

WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics 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

1. NAME OF THE MEDICINAL PRODUCT

[TB008 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of ethambutol hydrochloride.

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, smooth, round, biconvex, film-coated tablets, plain on both sides.

The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB008 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis* including in regimens for drug-resistant tuberculosis.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

[TB008 trade name] is always given in combination with other tuberculosis medicines, according to the selected regimen. Official national or international guidelines, e.g. WHO guidelines should be consulted for selecting the regimen and the duration of treatment.

Drug-susceptible tuberculosis

Adults and adolescents weighing over 30 kg

A fixed-dose combination product should be used when possible. [TB008 trade name] should be used only if a fixed-dose combination product is not available or is not suitable.

Patient's weight	Dose as 400-mg tablets	Dose in mg
30 kg to less than 35 kg	2 tablets once daily	800 mg once daily
35 kg to less than 65 kg	3 tablets once daily	1200 mg once daily
65 kg or more	4 tablets once daily	1600 mg once daily

The dose of ethambutol depends on the patient's weight and is around 15–25 mg/kg once daily. Recommended doses of [TB008 trade name] for treating drug-susceptible tuberculosis are shown below:

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

Children and adolescents weighing less than 30 kg

For patients weighing less than 30 kg, formulations containing lower amounts of ethambutol are more suitable.

If a suitable strength of ethambutol tablets is not available, an extemporaneous preparation of [TB008 trade name] may be used, but the bioavailability of such a preparation is uncertain. See section 6.6 for extemporaneous preparation of mixture for children.

Recommended doses of ethambutol for treating children and adolescents with drug-susceptible tuberculosis are shown below:

Patient's weight	Dose in mg
4 kg to less than 8 kg	100 mg once daily
8 kg to less than 12 kg	200 mg once daily
12 kg to less than 16 kg	300 mg once daily
16 kg to less than 25 kg	400 mg once daily
25 kg to less than 30 kg	600 mg once daily

Drug-resistant tuberculosis

Adults and adolescents weighing over 30 kg

The dose of ethambutol depends on the patient's weight and is around 15–25 mg/kg once daily.

Recommended doses of [TB008 trade name] for treating drug-resistant tuberculosis are shown below:

Patient's weight	Dose as 400-mg tablets	Dose in mg
30 kg to less than 46 kg	2 tablets once daily	800 mg once daily
46 kg to less than 70 kg	3 tablets once daily	1200 mg once daily
70 kg or more	4 tablets once daily	1600 mg once daily

Children and adolescents weighing less than 30 kg

For patients weighing less than 30 kg, formulations containing lower amounts of ethambutol are more suitable.

If a suitable strength of ethambutol tablets is not available, an extemporaneous preparation of [TB008 trade name] may be used, but the bioavailability of such a preparation is uncertain. See section 6.6 for extemporaneous preparation of mixture for children.

Recommended doses of [TB008 trade name] for treating children and adolescents with drug-resistant tuberculosis are shown below:

Patient's weight	Dose in mg
3 kg to less than 5 kg	60 mg once daily
5 kg to less than 7 kg	120 mg once daily
7 kg to less than 10 kg	160 mg once daily
10 kg to less than 16 kg	240 mg once daily
16 kg to less than 24 kg	400 mg once daily
24 kg to less than 30 kg	600 mg once daily

Renal impairment

If the patient's creatinine clearance is less than 30 mL/minute, the dosing frequency of the relevant weight-based ethambutol dose should be reduced from once a day to three times a week. Plasma ethambutol concentration should be monitored.

Missed doses and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB008 trade name] and reduce its effectiveness.

The patient should take a missed dose if it was due less than 12 hours ago. If more than 12 hours have passed since the dose was due, the patient should omit the missed dose and take the next scheduled dose at the usual time. The patient should not take a double dose.

If the patient vomits within 1 hour of taking [TB008 trade name], the patient should take an extra dose. If the patient vomits more than an hour after taking the dose, no extra dose is needed, and the patient should take the next dose as usual when it is due.

