

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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

Information for the patient

[TB168 trade name][†]

Rifampicin/Isoniazid/Pyrazinamide/Ethambutol

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 [TB168 trade name] is and what it is used for
2. What you need to know before you take [TB168 trade name]
3. How to take [TB168 trade name]
4. Possible side effects
5. How to store [TB168 trade name]
6. Contents of the pack and other information

1. What [TB168 trade name] is and what it is used for

[TB168 trade name] is a combination of four medicines that act against the bacteria that cause tuberculosis (TB). The active substances in [TB168 trade name] are:

- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol

[TB168 trade name] is used for the initial treatment of tuberculosis in adults and children weighing at least 25 kg.

2. What you need to know before you take [TB168 trade name]

Do not take [TB168 trade name] if you:

- are hypersensitive (allergic) to isoniazid, to rifampicin or related medicines called rifamycins, pyrazinamide or ethambutol, or to any of the other ingredients of [TB168 trade name] (see section 6, What [TB168 trade name] contains).
- have liver problems or have previously had a liver problem that was caused by a medicine,
- have had severe side effects of isoniazid or rifampicin, such as drug fever or chills,
- have acute gouty arthritis
- have severe kidney problems
- are using voriconazole (a medicine used to treat fungal infections)

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

- are using a medicine against HIV infection that belongs to the class protease inhibitors or a medicine against hepatitis C that belongs to the class of direct acting antivirals.

Do not take [TB168 trade name] if any of the above apply to you.

[TB168 trade name] is not suitable for patients who weigh less than 25 kg, or for use in tuberculosis treatment that is not taken daily.

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

Warnings and precautions

Talk to your health care provider before taking [TB168 trade name].

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

- Liver problems and chronic liver disease
- Kidney problems
- Gout
- Diabetes
- Epilepsy
- Inflammation of peripheral nerves or the optic nerve
- Problems with vision
- Chronic alcoholism
- Malnutrition (underfeeding).

Talk to your health care provider if you have any of these conditions, as [TB168 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 [TB168 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.

[TB168 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
- if you drink alcoholic beverages daily (see “[TB168 trade name] with food and drink”)
- if you have a chronic liver disorder
- if 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 [TB168 trade name]”),
- if you suffer from tingling in the hands and feet (peripheral neuropathy), –
- if you are pregnant
- if 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 [TB168 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 [TB168 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 [TB168 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 [TB168 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 [TB168 trade name].

[TB168 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 [TB168 trade name].

[TB168 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 [TB168 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 [TB168 trade name] regularly every day. Do not interrupt or stop your treatment without discussing it with your health care provider.

Other medicines and [TB168 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 [TB168 trade name] can affect the action of a great number of other medicines. Other medicines may also affect the action of {DotWP-ProductName}. 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 [TB168 trade name] with:

- voriconazole (a medicine used to treat fungal infections).
- HIV protease inhibitors (drugs used to treat HIV infection such as atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, ritonavir or tipranavir). - direct acting antivirals for the treatment of chronic Hepatitis C.

You should also avoid using [TB168 trade name] with

- aluminium hydroxide (antacid medicine used for indigestion)
- nevirapine (for HIV infection)
- simvastatin (to lower blood cholesterol)

As well as the medicines above, the active agents in [TB168 trade name] may also interact with a great number of other medicines, some of which include:

- many medicines for HIV infection (e.g. zidovudine, efavirenz, nevirapine, etravirine, raltegravir, maraviroc; in particular [TB168 trade name] must not be used with protease inhibitors)
- medicines to treat fungal infections (e.g. ketoconazole, fluconazole)
- antibiotics (e.g. clarithromycin, doxycycline, trimethoprim)
- medicines to treat malaria (e.g. atovaquone, mefloquine, quinine, lumefantrine, artemether, dihydroartemisinin)
- medicines to relieve pain (e.g. morphine, paracetamol, etoricoxib)
- medicines to treat epileptic seizures (e.g. phenytoin, carbamazepine, valproate, lamotrigine)
- immunosuppressant medicines, often used to prevent rejection (e.g. ciclosporin, tacrolimus)
- medicines to treat heart conditions (e.g. verapamil, lidocaine, 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)
- 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, repaglinide)
- oral contraceptive pills
- 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 [TB168 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.

[TB168 trade name] with food and drink

You should take [TB168 trade name] on an empty stomach (at least one hour before eating or two hours afterwards).

You should not drink alcohol while taking [TB168 trade name]. This increases the risk of liver damage.

Taking [TB168 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

[TB168 trade name] may affect your eyesight, or cause dizziness and other side effects that can make it harder or unsafe to drive or use machines safely.

[TB168 trade name] contains Sunset Yellow

This medicinal product contains a colorant (sunset yellow) which may cause allergic reactions.

