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/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB177 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains ethambutol hydrochloride 400 mg

Each tablet also contains 0.248 mg of lake of sunset yellow.

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

Light orange, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets are plain on both sides.

The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB177 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

[TB177 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. [TB177 trade name] should be used only if a fixed-dose combination product is not available or is not suitable.

The dose of ethambutol depends on the patient's weight and is around 15–25 mg/kg once daily. Recommended doses of [TB177 trade name] for treating drug-susceptible tuberculosis are shown below:

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

† 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 [TB177 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 [TB177 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 [TB177 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 [TB177 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 [TB177 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 [TB177 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

[TB177 trade name] can be taken with food or between meals. It should be swallowed with water.

[TB177 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 [TB177 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.

Excipients of [TB177 trade name]

[TB177 trade name] contains lake of Sunset Yellow. Sunset Yellow may cause allergic reactions.

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

[TB177 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

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

Eye disorders

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

Psychiatric disorders

Very rare	mental confusion and hallucination

Gastrointestinal disorders

Not known	nausea, vomiting, anorexia, flatulence, abdominal pain, diarrhoea, metallic taste, anorexia

Hepatobiliary disorders

Very rare	hepatic failure

Not known	hepatitis, jaundice, increase in liver enzymes
Renal and urinary disorders	
Very rare	nephrotoxicity including interstitial nephritis
Blood and lymphatic systems disorders	
Rare	thrombocytopenia,
Very rare	leucopenia, neutropenia
Respiratory, thoracic and mediastinal disorders	
Very rare	pneumonitis, pulmonary infiltrates, with or without eosinophilia
Metabolism and nutrition disorders	
Uncommon	hyperuricaemia
Very rare	gout
Immune system disorders	
Very rare	hypersensitivity, anaphylactoid reactions (see also 'Skin and subcutaneous tissue disorders')
Skin and subcutaneous tissue disorders	
Rare	rash, pruritus, urticaria
Very rare	photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very rare	joint pains
General disorders	
Very rare	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. To report SUSPECTED ADVERSE REACTIONS: dsrm@lupin.com

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 [TB177 trade name] have been determined after administration of one [TB177 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**
	Ethambutol
Maximum concentration (C_{max})	0.97. ± 0.327 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	6.04 ± 1.73 µg· h/mL
Time to attain maximum concentration (t_{max})	4.8 ± 2.0 hours

Pharmacokinetics of ethambutol

Absorption	
Oral bioavailability	70–80%
Food effect	None
Distribution	
Volume of distribution (mean)	20 L
Plasma protein binding *in vitro*	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: Colloidal silicon dioxide,
magnesium stearate,
maize starch,
povidone k-30 and
purified talc

Film coat: Ethylcellulose,
hypromellose,
lake of Sunset Yellow,
polyethylene glycol 4000,
propylene glycol,
purified talc and
titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Do not store above 30ºC. Store in a dry place.

6.5 Nature and contents of container

Plastic on Plastic and aluminium blisters (PVC-PVDC/Aluminium blisters)
Blister of 10 tablets. Such 10 blisters are packed in carton along with pack insert.
Blister of 28 tablets. Such 24 blisters are packed in carton along with pack insert.

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.

Preparation and administration - extemporaneous formulation for children

The following are needed for extemporaneous preparation:

- [TB177 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
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

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB177

9. DATE OF PREQUALIFICATION

8 April 2010

10. DATE OF REVISION OF THE TEXT

December 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/2008/016320s063lbl.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/prequal/medicines/prequalified/finished-pharmaceutical-products