Method of administration

[TB008 trade name] can be taken with food or between meals. It should be swallowed with water.

[TB008 trade name] may be made into a mixture with water if the patient cannot swallow tablets. Each tablet should be mixed with at least 10 mL water in a bowl or a cup.

The mixture should be swirled or stirred to mix the tablets completely. The patient should drink all the mixture. The container should then be rinsed with more water and the patient should drink this also to ensure that the whole dose is taken.

For instructions on preparing an extemporaneous formulation for children, see section 6.6.

4.3 Contraindications

- Hypersensitivity to ethambutol or to any of the excipients of [TB008 trade name].
- Patients with optic neuritis or severe visual problems unless clinical judgement determines that ethambutol may be used.

4.4 Special warnings and precautions for use

Renal impairment

Toxic effects are more common if renal function is impaired. In particular, visual acuity should be monitored more closely in these patients. For dose adjustment in patients with creatinine clearance of less than 30 mL/minute, see section 4.2.

Visual impairment

Ethambutol can cause ocular toxicity and patients should be advised to report any eye problems such as vision changes, blurring, colour blindness, trouble seeing, or eye pain.

An ophthalmic examination is recommended before starting treatment and monthly during treatment. It should include testing for visual acuity, colour discrimination, and field of vision. Each eye must be tested separately and both eyes tested together. For patients with visual defects or renal insufficiency ophthalmic examination should be more frequent.

Patients who cannot report changes to their vision should be monitored closely for deterioration during treatment with ethambutol. In young children and those with communication difficulties, parents or other family members should be given advice about the need to report visual side effects.

Ethambutol should be stopped immediately if vision is impaired.

Hepatic impairment

Liver function tests should be performed in patients who develop symptoms suggestive of hepatitis or who become generally unwell during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Aluminium hydroxide reduces the absorption of ethambutol. Therefore, if therapy for excess stomach acid is required, acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used during ethambutol therapy.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[TB008 trade name] can be used during pregnancy as part of a combination regimen to treat tuberculosis.

Ethambutol does not pose any additional risks to the patient or fetus. Tuberculosis can be particularly dangerous in pregnancy and should be managed with effective treatment. Close monitoring during pregnancy will allow any concerns to be managed promptly.

Breastfeeding

Ethambutol passes into breast milk. However, adverse effects in children breast-fed by women taking ethambutol have not been reported and it may be used during breastfeeding.

Fertility

There are no data on ethambutol's effects on fertility.

4.7 Effects on ability to drive and use machines

Patients should not drive or operate machinery if affected by visual disturbances or side effects such as numbness, paraesthesia, dizziness and disorientation.

4.8 Undesirable effects

The most important adverse reactions of ethambutol is retrobulbar neuritis with reduced visual acuity.

Adverse events considered at least possibly related to ethambutol are listed below. Frequencies are defined as very common (up to 1 in 10), common (between 1 in 100 and 1 in 10), uncommon (between 1 in 1000 and 1 in 100), rare (between 1 in 10 000 and 1 in 1000), very rare (less than 1 in 10 000), and 'not known'.

Nervous system disorders

<i>Rare</i>	peripheral neuritis, peripheral neuropathy, paraesthesia (especially in the extremities), numbness
<i>Very rare</i>	disorientation, dizziness, headache

Eye disorders

<i>Uncommon</i>	optic neuritis (decreased visual acuity, loss of vision, scotoma, colour blindness, visual disturbance, visual field defect, eye pain)
-----------------	--

Psychiatric disorders

<i>Very rare</i>	mental confusion and hallucination
------------------	------------------------------------

Gastrointestinal disorders

<i>Not known</i>	nausea, vomiting, anorexia, flatulence, abdominal pain, diarrhoea, metallic taste, anorexia
------------------	---

Hepatobiliary disorders

<i>Very rare</i>	hepatic failure
<i>Not known</i>	hepatitis, jaundice, increase in liver enzymes

Renal and urinary disorders

<i>Very rare</i>	nephrotoxicity including interstitial nephritis
------------------	---

