] may be unsuitable or require dose adjustment.

[TB369 trade name] with food and drinks

You should not drink alcohol while taking [TB369 trade name]. This increases the risk of liver damage.

When taken with matured cheese or some oily fish (histamine- or tyramine-rich food), [TB369 trade name] may cause redness, itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, and/or light-headedness. If you experience these side effects, you should avoid eating cheese and fish while taking this medicine.

Pregnancy and breast-feeding

If you become pregnant, or are planning to become pregnant, you must contact your health care provider to discuss the potential benefits and risks of the tuberculosis therapy for you and your child.

Isoniazid is excreted into the breast milk of breast-feeding mothers. It is not known whether rifapentine is excreted into human milk. No negative effects have been reported in breast-fed infants whose mothers were receiving these medicines. However, isoniazid drug concentrations in breast milk are so low that you cannot rely upon breast-feeding for adequate tuberculosis prophylaxis or therapy for your child.

Driving and using machines

[TB369 trade name] may cause visual disturbances, dizziness and other side effects on the nervous system that can impair your ability to drive and use machines.

3. How to take [TB369 trade name]

Always take your medicine exactly as your health care provider has told you. You should check with your health care provider if you are not sure.

[TB369 trade name] should be swallowed with water or another drink. When needed, the tablet can be split in half and then swallowed.

The tablets should be taken with a meal.

Usual dose

Age over 14 years

Take 3 tablets once weekly for 3 months (a total of 12 doses).

Age 2 to 14 years

The dose of [TB369 trade name] for children is based on body weight as shown in the table below. The following dose should be taken once a week for 3 months (a total of 12 doses):

Body weight	Number of tablets per week
10–15 kg	1
16–23 kg	1½
24–30kg	2
31 kg or more	2½

If you take more [TB369 trade name] than you should

If you accidentally take too many tablets, immediately contact your health care provider or the nearest hospital emergency department. Take the tablet container with you so that you can easily describe what you have taken. If you have taken too much [TB369 trade name], you may develop vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurring of speech, hallucinations and/or visual disturbances. You may also get a reddish-orange discolouration of the skin, facial swelling and itching.

If you forget to take [TB369 trade name]

It is important not to miss a dose. If you miss a dose, but you remember it within the next 2 days, take the dose as soon as possible and continue with the next treatments as originally planned. If you remember it more than 2 days later, take the missed dose immediately and then take your next dose on the same day one week later, so that there is a week between treatments. Continue taking your doses on that day each week until all 12 doses are taken.

If you miss 4 or more weekly doses talk to your health care provider.

If you vomit less than 1 hour after taking this medicine, take another dose. You do not need to take another dose if you were sick more than 1 hour after taking [TB369 trade name].

If you stop taking [TB369 trade name]

Do not stop taking this medicine without checking with your health care provider. Stopping your tablets too early may mean that your treatment will not work.

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

4. Possible side effects

Like all medicines, [TB369 trade name] can cause side effects, although not everybody gets them.

If you get any of the following side effects, contact your health care giver as soon as possible:

- yellowing of the skin or whites of the eyes, or urine getting darker and stools paler, tiredness, weakness, malaise, loss of appetite, nausea or vomiting caused by liver problems (hepatitis)
- severe pain in the abdomen and back which can be signs of inflammation of the pancreas
- severe extensive skin damage and blistering, often with flu-like symptoms (toxic epidermal necrolysis or TEN)
- a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and general illness (DRESS syndrome).

The following side effects have been reported in patients treated with [TB369 trade name]:

Very common and common side effects

(may affect more than 1 in 100 people):

- Increased non-protein nitrogen
- Elevated blood sugar
- Increased blood levels of an enzyme called LDH
- Elevated phosphate levels in the blood
- Decreased red blood cell counts (anaemia), possibly leading to tiredness, weakness and shortness of breath
- Changes in the white blood cell counts (neutropenia, lymphopenia, leucopenia), possibly resulting in an increased risk of infection
- High levels of white blood cells
- Decreased platelet count, possibly resulting in an increased risk of bruising and bleeding High levels of red blood cells
- Swollen or enlarged lymph nodes
- Rash
- Increased sweating
- Coughing up blood
- Coughing
- Nose bleeding
- Inflammation of the lining of lungs and chest cavity
- increases of liver enzymes as measured in blood samples. Usually, the enzyme levels return to normal within 3 months despite continued treatment. When the values rise above a certain level your health care provider may decide to stop treatment with [TB369 trade name].
- Difficulty sleeping
- Joint pain
- Pink eye (conjunctivitis)
- Reddish discoloration of body fluids such as urine, sputum, tears, saliva and sweat
- Diarrhoea
- Stomach pain
- Back pain

- Chest pain
- Fever
- Tiredness
- Feeling sick (nausea)
- Skin reactions with rash and/or itching
- Sensations of tingling, pricking, or numbness of the skin, especially in the feet and hands (peripheral neuropathy).

If you notice signs of illness suggestive for liver damage (see “Take special care with [TB369 trade name]”), you should inform your health care provider immediately.

