

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

[TB309 trade name][†]
Isoniazid/pyrazinamide/rifampicin

If you are a carer or parent looking after the person who takes this medicine, use this leaflet to give the medicine correctly and take note of the warnings and side effects.

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 [TB309 trade name] is and what it is used for
2. What you need to know before you take [TB309 trade name]
3. How to take [TB309 trade name]
4. Possible side effects
5. How to store [TB309 trade name]
6. Contents of the pack and other information

1. What [TB309 trade name] is and what it is used for

[TB309 trade name] is a combination of three medicines that act against the bacteria that cause tuberculosis (TB). The active substances in [TB309 trade name] are:

- Isoniazid
- Rifampicin
- Pyrazinamide

[TB309 trade name] is used for the initial treatment of tuberculosis in children weighing less than 25 kg.

[TB309 trade name] may be given alone or together with another TB medicine.

This product is intended for use in children. Nonetheless, safety information is provided for adult health issues such as liver disease, pregnancy and breast-feeding, to allow full access to all relevant information.

2. What you need to know before you take [TB309 trade name]

Do not take [TB309 trade name] if you:

- are hypersensitive (allergic) to isoniazid, pyrazinamide, to rifampicin or related medicines called rifamycins or to any of the other ingredients of [TB309 trade name] (see section 6, “What [TB309 trade name] contains”).

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

- are experiencing new (acute) liver problems
- have previously had liver problems (hepatitis) caused by [TB309 trade name], rifampicin or isoniazid
- have gouty arthritis or hyperuricemia (high levels of uric acid in the blood)
- have severe kidney problems
- have a condition called porphyria
- Are taking certain medicines:
 - o **Voriconazole** (a medicine used to treat fungal infections)
 - o **HIV infection medicines:** atazanavir, bictegravir/emtricitabine/tenofovir alafenamide, darunavir, doravirine, elvitegravir/cobicistat, etravirine, fosamprenavir, lopinavir, nevirapine, rilpivirine, ritonavir, tipranavir
 - o **Chronic hepatitis C medicines:** daclatasvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, sofosbuvir
 - o **Malaria medicines:** artemisinin and its derivatives (artemether, artemotil, artesunate, dihydroartemisinin)

Do not take [TB309 trade name] if any of the above apply to you.

If you are not sure about anything, ask your health care provider.

Warnings and precautions

The rifampicin in [TB309 trade name] may cause severe allergic reactions such rash, anaemia, low platelet count, difficulty breathing, shock, fever or kidney failure as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock or renal failure. You should stop taking [TB309 trade name] immediately if you experience a severe allergic reaction. If you experience such a reaction, you must never again be treated with rifampicin.

Talk to your health care provider before taking [TB309 trade name].

Tell your doctor if you have one of the following illnesses before taking this medicine:

- Kidney problems
- Liver problems
- Diabetes
- Epilepsy
- Inflammation of peripheral nerves or the optic nerve
- Problems with vision
- Chronic alcoholism
- Malnutrition (underfeeding)
- Psychosis (mental disorder)

Talk to your health care provider if you have any of these conditions, as [TB309 trade name] may not be suitable for you, or your health care provider may need to carry out additional checks.

Your health care provider will check your blood for liver function and metabolic changes before starting therapy, and at regular intervals during treatment with [TB309 trade name].

Your health care provider will also check your vision before and during treatment. Contact your health care provider at once if you notice any problems with your eyesight in between checks.

[TB309 trade name] may cause liver disease (hepatitis). You should look out for symptoms that might be due to liver damage, such as unexplained loss of appetite, nausea, vomiting, dark urine, yellow coloration of the skin and of the whites of the eyes (jaundice), persistent tiredness for more than 3 days and abdominal (belly) pain and tenderness. If these occur, you should immediately talk to your health care provider.

You may be at special risk for developing hepatitis if:

- you are older than 35 years
- you drink alcoholic beverages daily (see “[TB309 trade name] with food and drink”)
- you have a chronic liver disorder
- you are a user of injection drugs (e.g., heroin)

If any of these apply to you, your health care provider will check your liver function more often.

Furthermore, you will be carefully monitored if:

- you use other long-term medication at the same time (see “Other medicines and [TB309 trade name]”),
- you suffer from tingling in the hands and feet (peripheral neuropathy),
- you are pregnant
- you have HIV infection.