Blood and lymphatic systems disorders

<i>Rare</i>	thrombocytopenia,
<i>Very rare</i>	leucopenia, neutropenia

Respiratory, thoracic and mediastinal disorders

<i>Very rare</i>	pneumonitis, pulmonary infiltrates, with or without eosinophilia
------------------	--

Metabolism and nutrition disorders

<i>Uncommon</i>	hyperuricaemia
<i>Very rare</i>	gout

Immune system disorders

<i>Very rare</i>	hypersensitivity, anaphylactoid reactions (see also 'Skin and subcutaneous tissue disorders')
------------------	---

Skin and subcutaneous tissue disorders

<i>Rare</i>	rash, pruritus, urticaria
<i>Very rare</i>	photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis

Musculoskeletal and connective tissue disorders

<i>Very rare</i>	joint pains
------------------	-------------

General disorders

<i>Very rare</i>	Malaise, pyrexia
------------------	------------------

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

Gastrointestinal disturbances, vomiting, fever, headache, anorexia, dizziness, hallucinations and visual disturbances

Treatment

There is no specific antidote and treatment is supportive. Gastric lavage may be of value if started within a few minutes of ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial (other drugs for treatment of tuberculosis).

ATC code: J04AK02

Mechanism of action

Ethambutol at the recommended doses is bacteriostatic. It has very little sterilising activity. Its mechanism of action is not known, but it is thought to inhibit cell wall synthesis by preventing the incorporation of mycolic acids; this stops cell multiplication and can lead to cell death. Ethambutol is only active against bacteria undergoing cell division.

Ethambutol is active against virtually all strains of *Mycobacterium tuberculosis* and *M. bovis* and is also active against other mycobacteria such as *M. kansasii*. When used alone for treatment of tuberculosis, tubercle bacilli from these patients developed resistance to ethambutol. The development of resistance is unpredictable and may occur in a step-like manner. No cross-resistance between ethambutol and other antituberculosis agents has been reported. Ethambutol delays or prevents the emergence of mycobacterial resistance when it is used with other antituberculosis drugs.

5.2 Pharmacokinetic properties

The absorption characteristics of [TB008 trade name] have been determined after administration of one ethambutol hydrochloride 400 mg tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value* (\pm standard deviation)
Maximum concentration (C_{max})	1539 (\pm 446) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	8796 (\pm 1996) ng.h/mL
Time to attain maximum concentration (T_{max})	2.90 (\pm 1.03) hours

*arithmetic mean

Pharmacokinetics of ethambutol

Absorption	
Oral bioavailability	70–80%
Food effect	None
Distribution	
Volume of distribution (mean)	20 L
Plasma protein binding <i>in vitro</i>	10–40%
Tissue distribution	Relatively low concentrations distributed to CSF
Metabolism	

	Hepatic
Elimination	
Elimination half life	3–4 h
Mean systemic clearance (Cl/F)	41 L/h
% of dose excreted in urine	60–80%
% of dose excreted in faeces	20%

Special populations

Half-life is increased up to 8 hours in cases of renal impairment. Ethambutol is not removed from the blood by haemodialysis.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Dibasic calcium phosphate
Gelatin
Sorbitol
Maize starch
Magnesium stearate

Film-coat

Ethylcellulose
Hydroxypropylmethyl cellulose
Polyethylene glycol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

Alu/PVC blister pack

Blister card of 10 tablets (comprised of clear, transparent PVC blisters sealed with aluminium foil). Such 10 blister cards are packed into a carton.

Pack size: 10 x 10 tablets

Alu/PVC/ PVdC blister pack

Blister card of 28 tablets (comprised of orange, transparent PVC/PVDC blisters sealed with aluminium foil). Such 24 blisters are packed into a carton.

Pack size: 24 x 28 tablets

HDPE bottle pack

A round, white, opaque, HDPE bottle fitted with a white LDPE lid and white polypropylene screw cap.

