SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Ethambutol Hydrochloride 100 mg Tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg ethambutol hydrochloride.
For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Ethambutol Hydrochloride 100 mg Tablets is a white, circular, shallow, biconvex, film-coated tablet with break-line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Ethambutol Hydrochloride 100 mg Tablets is indicated in combination with other anti-tuberculosis agents for the treatment of all forms of tuberculosis caused by Mycobacterium tuberculosis in children weighing between 5 and 20 kg.

Ethambutol Hydrochloride 100 mg Tablets is also used in the treatment of infections caused by atypical mycobacteria, such as Mycobacterium avium complex.

Consideration should be given to official treatment guidelines for tuberculosis, e.g those of WHO: (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf)

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2 Posology and method of administration

Oral use

Ethambutol Hydrochloride 100 mg Tablets must always been given in combination with other antimycobacterial agents.

Daily regimen

Ethambutol is administered as a single daily dose of 20 (range 15-25) mg/kg body weight.

* Trade names are not prequalified. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Number of Ethambutol Hydrochloride 100 mg Tablets for daily treatment according to weight bands:

### Ethambutol 100 mg once daily dosing for NEW Cases

**Intensive phase, 2 months**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Intensive Phase, 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 7</td>
<td>1</td>
</tr>
<tr>
<td>8 to 14</td>
<td>2</td>
</tr>
<tr>
<td>15 to 20</td>
<td>3</td>
</tr>
</tbody>
</table>

**Children between 5 kg and 20 kg**

### Ethambutol 100 mg once daily dosing for RE-TREATMENT Cases

**Intensive and continuation phases**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Intensive phase, 3 months</th>
<th>Continuation phase, 5 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8 to 14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>15 to 20</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Children between 5 kg and 20 kg**

Ethambutol Hydrochloride 100 mg Tablets may be taken with or without food. Intake with food may improve the gastrointestinal tolerability.

**Renal impairment**

Ethambutol should be used with particular caution in patients with renal impairment (see section 4.4). It is recommended to increase the dosing interval as follows:

<table>
<thead>
<tr>
<th>Crcl* (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>15-20 mg every 48 hours with monitoring of ethambutol plasma levels</td>
</tr>
</tbody>
</table>

Alternatively, doses may be reduced according to following scheme:

<table>
<thead>
<tr>
<th>Crcl (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 50</td>
<td>Normal</td>
</tr>
<tr>
<td>10 – 20</td>
<td>7.5-15mg/kg/day</td>
</tr>
<tr>
<td>&lt;10</td>
<td>5-7.5mg/kg/day</td>
</tr>
</tbody>
</table>

*Creatinine clearance

**Hepatic impairment**

No dose adjustment is necessary in patients with hepatic impairment.

**Children and adolescents**

Appropriate studies on the relationship of age to the effects of ethambutol have not been performed in children up to 13 years of age. Ethambutol should be considered for all children with strains resistant to other agents, and in whom susceptibility to ethambutol has been demonstrated or is likely. As children might be less likely to report ocular toxicity, particular caution may be warranted (see section 4.4).
Duration of therapy
The duration of antimycobacterial therapy depends on the regimen chosen, the patient’s clinical and radiographical responses, smear and culture results, and susceptibility studies of *Mycobacterium tuberculosis* isolates from the patient or the suspected source case.
If therapy is interrupted, the treatment schedule should be extended to a later completion date depending, e.g. on the length of the interruption, the time during therapy (early or late) or the patient’s status.

4.3 Contraindications

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

Ethambutol is contraindicated in patients with optic neuritis.

4.4 Special warnings and precautions for use

Patients should be advised to report promptly any changes in visual acuity since ethambutol causes ocular toxicity. Visual acuity should be tested prior to therapy and at regular intervals during treatment; in patients with pre-existing visual defects or renal impairment every second week and more frequently when considered necessary.

Patients who cannot report their visual acuity should be closely monitored for signs of ocular toxicity when treated with ethambutol (see section 4.2). As a basic examination step, testing should assess whether visual stimuli can be fixed, centred and followed. Ophthalmologic examination should include tests for black-white/chromatic visual acuity (e.g. Snellen eye chart and 65-test) and ophthalmoscopy.