Uncommon and rare side effects

(may affect up to 1 in 1000 people)

- Elevated liver enzymes
- Increased white blood cells in the blood (lymphocytosis)
- Collection of blood outside the blood vessels (haematoma)
- Purple coloured spots or patches on the skin
- Anaemia (hypochromic and normocytic)
- Changes in the white blood cell counts (eosinophilia, agranulocytosis), possibly resulting in an increased risk of infection
- Inflammation of blood vessels (vasculitis)
- Skin reactions with rash and/or itching
- A drug reaction that causes rash, fever, inflammation of internal organs, haematologic abnormalities and systemic illness (DRESS syndrome)
- Severe extensive skin damage (blistering on the skin and in body openings such as the mouth and nose): toxic epidermal necrolysis (life-threatening reaction with flu-like effects and blistering in the skin, mouth, eyes and genitals)
- Skin reactions, such as rash (exanthema, erythema) and/or itching (pruritus), but also severe forms with fever, blisters and involvement of the mucous membranes (e.g. erythema multiforme, Stevens-Johnson syndrome)
- Sensation of a lump in the throat, a feeling of tightness in the throat, voice changes including hoarseness or loss of voice
- Poor voice quality (dysphonia)
- Diarrhoea and vomiting (gastroenteritis)
- Dry mouth
- Severe pain in the abdomen and back which can be signs of inflammation of the pancreas
- Enlargement of the salivary gland
- Fungal infections
- Elevated levels of bilirubin in the blood
- Enlarged liver
- Inflammation of the liver (hepatitis), which can cause yellowing of the skin or whites of the eyes,

or urine getting darker and stools paler, fatigue, weakness

- Excess sleepiness
- Inflammation of the protective membranes that surround the brain and spinal cord (meningitis)
- Mental disturbances including psychotic reactions such as hallucinations and delusions
- Elevated mood, personality changes
- Memory problems
- Weak, painful or aching muscles
- Painful disorder affecting joints, muscles, tendons (rheumatic syndrome)
- Inflammation of the joints (arthritis)
- Connective tissue disorders such as lupus syndrome which can affect the skin and kidneys (symptoms may include a butterfly-shaped rash over the cheeks and nose, tiredness, a high temperature, feeling or being sick, joint pain and weight loss)
- Inflammation of the lungs (pneumonitis)
- Muscle spasm
- Temporary loss of consciousness (syncope)
- Rapid heartbeat which may be regular or irregular (tachycardia)
- Rapid, strong, irregular heartbeat (palpitation)
- Low blood pressure that happens when standing after sitting or lying down
- Swelling and irritation of the thin, sac-like membrane surrounding the heart (pericarditis)
- Eye problems such as visual disturbances and eye pain
- Deafness
- Vertigo (spinning sensation and loss of balance)
- Loss of hearing and ringing in your ears may occur if you have severe problems with your kidneys
- Abortion
- Vaginal bleeding
- Vaginal discharge
- Pain or a burning sensation when urinating (dysuria)
- Male breast inflammation
- Abnormal laboratory test results
- Swelling of the blood vessels (vasculitis)
- Facial swelling
- General sense of being unwell, often accompanied by fatigue, diffuse pain or lack of interest in activities (malaise)
- Build-up of acid in the body (metabolic acidosis); increased blood levels of glucose; a vitamin B3 deficiency syndrome called pellagra (with symptoms such as dementia, loose stools and skin inflammation); vitamin B6 deficiency (irritability, difficulty sleeping, weak muscles, cracks at the corner of the mouth and weight loss)
- Muscle weakness, overactive reflexes

- Increased size of breasts in men (gynaecomastia)
- A positive test result for antibodies against your body's tissues
- Withdrawal symptoms, which may occur after you stop taking [TB369 trade name], include headache, insomnia, excessive dreaming, irritability and nervousness.
- Severe allergic reaction which can be life-threatening (anaphylactic shock)

Side effects with this medicine are more common in people aged over 35 and in people who break down isoniazid more slowly. The risk of having side effects increases with high doses of [TB368 trade name].

If you notice any of the side effects listed above or if any of the side effects get serious, talk to your health care provider.

Reporting of side effects

If you get a side effect, talk to your health care provider. This includes side effects not listed in this leaflet. You may also be able to report such effects directly to your national reporting system if one is available. By reporting side effects, you can help to improve the available information on this medicine.

5. How to store [TB369 trade name]

Do not store above 30°C. Protect from excessive heat and humidity.

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 carton after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines in wastewater or household waste. Ask your health care provider 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 [TB369 trade name] contains

- The active ingredients are isoniazid and rifapentine.
- The other ingredients of [TB369 trade name] are:

Core tablet

Microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, iron oxide red, povidone, low-substituted hydroxypropyl cellulose, sodium starch glycolate, sodium ascorbate, EDTA disodium, sodium lauryl sulfate, hydroxypropyl cellulose and calcium stearate;

Film coat

Hypromellose; and the film-coating mixture contains hypromellose, macrogol/ polyethylene glycol, titanium dioxide, iron oxide red and talc.

There is too little sodium in this medicine to have any effect, even if you are on a low-sodium diet.

What [TB369 trade name] looks like and contents of the pack

[TB369 trade name] are reddish-brown, capsule-shaped, film-coated tablets. They are biconvex, (rounded on top and bottom) with a bevelled edge. The tablets are debossed with "J" and "21" on either side of the breakline on one side and plain on the other side. The tablets can be divided into equal doses.

[TB369 trade name] is available in:

- Aluminium on aluminium (Alu/Alu) strips. Each strip contains 6 tablets. Such 7 strips are packed in a carton along with a patient information leaflet. Pack size: 7 x 6 tablets.
- Aluminium on aluminium (Alu/Alu) strips. Each strip contains 12 tablets. Such 3 strips are packed in a carton along with a patient information leaflet. Pack size: 3 x 12 tablets.

Supplier and Manufacturer

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For any information about this medicine, contact the local representative of the supplier.

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Detailed information on this medicine is available on the World Health Organization (WHO) website:
<https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products>