

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

[TB183 trade name][†]

Ethambutol hydrochloride/isoniazid/rifampicin

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 [TB183 trade name] is and what it is used for
2. What you need to know before you take [TB183 trade name]
3. How to take [TB183 trade name]
4. Possible side effects
5. How to store [TB183 trade name]
6. Contents of the pack and other information

1. What [TB183 trade name] is and what it is used for

[TB183 trade name] is a medicine used for the initial treatment of tuberculosis (TB), an infection caused by bacteria called *Mycobacterium tuberculosis*, in adults and children weighing at least 25 kg.

[TB183 trade name] is a combination of three medicines that act against tuberculosis bacteria. The active substances in [TB183 trade name] are:

- Rifampicin
- Isoniazid
- Ethambutol.

[TB183 trade name] is usually given together with other medicines for the treatment of tuberculosis and your health care provider has chosen the right combination for your condition.

2. What you need to know before you take [TB183 trade name]

Do not take [TB183 trade name] if you

- are hypersensitive (allergic) to isoniazid, rifampicin or related medicines called rifamycins, ethambutol or any of the other ingredients of [TB183 trade name] (see section 6, What [TB183 trade name] contains).
- have acute liver disease,
- have drug-induced liver disease,
- have experienced liver damage linked to isoniazid or rifampicin before,

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

- have had severe side effects before from isoniazid or rifampicin, such as drug fever or chills.
- are using voriconazole (a medicine used to treat fungal infections)
- 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 [TB183 trade name] if any of the above apply to you.

[TB183 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 [TB183 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
- Porphyria
- Inflammation of nerves especially the optic nerve
- Problems with vision
- Chronic alcoholism
- Malnutrition (underfeeding).

Talk to your health care provider if you have any of these conditions, as [TB183 trade name] may not be suitable for you, or your health care provider may need to carry out additional checks.

[TB183 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 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 report this to your doctor.

Your health care provider will check your blood for liver function and metabolic changes before starting therapy, and at regular intervals during treatment with [TB183 trade name].

You may be at special risk for developing hepatitis

- if you are older than 35 years,
- if you drink alcoholic beverages daily (see “[TB183 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 any other long-term medication at the same time (see “Other medicines and [TB183 trade name]”),
- if you suffer from tingling in the hands and feet (peripheral neuropathy),
- if you are pregnant
- if you have HIV infection.

Ethambutol, one of the active substances in [TB183 trade name], can cause problems with your eyes. Your health care provider will 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.

Patients not able to report visual changes (such as young children) and patients with visual changes prior to start of therapy with [TB183 trade name] will be monitored more closely.

If you get flu-like symptoms such as fever, headache, muscle aches etc., you should report this to your health care provider, since [TB183 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 [TB183 trade name] (see “Possible side effects). You should report any such symptoms to your care provider. Your health care provider may prescribe vitamin B₆ (pyridoxine) to take during treatment with [TB183 trade name], since it reduces the risk of developing neuropathy.

If you are hypersensitive to ethionamide or niacin (nicotinic acid), you should inform your doctor, because you may also be hypersensitive to [TB183 trade name].

If you are taking cortisone or any cortisone-like medicines (called corticosteroids), you should say this to your doctor, since the cortisone dose may have to be increased while taking [TB183 trade name].

[TB183 trade name] may cause a reddish orange discoloration of body fluids such as urine, sputum and tears. This is due to rifampicin, and does not require medical attention. Also, contact lenses may become stained due to [TB183 trade name].

[TB183 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 [TB183 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 [TB183 trade name] regularly every day. Do not interrupt or stop your treatment without discussing it with your health care provider.

Other medicines and [TB183 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 [TB183 trade name] can affect the action of a great number of other medicines. Other medicines may also affect the action of [TB183 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 [TB183 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 [TB183 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 [TB183 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 [TB183 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)

Taking any of these medicines together with [TB183 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.

[TB183 trade name] with food and drink

You should take [TB183 trade name] on an empty stomach (at least one hour before eating or two hours afterwards).

You should not drink alcohol while taking [TB183 trade name]. This increases the risk of liver damage.

Eating cheese or fish (histamine- or tyramine-rich food) during treatment with [TB183 trade name] may cause redness/itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, and/or lightheadedness. If you get these side effects you should avoid eating 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, it is important that you talk to your health care provider to discuss the potential benefits and risks of the tuberculosis therapy for you and your baby.

If you are planning to breastfeed your baby, you should discuss the risks and benefits with your health care provider. Isoniazid, rifampicin and ethambutol pass in small amounts into 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.