Therapy with ethambutol must be discontinued immediately if visual disturbances emerge (see section 4.8).

Since ethambutol is mainly eliminated via the kidneys, dose adjustment is required in patients with impaired renal function (see section 4.2). Visual acuity should be more closely monitored in these patients.

Ethambutol is excreted via the same pathway as uric acid, thereby leading to increased serum concentration of uric acid. Concomitant therapy with isoniazid or pyridoxin may enhance this effect. Patients with pre-existing hyperuricaemia or symptoms of gout should be monitored for signs of deterioration when treated with ethambutol (see sections 4.5 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Aluminium hydroxide impairs the absorption of ethambutol. During therapy with ethambutol acid-suppressing drugs or antacids not containing aluminium hydroxide should be used.

Doses of uricosurics may need to be increased, since ethambutol competes with uric acid for its renal excretion (see section 4.4 and 4.8).

Concomitant therapy with disulfiram may increase the risk for ocular toxicity.
4.6 Pregnancy and lactation

Pregnancy
No adverse effects of ethambutol on the foetus have been detected. However, ethambutol is to be used only when the benefits outweigh the potential risks.

Lactation
Ethambutol is excreted into the breast milk of lactating mothers. No adverse effects in the baby have been reported.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse reaction profile of Ethambutol Hydrochloride 100 mg Tablets should be borne in mind when considering the patient’s ability to drive or operate machinery.

4.8 Undesirable effects

The most important adverse effect of ethambutol is retrobulbar neuritis with a reduction in visual acuity. The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. They are not based on adequately sized randomized controlled trials, but on published literature data generated mostly during post-approval use. Therefore, often no frequency data can be given. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), ‘not known’.
The frequencies reported below are based on data from adult studies, unless otherwise stated.

Nervous system disorders
Common: visual disturbances due to optic neuritis (retrobulbar neuritis). The frequency depends on the dose and duration of therapy. It has been reported in up to 3% of adult patients receiving ethambutol 20 mg/kg/day and in up to 0.8% of paediatric patients receiving up to 35 mg/kg/day. Typical initial signs include impairment of colour vision (red-green blindness) and constriction of visual field (central or peripheral scotoma). These changes are often reversible upon discontinuation of therapy. To avoid development of irreversible optic atrophy visual acuity should be regularly monitored and ethambutol therapy must be immediately discontinued when visual disturbances occur (see section 4.4).
Not known: Peripheral neuropathy (paraesthesia), especially in the legs, dizziness, headache, tremor.

Psychiatric disorders
Not known: confusion, disorientation, hallucination

Gastrointestinal disorders
Not known: metallic taste, nausea, vomiting, anorexia, flatulence, abdominal pain

Hepatobiliary disorders
Not known: jaundice, transient increases in liver enzymes

Renal and urinary disorders
Very common: increases in uric acid, especially in patients with gout.
Not known: nephrotoxicity including interstitial nephritis.
General disorders
Not known: allergic reactions with skin reactions (exanthema, erythema), pruritus, fever, leucopenia, anaphylaxia, allergic pneumonitis, neutropenia, eosinophilia, Stevens-Johnson syndrome

Blood and lymphatic systems disorders
Not known: thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia

Respiratory, thoracic and mediastinal disorders
Not known: pneumonitis (allergic)

Musculoskeletal disorders:
Not known: gout

4.9 Overdose

Symptoms
Anorexia, vomiting, gastrointestinal disturbances, fever, headache, dizziness, hallucinations and/or visual disturbances

Treatment
Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. Subsequently, haemo- or peritoneal dialysis may be of value. There is no specific antidote and treatment is supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimycobacterials
ATC Code: J04AK02

Mechanism of action
Ethambutol at the recommended doses is a bacteriostatic that acts specifically against tubercle bacilli, also those resistant to other antimycobacterial agents. It possesses very little sterilizing activity. One suggested mechanism of action is that ethambutol inhibits cell wall synthesis by preventing the incorporation of mycolic acids.