If you get flu-like symptoms such as fever, headache, muscle aches etc, you should report this to your health care provider straight away, since [TB309 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 [TB309 trade name] (see “Possible side effects”). You should report any such symptoms to your health care provider. Your health care provider may prescribe vitamin B₆ (pyridoxine) to take during treatment with [TB309 trade name], since it reduces the risk of developing neuropathy.

If you are hypersensitive (allergic) to ethionamide or niacin (nicotinic acid), you should tell your health care provider, because you may also be hypersensitive to [TB309 trade name].

If you are taking cortisone or any cortisone-like medicines (called corticosteroids), you should say this to your health care provider, since the cortisone dose may have to be increased while you are taking [TB309 trade name].

[TB309 trade name] causes a reddish orange discoloration of body fluids such as urine, sputum and tears as well as of your stool. This is due to rifampicin, and does not require medical attention. Also, contact lenses can become stained due to [TB309 trade name].

[TB309 trade name] may reduce the effectiveness 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 [TB309 trade name].

It is important that your health care provider knows about all your signs of illness, even when you think they are not related to tuberculosis infection.

You should take [TB309 trade name] regularly every day. Do not interrupt or stop your treatment without discussing it with your health care provider.

Other medicines and [TB309 trade name]

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

The active substances in [TB309 trade name] can affect the action of a great number of other medicines. Other medicines may also affect the action of [TB309 trade name]. Side effects of either medicine may become worse, or the medicines may become less effective. Your health care provider may need to recommend a different medicine or may adjust your dose or carry out additional checks.

You must **not** take [TB309 trade name] with:

- **voriconazole** (a medicine used to treat fungal infections).
- **HIV infection medicines:** atazanavir, bictegravir/emtricitabine/tenofovir alafenamide, darunavir, doravirine, elvitegravir/cobicistat, etravirine, fosamprenavir, lopinavir, nevirapine, rilpivirine, ritonavir, tipranavir

- **Chronic hepatitis C medicines:** daclatasvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, sofosbuvir
- **Malaria medicines:** artemisinin and its derivatives (artemether, artemotil, artesunate, dihydroartemisinin)

As well as the medicines above, the active agents in [TB309 trade name] may also interact with a great number of other medicines. As a result, your health care provider may change the dose of your medicine and/or monitor you more closely for side effects. Medicines that may interact with [TB309 trade name] include:

- many medicines for **HIV infection** (e.g., zidovudine, efavirenz, raltegravir, maraviroc)
- medicines to treat **fungal infections** (e.g., ketoconazole, fluconazole, itraconazole)
- **antibiotics** (e.g., chloramphenicol, clarithromycin, dapsone, doxycycline, ethionamide, para-aminosalicylic acid, trimethoprim)
- medicines to treat **malaria** (e.g., atovaquone, chloroquine, mefloquine, quinine, lumefantrine)
- medicines to relieve **pain** (e.g., morphine, paracetamol, etoricoxib)
- medicines to treat **epileptic seizures** (e.g., phenytoin, carbamazepine, valproate, lamotrigine, phenobarbital)
- **immunosuppressant medicines**, often used to prevent rejection (e.g., ciclosporin, tacrolimus)
- medicines to treat **heart conditions** (e.g., verapamil, digoxin)
- medicines used to manage **blood pressure**, including medicines called beta blockers (e.g., atenolol) and calcium-channel blockers (e.g., amlodipine)
- medicines for **prevention of blood clots** (e.g., warfarin)
- medicines to **lower blood cholesterol** (e.g., simvastatin, atorvastatin)
- medicines to **control stomach acid or ulcers** (e.g., antacids containing aluminium hydroxide, ranitidine). If taking aluminium hydroxide cannot be avoided, take [TB309 trade name] 1 hour before this antacid.
- medicines used to **relieve anxiety or help you sleep** (e.g., benzodiazepines such as diazepam, flurazepam, triazolam, midazolam; zolpidem, zopiclone)
- medicines for the treatment of **certain psychiatric conditions** (neuroleptics, e.g., chlorpromazine, haloperidol, clozapine, and antidepressants, e.g., amitriptyline)
- corticosteroids (e.g., prednisolone, medicines for the treatment of inflammations and other diseases, such as asthma or rheumatoid arthritis)
- some medicines to treat **diabetes** (e.g., glibenclamide, gliclazide, repaglinide)
- **oral contraceptive pills**. An additional method of contraception is recommended.
- medicines used in surgery (e.g., alfentanil, enflurane)
- codeine (medicine to treat cough)
- methadone (medicine used to manage drug addiction)
- disulfiram (medicine used for the treatment of chronic alcoholism)
- praziquantel (medicine used to treat certain parasite infections)
- typhoid vaccine taken by mouth

Taking any of these medicines together with [TB309 trade name] may be unsuitable or require dose adjustment, so it is very important that you tell your health care provider about any other medicines that you may take.

