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	[TB134trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Ltd Phase II / Phase III, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India
Active Pharmaceutical Ingredient(s) (API)	Ethambutol hydrochloride
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK02)
Therapeutic indication	[TB134 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis.* [TB134 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex.*

1. Introduction

[TB134 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*

[TB134 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex.*

[TB134 trade name] is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, and in patients with optic neuritis.

It is recommended that therapy is given only on the advice of a tuberculosis experienced physician.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

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

Active pharmaceutical Ingredient (API)

Ethambutol Hydrochloride is described in the PhInt, PhEur and USP.

Specifications control the quality of API including 1,2-dichloroethane, a Class I solvent, which is used as a starting material in the synthesis of Ethambutol Hydrochloride.

60 month real-time data were submitted for three Ethambutol Hydrochloride batches. All results remained within specifications. The data showed neither visible variability nor trend over time.

Other ingredients

All other ingredients in the FPP meet pharmacopoeial requirements as well as in-house specifications. Evidence has been provided to demonstrate that Magnesium Stearate and Stearic Acid comply with the requirements of the WHO "Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products".

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Macleods Pharmaceuticals Limited has manufactured and marketed [TB134 trade name] for several years.

The manufacturing process of [TB134 trade name] is divided into ten operations: weighing, sifting, dry mixing, wet granulation, fluid-bed drying, sizing the granules, blending, compression, film coating and packing.

The in-process control methods are relevant to the pharmaceutical form/manufacturing process and have been set to ensure batch-to-batch reproducibility.

Specifications

Finished product specifications were adequately justified and are based on current standards, including WHO guidelines. The specifications were supported by the results from batch analysis

Stability testing

Stability studies were performed according to WHO requirements. The tablets are chemically stable in all packaging configurations and under all conditions. Stability results supported a shelf-life of 36 months for Ethambutol Hydrochloride 400mg tablets, when stored in its packaging.

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 Reimser 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 hydrochloride 400 mg tablets with the same dose of Myambutol tablets (ethambutol hydrochloride 400 mg). 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 – Ethambutol Hydrochloride 400 mg tablet
Batch no. EG402 (M/s Macleods Pharmaceutical Ltd., India)
Treatment R: Reference – Myambutol® 400 mg tablet
Batch no. 208770 (Reimser Arzneimittel AG, Germany

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.

Arithmetic 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)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**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

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 [TB134 trade name] tablets (M/s 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).

4. Summary of product safety and efficacy

[TB134 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [TB134 trade name] is pharmaceutically and therapeutically equivalent to the comparator product, Myambutol® (ethambutol hydrochloride 400 mg tablets).

The clinical safety of [TB134 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[TB134 trade name] has shown to be bioequivalent with Myambutol® (ethambutol hydrochloride 400 mg tablets, Reimser Arzneimittel AG, Germany).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB134 trade name] is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [TB134 trade name] was acceptable for the following indications: **"in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis"*** and **"in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex*"** and has advised to include [TB134 trade name], manufactured at Macleods Pharmaceuticals Ltd, Phase II / Phase III, Unit II, Plot No. 25 - 27, Sr. No. 366, Premier Ind. Estate, Kachigam, Daman- 396210, India in the list of prequalified medicinal products.