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 ethambutol has been used alone for treatment of tuberculosis, tubercle bacilli from these patients have developed resistance to ethambutol hydrochloride by in vitro susceptibility tests; the development of resistance has been unpredictable and appears to occur in a step-like manner. No cross resistance between ethambutol and other antituberculous agents has been reported. Ethambutol has reduced the incidence of the emergence of mycobacterial resistance to isoniazid when both drugs have been used concurrently.

5.2 Pharmacokinetic properties
Approximately 80% of ethambutol is absorbed after oral administration. Following intake of 15 mg/kg body weight, a peak serum concentration of approximately 4 mg/l are achieved in 2-4 hrs. When the drug is administered daily for longer periods of time at this dose, serum levels are similar. The intracellular concentrations of erythrocytes reach peak values approximately twice those of plasma and maintain this ratio throughout the 24 hours. The mean volume of distribution has been estimated to 3.89 l/kg - 8.1 l/kg.

No pharmacokinetic data are available for Ethambutol Hydrochloride 100 mg Tablets. A bioequivalence study was conducted with 400 mg tablets, which is proportionally similar to
Ethambutol Hydrochloride 100 mg Tablets in composition. Following single dose administration of Ethambutol 400 mg tablets in healthy volunteers, the arithmetic mean (SD) ethambutol Cmax value was 0.972 μg/ml (± 0.327) and the corresponding values for AUC0-t was 5.46 μg.h/ml (± 1.73), and AUC0-∞ was 6.04 μg.h/ml (±1.73). The median ethambutol tmax value was 3.3 ± 1.3 hours.

It is reported that, depending on the administered dose, about 10-40% of the drug is bound to plasma protein. The plasma concentration falls biphasically, the half-life being about 4 hrs initially and 10 hrs subsequently; 50 to 70% of the dose being excreted unchanged in the urine and another 7 to 15% as inactive aldehyde and carboxylic acid metabolites. The main path of metabolism appears to be an initial oxidation of the alcohol to an aldehydic intermediate, followed by conversion to a dicarboxylic acid. From 20 to 22% of the initial dose is excreted in the faeces as unchanged drug. The elimination of the drug is delayed in subjects with reduced renal function.

Paediatric population

The recommended daily dose of ethambutol is higher in children (20 mg/kg) than in adults (15mg/kg), because the pharmacokinetics are different (peak serum ethambutol concentrations are lower in children than in adults receiving the same mg/kg dose). Although ethambutol was frequently omitted from treatment regimens for children in the past, due in part to concerns about the difficulty of monitoring for toxicity (particularly for optic neuritis) in young children, a literature review indicates that it is safe in children at a dose of 20 mg/kg (range 15–25 mg/kg) daily.

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 and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core: Microcrystalline cellulose, povidone, stearic acid, maize starch, sodium starch glycolate, colloidal anhydrous silica, purified talc, magnesium stearate

Film-coat: Hypromellose, ethylcellulose, macrogol, purified talc, titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Bulk pack: 1000 tablets in a self-sealing polythene bag, inside a 650 ml HDPE container sealed with aluminium tagger.

Blister packs: Dark amber coloured PVC/PVdC-Alu blisters: 10x10, 24x28, and 7x10.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.
7. Supplier
Macleods Pharmaceuticals Limited
Atlanta Arcade, 3rd Floor, Church Road, near Leela Hotel,
Andheri-Kurla Road
Andheri (East)
400 059 Mumbai
India
Tel: + 91 22 66 76 28 00
Fax: 91 22 29 25 62 29
E-mail: sjadhav@macleodspharma.com
vijay@macleodspharma.com
sushil@macleodspharma.com

8. WHO Reference Number (Prequalification Programme)
TB226

9. Date of First Prequalification
04 November 2013

10. Date of Revision of the Text
August 2014
Section 6 updated in June 2019
References:

9. ATS, CDC, and IDSA, Treatment of Tuberculosis, MMWR 2003; 52 (RR 11):1-77
   http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm
10. Thompson: Micromedex 2012
    http://www.micromedex.com/index.html