[TB309 trade name] with food and drink

You should take [TB309 trade name] on an empty stomach (at least one hour before eating or two hours afterwards).

You should not drink alcohol while taking [TB309 trade name]. This increases the risk of liver damage.

Taking [TB309 trade name] with cheese or fish (histamine- or tyramine-rich food) may cause redness, itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, and lightheadedness. If you get these side effects, you should not eat cheese and fish while taking this medicine.

Pregnancy and breast-feeding

If you become pregnant, think you may be, or are planning to become pregnant, talk to your health care provider to discuss the potential benefits and risks of the tuberculosis therapy for you and your baby.

Isoniazid and rifampicin pass in small amounts into the breast milk. No ill effects have been reported in breast-fed infants whose mothers were receiving these medicines. However, there is not enough medicine in breast milk to treat or protect your child from tuberculosis.

Driving and using machines

[TB309 trade name] can cause dizziness, drowsiness or affect your eyesight. If you experience any of these side effects while taking [TB309 trade name], do not drive and do not use any hazardous tools or machines.

Other ingredient of [TB309 trade name]

[TB309 trade name] contains 3.13 mg aspartame in each tablet. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

3. How to take [TB309 trade name]

[TB309 trade name] 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.

[TB309 trade name] 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. The usual doses are shown in the table below:

Patients' weight	Dose
4 to less than 8 kg	1 tablet once daily
8 to less than 12 kg	2 tablet once daily
12 to less than 16 kg	3 tablets once daily
16 to less than 25 kg	4 tablets once daily
25 kg or more	Adult dosages recommended

[TB309 trade name] is not recommended for adults or children who weigh 25 kg or more.

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

[TB309 trade name] should be taken on an empty stomach (at least one hour before or two hours after a meal).

Disperse the tablets in drinking water before taking the dose. Each tablet should be dispersed in 10 mL water.

Instructions for giving [TB309 trade name] tablets

Look up the patient's weight in the table above.

1. Then look for the number of tablets that will be required.
2. Place the required volume of water in a small, clean cup or bowl and add the required number of tablets.
3. Stir gently until the tablets disperse.

4. Give the child the entire medicine mixture immediately using a syringe.
5. Rinse the cup with a little additional water and give the child to drink to ensure the entire dose is taken.

If your child takes too many [TB309 trade name] tablets

Taking too many [TB309 trade name] 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 [TB309 trade name] 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 [TB309 trade name]

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, [TB309 trade name] can cause side effects, although not everybody gets them. It is important that you tell your health care provider of any change in your health during treatment.

If you get any of the following symptoms of a severe allergic reaction, tell your health care provider **immediately** or go to the emergency department at your nearest hospital:

- Sudden difficulty in breathing, speaking and swallowing
- Swelling of lips, tongue, face or neck
- Extreme dizziness or collapse

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

- Inflammation of the pancreas, which causes severe pain in the abdomen (belly) and back
- Severe extensive skin damage with blistering or peeling of the skin
- Yellowing of the skin or whites of the eyes, or urine getting darker and stools paler, tiredness, weakness, feeling generally unwell, loss of appetite, pain just below your ribs, nausea or vomiting caused by liver problems (hepatitis)
- Diarrhoea that is serious, lasts a long time or has blood in it with belly pain or fever: This can be a sign of serious bowel infection (pseudomembranous colitis)
- Unexplained bleeding, small purple spots or blood blisters in the skin (thrombocytopenic purpura)
- Vision disturbances like blurred vision, eye pain, red-green colour blindness or even loss of vision
- Shortage of white blood cells, accompanied by sudden high fever, severe sore throat and ulcers in the mouth (agranulocytosis).

