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	[TB334 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Unit II, Plot No 25-27, Survey No 366 Premier Industrial Estate Kachigam, Daman, 369 210 India
Active Pharmaceutical Ingredient(s) (API)	Ethambutol (as hydrochloride)
Pharmaco-therapeutic group (ATC Code)	Antiinfectives for systemic use, antimycobacterial, drugs for treatment of tuberculosis (J04AK02)
Therapeutic indication	[TB334 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* in children weighing less than 20 kg.

1. Introduction

[TB334 trade name] is indicated, in combination with other antituberculosis agents, for the initial treatment of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis* in children weighing less than 20 kg.

[TB334 trade name] should be prescribed by a health care provider experienced in the management of tuberculosis infection.

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*.

Active pharmaceutical Ingredient (API)

Based on scientific principles, the WHO PQTm has identified ethambutol hydrochloride up to 400 mg oral dose as a BCS class 3 API. 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.

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

Other ingredients

Other ingredients used in the tablet formulation include colloidal silicon dioxide, microcrystalline cellulose, corn starch, sodium starch glycolate, croscarmellose sodium, aspartame, povidone, low substituted hydroxypropyl cellulose, purified talc, silicified microcrystalline cellulose, orange flavour (containing propylene glycol) and magnesium stearate. BSE/TSE free certificates are provided from suppliers of all excipients. Magnesium stearate is of vegetable origin. A declaration has been provided that the orange flavour complies with EU and USFDA regulations on foodstuff.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The dispersible tablets are white to off-white, circular, flat, uncoated tablets having 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. The tablets are presented in Alu-Alu strip packs and amber-coloured PVC/PE/PVdC-Alu blister packs.

The objective of the developmental activities was to obtain a stable and robust formulation of [TB334 trade name] tablets that is bioequivalent to the WHO recommended comparator product Myambutol 100 mg Tablets, manufactured by Labatec Pharma S.A. The selection of excipients in the formulation of the dispersible tablets was based on their demonstrated compatibility with ethambutol hydrochloride and their suitability to achieve the desired characteristics of the dispersible tablets. Aspartame was selected as sweetener to mask unpleasant tastes of the API. Orange flavour is included as flavouring agent.

The compressibility index as determined from the bulk density and the tapped density indicated that the API exhibits poor flow properties. Thus a non-aqueous wet granulation strategy was explored to obtain better flow properties and uniformity of the API. The target was to develop dispersible tablets matching the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications, regarded adequate for control of the product, include tests for description, identification of the API (HPLC, IR), average weight, hardness, friability, disintegration time (≤ 3 minutes), fineness of dispersion, subdivision of tablets (on validation batches), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (TLC), assay (HPLC), residual solvent (GC), loss on drying and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH and 25°C/60%RH as long term storage conditions and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. In Alu-Alu strip packs, the product proved to be quite stable at all these storage conditions. However, when packed in the PVC/PE/PVdC-Alu blisters, a significant change was observed for assay at accelerated conditions, thus when the tablets are presented in the blister packs, excursions above 30°C should be avoided. 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 2016 according to internationally accepted guidelines.

Bioequivalence study of single dose of ethambutol dispersible 100 mg tablets manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Myambutol® (ethambutol hydrochloride) tablets 100 mg marketed by Labatec Pharma. S.A. in healthy, adult, human subjects under fasting condition (study no. BEQ-1612-ETHA-2015).

The objective of the study was to compare the bioavailability of the stated ethambutol hydrochloride 100 mg dispersible tablets manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Myambutol® (Labatec Pharma S.A.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 Ethambutol dispersible tablet 100 mg (ethambutol hydrochloride 100 mg) Batch no. EEC2502A.
Treatment R: Reference – 1 Myambutol® tablet (ethambutol hydrochloride 100 mg) Batch no. 2592.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 48 hours post-dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ethambutol were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 8 ng/mL for ethambutol.

The study was performed with 36 participants. Data generated from a total of 31 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for ethambutol as well as statistical results are summarised in the following table:

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)	2.81 ± 1.03	3.15 ± 1.12	--	--
C_{max} (ng/mL)	302 ± 89 (287)	297 ± 83 (285)	100.9	91.3 – 111.4
AUC_{0-t} (ng·h/mL)	1818 ± 442 (1760)	1858 ± 429 (1806)	97.5	91.2 – 104.2
AUC_{0-inf} (ng·h/mL)	1982 ± 471 --	2025 ± 449 --	--	--

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 [TB334 trade name] tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Myambutol® (Labatec Pharma S.A.).

4. Summary of product safety and efficacy

[TB334 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, [TB334 trade name] is pharmaceutically and therapeutically equivalent and thus,

interchangeable with the comparator product (Myambutol®, Labatec Pharma S.A.), for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB334 trade name] is considered to be acceptable when guidance and restrictions as stated in the summary of product characteristics (SmPC) are taken into account. Refer 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 [TB334 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB334 trade name] has shown to be bioequivalent with Myambutol® (Labatec Pharma S.A., Switzerland).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB334 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB334 trade name] was acceptable for the following indication: **"in combination with other antituberculosis agents, in the initial treatment of all forms of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis* in children weighing less than 20 kg."** and has advised that the quality, efficacy and safety of [TB334 trade name] allow inclusion of [TB334 trade name], manufactured at Macleods Pharmaceuticals Limited, Unit II, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman, 369 210, India in the list of prequalified medicinal products.