Pack size: 1000 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

Extemporaneous preparation of mixture for children

The following are needed for extemporaneous preparation:

- [TB008 trade name] – either one or two tablets, according to the dose, see table below
- Cool drinking water
- Two small, clean, dry bowls
- 10-mL oral syringe
- Small amount of flavoured liquid or semi-solid food to mask the medicine's taste

Instructions

1. For a dose of up to 400 mg, one 400-mg tablet (or for a dose exceeding 400 mg, two 400-mg tablets) should be placed in a small bowl.
2. For each tablet, 10 mL of drinking water (measured with an oral syringe) should be added to the bowl and the contents swirled or stirred until the tablet has disintegrated completely.
3. Using an oral syringe, a proportion of the mixture should be withdrawn according to the child's dose (see table below). Throw away the mixture that remains in the bowl.
4. Using another clean bowl, the withdrawn mixture may be mixed with more liquid or with semi-solid food to improve palatability.
5. The patient may then receive a small amount of milk or liquid to help remove the aftertaste.
6. The entire mixture should be given immediately to the patient and any residue in the bowl should be rinsed with further water, which the patient should drink.

Dose of extemporaneously prepared liquid – see section 4.2 for recommended weight-based doses

Recommended dose in mg	Mixture to be prepared	Dose of mixture to give to the child
60 mg once daily	One 400-mg tablet dispersed in 10 mL	1.5 mL once daily
100 mg once daily		2.5 mL once daily
120 mg once daily		3 mL once daily
160 mg once daily		4 mL once daily
200 mg once daily		5 mL once daily

Recommended dose in mg	Mixture to be prepared	Dose of mixture to give to the child
240 mg once daily		6 mL once daily
300 mg once daily		7.5 mL once daily
400 mg once daily ¹		10 mL once daily
600 mg once daily	Two 400-mg tablets dispersed in 20 mL	15 mL once daily
1. For the 400-mg dose, it is preferable for the patient to swallow the 400-mg tablet, rather than mixing it with water.		

7. SUPPLIER

Cadila Pharmaceuticals Limited
1389, Dholka – 382225
District: Ahmedabad
Gujarat, India

Tel. No.: +91 2714-221481 / 221483 / 221484

Email: pharmacovigilance@cadilapharma.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB008

9. DATE OF PREQUALIFICATION

13 November 2003

10. DATE OF REVISION OF THE TEXT

October 2023

References

Drug-susceptible tuberculosis

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240048126>, accessed 25 August 2023).

WHO operational handbook on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240050761>, accessed 25 August 2023).

Drug-resistant tuberculosis

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240063129>, accessed 25 August 2023).

WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240065116>, accessed 25 August 2023).

Web Annexes. In: WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/bitstream/handle/10665/365309/9789240065352-eng.pdf>, accessed 25 August 2023).

Children and adolescents

WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240046832>, accessed 25 August 2023).

Note WHO guidelines and handbooks are available on WHO TB knowledge sharing platform (<https://tbksp.org/en>, accessed 25 August 2023)

Product information

Myambutol (ethambutol hydrochloride): label. U.S. Food and Drug Administration; January 2007 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/016320s0631b1.pdf, accessed 25 August 2023).

Ethambutol 100 mg Tablets (Kent Pharma UK Ltd): summary of product characteristics. London: Medicines and Healthcare products Regulatory Agency; 6 April 2021 (<https://mhraproducts4853.blob.core.windows.net/docs/a842c1b4891938d074441414d7fa24e9230c5842>, accessed 25 August 2023).

Ethambutol/Myambutol Tablets 400mg (Genus Pharmaceuticals Holdings Limited): summary of product characteristics. London: Medicines and Healthcare products Regulatory Agency; 31 January 2019 (<https://mhraproducts4853.blob.core.windows.net/docs/5cf69bf9d9deaa32d8913ee75a2abd5006eca029>, accessed 16 September 2023)

Detailed information on this medicine is available on the World Health Organization (WHO) website:
<https://extranet.who.int/pqweb/medicines>