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

The following side effects may affect people taking [TB309 trade name]:

Very common side effects (may affect more than 1 in 10 people):

- sensations of tingling, pricking, or numbness of the skin, especially in the feet and hands (peripheral neuropathy). Your health care provider may prescribe a vitamin B₆ (pyridoxine) supplement, in order to counteract this.
- increased liver enzymes as measured in blood samples. Usually, liver enzyme increases occur during the first 1-3 months of therapy and return to normal despite continued treatment. When

the values rise above a certain level, your health care provider may decide to stop treatment with [TB309 trade name]

- flushing
- fever, chills
- increased levels of uric acid in the blood (hyperuricaemia)
- joint pain

Common side effects (*may affect up to 1 in 10 people*):

- reddish discoloration of body fluids such as urine, sputum, tears, saliva and sweat
- staining of contact lenses
- belly pain, feeling bloated
- loss of appetite
- feeling sick (nausea)
- vomiting
- skin reactions with rash and/or itching
- tiredness, drowsiness
- headache
- lightheadedness or dizziness
- reddening of the eyes.

Uncommon side effects (*may affect up to 1 in 100 people*)

- inflammation of the liver (hepatitis), jaundice (yellowing of skin or eyes)
- epileptic seizures
- inflammation of the brain
- personality changes and difficulty remembering
- damage to the optic nerve resulting in effects on vision, eye pain.

Rare side effects (*may affect up to 1 in 1000 people*)

- inflammation of the stomach lining (gastritis)
- inflammation of the pancreas
- infection of the intestines (bowel infection, pseudomembranous colitis)
- diarrhoea
- liver failure
- inflammation of the kidney (nephritis)
- skin sensitivity to light (photosensitivity reactions)
- severe skin reactions with rashes, fever and skin breakdown or blistering (Steven-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigoid)
- muscle weakness, muscle pain and loss of coordination
- confusion, altered sense of reality
- triggering of porphyria (a metabolic condition)
- menstrual disturbances
- low white blood cell counts
- low blood platelet counts (thrombocytopenia), purple patches on the skin like bruising (purpura)
- inflammation or swelling of the conjunctiva or pink eye (conjunctivitis)

Very rare side effects (*may affect up to 1 in 10 000 people*)

- anaphylaxis (severe allergic reaction)
- a vitamin deficiency syndrome called pellagra (with e.g. dementia, loose stools and skin inflammation)
- inflammation of the lungs (pneumonitis)

Side effects of which it is not known how often they may occur

- gout
- allergic reactions with fever, muscle aches, and cough
- reduced function of adrenal glands
- breakdown of red blood cells (haemolysis)

- small blood clots throughout the body (disseminated intravascular coagulation)
- bone pain
- collapse, shock (steep fall in blood pressure)
- fluid build-up under the skin (oedema)
- high blood pressure
- inflammation of blood vessels (vasculitis)
- flushing
- build-up of acid in the body (metabolic acidosis), increased blood levels of glucose
- dry mouth, flatulence (gas), constipation.
- painful urination
- acne
- systemic lupus erythematosus, antibodies against the body's own tissues, arthritis, rheumatic disorders
- deafness, tinnitus
- vertigo
- raised mood
- sleep disorders
- breast enlargement in men (gynaecomastia)
- decreased red blood cell counts (anaemia), possibly leading to fatigue, weakness and shortness of breath
- bleeding
- weight loss

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 [TB309 trade name]

Keep this medicine out of the sight and reach of children.

Keep this medicine out of the sight and reach of children.

Bottle pack

- o Do not store above 25°C. Store in dry place. Protect from light.
- o Once opened, use within 120 days

Strip packs

- o Do not store above 30°C. Store in dry place. Protect from light

Do not use this medicine after the expiry date stated on the label, carton or bottle after 'EXP'. The expiry date refers to the last day of that month.

Do not use this medicine if you notice description of the visible signs of deterioration that it is different from the description below.

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 [TB309 trade name] contains

- The active ingredients are 50 mg isoniazid, 150 mg pyrazinamide and 75 mg rifampicin.
- The other ingredients of [TB309 trade name] are microcrystalline cellulose, crospovidone, povidone, bleached shellac, croscarmellose sodium, aspartame, strawberry flavour, and magnesium stearate.

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

What [TB309 trade name] looks 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 not intended for breaking the tablet.

[TB309 trade name] is available in the following packs.

Bottle pack

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 pack

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 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>