3. How to take [TB168 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.

The dose of [TB168 trade name] is decided based on your body weight, as shown in the table below:

Body weight	Dose
25 to less than 30 kg	2 tablets once daily
30 to less than 35 kg	3 tablets once daily
35 to less than 65 kg	4 tablets once daily

65 kg and over	5 tablets once daily
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[TB168 trade name] is usually given for 2 months at the start of tuberculosis treatment. After this you will need to take other medicines to complete your treatment. Your health care provider will explain to you how long your treatment will last.

In some cases, your health care provider may recommend that you take vitamin B₆ as long as you take [TB168 trade name].

[TB168 trade name] is not recommended for children who weigh less than 25 kg.

Older people

[TB168 trade name] is suitable for most older patients, but you should tell your health care provider if you are suffering from liver or kidney disease, as other medicines may be more suitable.

How to take [TB168 trade name]

You should take [TB168 trade name] once a day usually during the first 2 months of treatment. Take [TB168 trade name] at the same time each day as this will help you remember to take it.

Swallow the tablets whole with a drink of water.

You should take [TB168 trade name] on an empty stomach, that is, at least 1 hour before eating or at least 2 hours after you eat.

If you take more [TB168 trade name] than you should

If you accidentally take one tablet too many, nothing is likely to happen. If you take several tablets too many, contact your health care provider or your nearest hospital emergency department immediately. If possible, take your tablets or the box with you to show what you have taken.

If you forget to take [TB168 trade name]

If you forgot to take a dose, take it as soon as possible. However, if your next dose is due in less than 6 hours, skip the missed dose and take the next tablet at the usual time.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking [TB168 trade name]

Do not stop taking this medicine without checking with your health care provider. Stopping your tablets too early may no longer protect you from the infection or cause it to come back.

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

4. Possible side effects

Like all medicines, [TB168 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 [TB168 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 [TB168 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)
- hallucinations
- inflammation of the lungs (pneumonitis)
- gout

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

- 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 - metallic taste, dry mouth, flatulence (gas), constipation.
- difficulty in passing urine
- 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 any side effects, talk to your health care provider. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

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 [TB168 trade name]

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

Blister pack: Store in a dry place below 25°C and protect from light.

Strip Pack: Store in a dry place below 30°C and protect from light.

For bulk HDPE bottle pack: Store at a temperature not exceeding 25° C in a dry place and protect from light.

Do not use this medicine after the expiry date stated on the bottle label, bottle label or blister label 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 [TB168 trade name] contains

- The active ingredients are 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide and 275 mg ethambutol.
- The other ingredients of [TB168 trade name] are:

Tablet core

Calcium stearate, colloidal silicon dioxide, croscarmellose sodium, crospovidone, disodium edetate, maize starch, povidone, purified talc and shellac.

Seal Coating: Hypromellose

Film coating: Polyvinyl alcohol, Titanium dioxide, Talc, Lecithin, Xanthan Gum and Colour Lake of sunset yellow.

What [TB168 trade name] looks like and contents of the pack

Light buff coloured biconvex capsule shaped film-coated tablets with plain surface on both sides. The tablet should not be divided.

Transparent LDPE bag, packed in a triple laminated aluminium sachet which is further packed in an HDPE bottle along with a leaflet. Each bottle is sealed with an aluminium tagger and closed with a screw cap. Pack size: 500 and 1000 tablets.

Alu/PVC/PVDC blister of 10 tablets. Such 10 blisters per box.

Pack size: 100 (10 x 10) tablets.

Alu/PVC/PVDC blister of 28 tablets. Such 3 or 24 blisters per box.

Pack sizes: 84 (28 x 3) and 672 (28 x 24) tablets.

Alu/PVC/PE/PVDC blister of 10 tablets. Such 10 blisters per box.

Pack size: 100 (10 x10) tablets.

Alu/PVC/PE/PVDC blister of 28 tablets. Such 3 or 24 blisters per box.

Pack sizes: 84 (28 x 3) and 672 (28 x 24) tablets.

Alu/PVC/PE/PVDC blister of 7 tablets. Such 10 blister per box. Pack size: 70 tablets (7 x 10)

Alu/Alu strip of 10 tablets. Such 10 strips in a carton. Pack sizes: 100 (10 x 10) tablets.

Alu/Alu strip of 12 tablets. Such 14 strips in a carton. Pack sizes: 168 (12 x 14) tablets.

Alu/Alu strip of 14 tablets. Such 48 strips in a carton. Pack sizes:
672 (48 x 14) tablets

Alu/Alu strip of 28 tablets. Such 3 or 24 strips in a carton. Pack
sizes: 84 (28 x 3) and 672 (28 x 24) 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/pgweb/medicines>