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

[TB134 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ethambutol hydrochloride 400 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

[TB134 trade name] is a white, circular, film-coated tablet with a breakline on one side and a plain surface on the other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB134 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by *Mycobacterium tuberculosis*.

Consideration should be given to official guidelines for prevention and treatment of tuberculosis, e.g., those of the WHO.

4.2 Posology and method of administration

Posology
[TB134 trade name] is always given in combination with other anti-tuberculosis medicines for the treatment of MDR-TB.

The duration of therapy depends on the combination of medicines used together with [TB134 trade name]. Official national and/or international guidelines, e.g. of the WHO, should be consulted.

Adults and children aged 15 years and older
The dose is 15-25 mg/kg body weight, taken once daily.

Weight-based daily dose	Weight bands in patients 15 years old or older				
	30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg
Number of tablets of [TB134 trade name]	2	2	3	3	3

Children younger than 15 years

The dose is 15-25 mg/kg body weight, taken once daily:

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

Weight-based daily dose	Weight bands in patients under 15 years old						
	5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg	> 34 kg
Number of tablets of [TB134 trade name] or volume of dispersed tablet	3 mL[a]	4 mL[a]	6 mL [a]	1 tablet	1 or 1 ½ tablets	2 tablets	(> 14 years) [b]

[a] This is the volume to be drunk after one tablet has been mixed in 10 mL of water. See "How to take [TB134 trade name]" for further instructions.
[b] For these patients, use adult dosing.

Renal impairment
If creatinine clearance is less than 30 mL/minute, ethambutol should be given at a dose of 15–25 mg/kg 3 times a week (rather than once a day) and plasma ethambutol concentration monitored.
As children might be less likely or unable to report ocular toxicity, particular caution may be warranted.

Missed doses
It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB134 trade name] and reduce its effectiveness.
In case a dose is missed, this dose should be taken as soon as possible. However, if the next regular dose is due within 6 hours, the missed dose should be omitted.

Method of administration
[TB134 trade name] can be taken with food or between meals. Taking it with food may reduce gastrointestinal side effects.

[TB134 trade name] should be swallowed with water. If the patient weighs between 5 and 15 kg, one tablet of [TB134 trade name] should be dispersed in 10 mL of water and only some of the volume (as indicated in the table above) should be drunk.

4.3 Contraindications

- Hypersensitivity to ethambutol or to any of the excipients of [TB134 trade name].
- Patients with known optic neuritis and poor vision 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.

Visual impairment
Ethambutol causes ocular toxicity and patients should be advised to report any changes of visual acuity. An ophthalmic examination is recommended before starting treatment and every 4 weeks during treatment. It should include visual acuity, colour vision, field of vision and ophthalmoscopy. For patients with visual defects or renal insufficiency the frequency of tests should be increased to every second or third week. Patients who cannot report changes to their visual acuity should be more closely monitored for any 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 (see section 4.8).

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. Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used during ethambutol therapy.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are reports of ophthalmic abnormalities occurring in infants born to women on antituberculous therapy that included ethambutol. Therefore, [TB134 trade name] should be used only when the benefits are considered to outweigh any risk.

Breastfeeding

Ethambutol passes into the breast milk. However, adverse effects in children breastfed by women taking ethambutol have not been reported. Breast-feeding is not recommended during treatment with [TB134 trade name] unless the benefit of breast-feeding to the child is considered to outweigh any possible risks.

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 possible 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 by body system, organ class and frequency. 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
Psychiatric disorders	
Very rare	mental confusion and hallucination
Gastrointestinal disorders	
Not known	nausea, vomiting, anorexia, flatulence, abdominal pain, diarrhoea
Hepatobiliary disorders	
Very rare	hepatic failure
Not known	hepatitis, jaundice, increase in liver enzymes
Renal and urinary disorders	
Very rare	nephrotoxicity including interstitial nephritis
Eye disorders	
Uncommon	optic neuritis (decreased visual acuity, loss of vision, scotoma, colour blindness, visual disturbance, visual field defect, eye pain)

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, urticarial
Very rare	photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very rare	joint pains

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

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. Emesis and gastric lavage may be of value if started within a few hours of ingestion. Subsequently, haemodialysis or peritoneal dialysis may be of value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial (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 now 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 [TB134 trade name] have been determined after administration of single dose tablet in healthy, adult, male, human subjects under fasting conditions as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**
Maximum concentration (C_{max})	0.972 ± 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 (Tmax)	3.3 ± 1.3hours

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

Maize starch, microcrystalline cellulose, povidone, stearic acid, sodium starch glycolate, colloidal,anhydrous silica, purified talc, magnesium stearate, hypromellose, ethyl cellulose, macrogol 6000 and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.
Keep out of reach and sight of children.

6.5 Nature and contents of container

Bottle pack
[TB134 trade name] is packed in an LDPE bag; each bag is packed in a triple laminated aluminium sachet and sealed. The sachet is further packed in a HDPE plastic container and is tagger sealed.

Pack size: 1 000 tablets

Blister pack (90 or 100 tablets)
The primary packs are blister strips of 10 tablets (comprised of aluminium foil and amber-coloured PVC/PVDC foil).

Such 9 or 10 blister strips are kept packed in a carton.
Pack size: 9 x 10 tablets and 10 x 10 tablets

Blister pack (672 tablets)
The primary packs are blister strips of 28 tablets (comprised of aluminium foil and amber-coloured PVC/PVDC foil).

Such 24 blister strips are kept packed in a carton.
Pack size: 24 x 28 tablets

6.6 Instructions for use and handling and disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB134

9. DATE OF PREQUALIFICATION

23 March 2007

10. DATE OF REVISION OF THE TEXT

March 2021

References

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