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 (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

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 antituberculosis agents for the initial treatment of all forms of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis*.

4.2 Posology and method of administration

For oral use.

Treatment with [TB134 trade name] should continue throughout the initial phase, according to the selected treatment regimen. It must always be given in combination with other antituberculosis agents.

Daily dosing

The dose of ethambutol hydrochloride is 15–20 mg/kg daily, up to a maximum of 1.6 g daily.

For patients being re-treated for tuberculosis, the dose of ethambutol hydrochloride is 25 mg/kg daily. If ethambutol is given for longer than 60 days, the dose is reduced to 15 mg/kg daily.

Intermittent dosing: three times a week

The dose of ethambutol hydrochloride for intermittent treatment, the dose of ethambutol hydrochloride is 30 mg/kg (up to a maximum of 2 g) three times a week.

Children and adolescents

The dose of ethambutol hydrochloride is 15–20 mg/kg daily. However, [TB134 trade name] may not be suitable for individuals weighing less than 20 kg for whom other formulations of ethambutol hydrochloride may be more appropriate.

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.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

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

4.4 Special warnings and special precautions for use

Visual impairment

Ethambutol should generally be avoided in patients with optic neuritis or retrobulbar neuritis unless treatment outweighs the risk of visual deterioration.

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).

Renal impairment

Since ethambutol is mainly eliminated by the kidneys, the dose may need to be adjusted in patients with impaired renal function (see section 4.2). Visual acuity should be monitored more closely in these patients.

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 Pregnancy and lactation

Pregnancy

Ethambutol has not been known to cause harmful effects on the fetus. However, it should be used only when the benefits are considered to outweigh any risk.

Breastfeeding

Ethambutol passes into the breast milk. However, adverse effects in the baby have not been reported.

4.7 Effects on ability to drive and use machines

Patients whose vision is impaired during treatment with ethambutol should not drive or operate machinery.

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

Common	visual disturbances caused by optic neuritis (blurred vision, eye pain, red-green colour blindness, constricted visual field (central or peripheral scotoma), and any loss in vision); this effect occurs most frequently with doses of 25 mg/kg and after treatment for 2 months

Rare	peripheral neuritis, peripheral neuropathy, paraesthesia (especially in the extremities), numbness
Very rare	burning pain, weakness (hands and feet), dizziness, headache, eye disorders
Not known	tremor

Psychiatric disorders

Very rare	confusion, disorientation, hallucination

Gastrointestinal disorders

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

Hepatobiliary disorders

Very rare	hepatic failure
Not known	hepatitis, jaundice, increase in liver enzymes

Renal and urinary disorders

Very rare	nephrotoxicity including interstitial nephritis

General disorders

Very rare	malaise, joint pains, pyrexia

Blood and lymphatic systems disorders

Not known	thrombocytopenia, leucopenia, neutropenia with eosinophilia

Respiratory, thoracic and mediastinal disorders

Very rare	pneumonitis, pulmonary infiltrates, with or without eosinophilia

Metabolism and nutrition disorders

Very common	hyperuricaemia
Very rare	gout

Immune system disorders

Very rare	hypersensitivity, allergic reactions, anaphylaxis, allergic pneumonitis

Skin and subcutaneous tissue disorders

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

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

About 80% of ethambutol is absorbed into the blood after an oral dose. Taking ethambutol with food does not markedly affect its absorption. It is distributed to most tissues and fluids; high concentrations occur in lungs, kidneys and erythrocytes. Binding to plasma protein accounts for less than 40% (usually around 20%) of the total concentration. Ethambutol crosses the placenta and is also present in breast milk. Diffusion into the cerebrospinal fluid is increased when the meninges are inflamed. It is mainly eliminated as unchanged drug in the urine and a proportion is inactivated in the liver; reduced renal function delays elimination of the drug.

Following single-dose of [TB134 trade name] in healthy volunteers, the mean (± SD) ethambutol C_{max} value was 0.972 μg/ml (± 0.327), and the corresponding value for AUC_{0-t} was 5.46 μg.h/ml (± 1.73) and $AUC_{0-\infty}$ was 6.04 μg.h/ml (±1.73). The median (± SD) ethambutol t_{max} value was 4.8 ± 2.0 hours.

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 (PREQUALIFICATION PROGRAMME)

TB134

9. DATE OF FIRST PREQUALIFICATION

23 March 2007

10. DATE OF REVISION OF THE TEXT

July 2019

References

General references

Treatment of Tuberculosis: guidelines 4th edition, WHO, available at:

http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update), is available at:

http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/

Pharmaceutical Press. Martindale: The Complete Drug Reference (2018 update) [https://www.medicinescomplete.com/mc/]

Ethambutol 400 mg Tablets (Fannin (UK) Ltd) SmPC, revised 24 Jan 2017 available on Electronic Medicines Compendium [https://www.medicines.org.uk/emc/product/8557/smpc]

Section 4.2

Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. Int J Tuberc Lung Dis 2006; 10: 1318–30

Section 5.1

American Society of Health-System Pharmacists. AHFS Drug Information. [https://www.medicinescomplete.com/mc/]

All web links accessed in July 2019.

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/ .