While breastfeeding, you and your baby should take supplementary pyridoxine (vitamin B6). Ask your health care provider for further information.

Driving and using machines

[TB183 trade name] may affect your eyesight or cause dizziness and other side effects that can make it harder or unsafe to drive and to use machinery.

Excipients

This medicine contains a colorant (Color Ponceau 4R Aluminium Lake) which may cause allergic reactions.

3. How to take [TB183 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 [TB183 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

[TB183 trade name] is usually given with another tuberculosis medicine 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 what medicines to take and 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 [TB183 trade name].

[TB183 trade name] is not recommended for children who weigh less than 25 kg. Other medicines may also be more appropriate if you have liver or kidney disease, so tell your health care provider if this is the case.

Older people

[TB183 trade name] is suitable for most older patients, but as mentioned above you should tell your health care provider if you are suffering from liver or kidney disease, since other medicines may be more suitable.

How to take [TB183 trade name]

You should take [TB183 trade name] once a day usually during the first 2 months of treatment. Take [TB183 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 [TB183 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 [TB183 trade name] than you should

If you accidentally take one tablet too many, it is unlikely to cause serious problems. If you take several tablets too many, you may get side effects that can be serious. 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 [TB183 trade name]

If you miss or forget to take a dose, the missed dose should be taken 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 [TB183 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, [TB183 trade name] can cause side effects, although not everybody gets them. It is important that you inform the doctor or 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 [TB183 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 [TB183 trade name]
- fever, chills

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
- flushing
- 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
- increased levels of uric acid in the blood (hyperuricaemia)

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)
- 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)
- hallucinations
- inflammation of the lungs (pneumonitis)
- gout
- skin sensitivity to light (photosensitivity reactions)

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)
- inflammation of blood vessels (vasculitis)
- flushing
- build up of acid in the body (metabolic acidosis), increased blood levels of glucose
- a vitamin deficiency syndrome called pellagra (with e.g. dementia, loose stools and skin inflammation)
- 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
- breast enlargement in men (gynaecomastia)

- decreased red blood cell counts (anaemia), possibly leading to fatigue, weakness and shortness of breath
- bleeding

When [TB183 trade name] is given with other medicines for tuberculosis, those medicines may also cause side effects. Read the patient leaflet for any other medicines you are given to understand the possible side effects that they can cause.

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 [TB183 trade name]

Keep this medicine out of the sight and reach of children

For [TB183 trade name], packaged in blister packs are to be stored in a dry place below 25°C and protect from light. For [TB183 trade name] packaged in strip packs are to be stored in a dry place below 30°C and protect from light. For [TB183 tradename] packaged in bulk packs are to be stored in a dry place at temperature not exceeding 25°C. Tablets should be stored in the original container. Close the container tightly immediately after taking out tablets.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist 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 [TB183 trade name] contains

The active ingredients are Ethambutol hydrochloride 275mg, isoniazid 75 mg and rifampicin 150 mg

The other ingredient(s) of [TB183 trade name] are

Tablet core: Colloidal anhydrous silica, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch, shellac (bleached) and Purified Talc.

Film-coating: Hypromellose , Polyvinyl alcohol- part hydrolyzed, Color Ponceau 4R Aluminium Lake, purified talc, titanium dioxide, Lecithin and Xantham gum.

What [TB183 trade name] looks like and contents of the pack

[TB183 trade name] are maroon coloured, circular, biconvex, film-coated tablets having plain surface on both the sides. The tablet should not be divided.

[TB183 trade name] tablets are packed in a triple laminated Al/PET/LDPE bag. The bag is packed in a round, white opaque HDPE bottle, sealed with an aluminium tagger and closed with a polypropylene screw cap. Pack size: 1000 tablets.

Al/PVC/PVDC blister of 10 tablets. Such 3, 10 or 24 blisters per box. Pack sizes: 30 (10x3), 100 (10x10), 240 (10x24).

Al/PVC/PVDC blister of 28 tablets. Such 3, 10 or 24 blisters per box. Pack sizes: 84 (28x3), 280 (28x10), 672 (28x24).

Al/PVC/PE/PVDC blister of 10 tablets. Such 3, 10 or 24 blisters per box. Pack sizes: 30 (10x3), 100 (10x10), 240 (10x24).

Al/PVC/PE/PVDC blister of 28 tablets. Such 3, 10 or 24 blisters per box. Pack sizes: 84 (28x3), 280 (28x10), 672 (28x24).

Alu-Alu blister strips. Pack size: 30 (5x6), Pack size:100 (10x10) and Pack size:672 (24x28) tablets

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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/pqweb/medicines>

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