This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[TB226 trade name][*]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Plot No. 25-27 Sr. No. 366, Premier Industrial Estate Kachigam, 396 210 Daman India
Active Pharmaceutical Ingredients (APIs):	Ethambutol hydrochloride
Pharmaco-therapeutic group (ATC Code):	Antimycobacterial (J04AK02)
Therapeutic indication:	[TB226 trade name] 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. [TB226 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex.*

1. Introduction

[TB226 trade name] 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.
[TB226 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex*. [TB226 trade name] is not indicated for use in patients with clinically significant hypersensitivity to ethambutol or to any of the components contained in the formulation, and in patients with optic neuritis. [TB226 trade name] should be prescribed by a physician experienced in the management of tuberculosis.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

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

Active pharmaceutical Ingredient (API)

Ethambutol hydrochloride

Ethambutol hydrochloride is a class 3 API according to Biopharmaceutics Classification System, eligible for BCS-based biowaiver applications (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*). The API is thus BCS highly soluble.

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph.Eur. monograph to control quality of the API.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the tablet core formulation include microcrystalline cellulose, povidone, stearic acid, maize starch, sodium starch glycolate, colloidal anhydrous silica, purified talc and magnesium stearate. Magnesium stearate and stearic acid are of vegetable origin. The film coating contains hypromellose, ethylcellulose, macrogol, purified talc and titanium dioxide

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
The product is a white, circular, shallow, biconvex, film-coated tablet with a break-line on one side and plain on the other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are presented in dark amber coloured PVC/PVdC-Alu blister packs. Bulk packs contain 1 000 tablets in a self-sealing polythene bag, inside a white opaque HDPE container sealed with aluminium tagger and closed with a screw thread cap.

The application concerns an additional strength of Ethambutol 400 mg Tablets, listed under TB134. The 400 mg tablet has been accepted based upon the outcome of a bioequivalence study. The 100 mg tablet is a direct scale down of the 400 mg tablet. For manufacture of the core tablets a conventional wet granulation process was used. The higher and lower strength showed similar profiles for dissolution conducted in the three BCS media and the quality control medium.

Product Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification of the API and colorant, average weight, disintegration time, uniformity of dosage units (by mass variation), loss on drying, dissolution, related substances, assay, residual solvents and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage condition and for six months at accelerated conditions for tablets presented in both packaging configurations proposed for marketing of the product. The product proved to be quite stable at both long term and accelerated storage conditions with no apparent negative trend. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2005 according to internationally accepted guidelines.
An open label, randomized, two-treatment, two-sequence, two period, two-way crossover, single dose bioequivalence study of Ethambutol tablets (containing ethambutol 400 mg) manufactured by Macleods Pharmaceuticals Ltd., India comparing with Myambutol tablets (containing ethambutol 400 mg) manufactured by Riemser Arzneimittel AG (Wyeth Lederle Germany), in healthy, adult, male, human subjects under fasting conditions (study no. BEQ-002-ETHA-2005).

The objective of the study was to compare the rate and extent of absorption of the stated ethambutol 400 mg tablet with the same dose of Myambutol (ethambutol 400 mg tablet). The comparison was performed as a randomized, two-treatment, two-period, single-dose, crossover study in healthy male subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

Treatment T: Test – 1 tablet ethambutol 400 mg (ethambutol 400 mg) Batch no. EG402
Treatment R: Reference – 1 tablet Myambutol® (ethambutol 400 mg) Batch no. 208770

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 17 samples within 48 h post dose) were taken during each study period to obtain bioavailability characteristics AUC_{inf}, AUC_{0-t}, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ethambutol in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 0.05 µg/mL for ethambutol.

The study was performed with 24 (+ 4 standby) participants, data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmic means (± sd), geometric means (AUC, C_{max}) for ethambutol as well as statistical results are summarised in the following table:

Ethambutol

Pharmacokinetic Parameter	Test formulation (T) arrithm.mean ± SD (*)	Reference (R) arrithm. mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	3.3 ± 1.3	3.0 ± 1.0	-	-
C_{max} (µg/mL)	0.972 ± 0.327 (0.917)	1.050 ± 0.481 (0.951)	96.4	85.9 – 108
AUC_{0-t} (µg.h/mL)	5.46 ± 1.73 (5.187)	5.16 ± 2.03 (4.786)	108	99.4 – 118
AUC_{0-inf} (µg.h/mL)	6.04 ± 1.73 (5.806)	5.83 ± 2.14 (5.484)	106	98.0 – 114

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ethambutol. Accordingly, the test product Ethambutol 400 mg tablets (Macleods Pharmaceutical Ltd., India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference, Myambutol 400 mg tablets (Riemser Arzneimittel AG, Germany).

A biowaiver was granted for the additional tablet strength Ethambutol 100 mg (Macleods Pharmaceutical Ltd., India) in accordance to the WHO guideline. In comparison with the strength of

the test product used in the bioequivalence study, the Ethambutol 100 mg tablet strength was determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the API were determined to be similar.

4. Summary of Product Safety and Efficacy

[TB226 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator product. [TB226 trade name] fulfilled all criteria for waiving an *in vivo* bioequivalence study as per relevant WHO guidance.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way.
The quality of this product is considered to lead to an acceptable clinical performance when [TB226 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB226 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB226 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB226 trade name] was acceptable for the following indications: **"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; treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex*."** and has advised that the quality, efficacy and safety of [TB226 trade name] allow inclusion of [TB226 trade name], manufactured at Macleods Pharmaceuticals Limited, Plot No. 25-27, Sr. No. 366, Premier Industrial Estate, Kachigam, 396 210 Daman, India, in the list of prequalified medicinal products.