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	[TB367 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited (Unit-03) 92, Sipcot Industrial Complex Hosur Tamil Nadu, 635126 India
Active Pharmaceutical Ingredient(s) (API)	Ethambutol hydrochloride
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK02)
Therapeutic indication	[TB367 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. [TB367 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex*.

1. Introduction

[TB367 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.

[TB367 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex*. [TB367 trade name] should be prescribed by a physician experienced in the management of tuberculosis.

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 has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB367 trade name] is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include povidone, microcrystalline cellulose, crospovidone, croscarmellose sodium, colloidal silicon dioxide, peppermint flavour, sucralose and magnesium stearate. The commercially sourced proprietary peppermint flavour which is included in the tablet formulation is supported by appropriate declarations and controlled by acceptable specifications. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, circular, flat-faced, beveled edge uncoated tablet, debossed with '50'on one face and break line on the other face. The break line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are presented in aluminium strip packs.

Two strengths of ethambutol hydrochloride dispersible tablets, proportionally similar in composition and manufactured from a common blend, were developed: 100 mg and 50 mg. The development focused on the lower strength. Once the formulation for the 50 mg strength was finalized, the 100 mg strength was pursued using dose-proportionality approach. The 100 mg strength was used in the bioequivalence study against the WHO recommended comparator product ethambutol hydrochloride USP 100 mg tablets of STI Pharma, LLC Langhorne, PA 19047, USA. The selection of excipients was based on previous formulation experience and knowledge about excipients that have been used successfully in prequalified products of dispersible tablets from the same manufacturer. The flavouring agent and sweetener were included to improve the taste of the paediatric formulation. Wet granulation manufacturing process was used to improve the poor flowability of the API. Based on satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.
According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for appearance, identification (HPLC, IR and chloride), average mass, uniformity of mass, tablet dimensions, disintegration time, resistance to crushing, friability, water content (by KF), uniformity of dosage units (by mass variation), fineness of dispersion, dissolution (HPLC detection), assay (HPLC), related substances (TLC), subdivision of tablets and microbial limit test. The analytical methods have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the package proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with no negative trend reported. 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 2018 according to internationally accepted guidelines.

A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two way crossover, oral bioequivalence study of ethambutol hydrochloride dispersible tablets 100 mg manufactured by Micro Labs Limited, India and ethambutol hydrochloride tablets, USP 100 mg of STI Pharma, LLC Langhorne, PA 19047, in healthy, adult, human subjects under fasting conditions (study no. 051-17).

The objective of the study was to compare the bioavailability of the stated ethambutol hydrochloride 100 mg dispersible tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation ethambutol hydrochloride USP 100 mg tablet (STI Pharma) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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 tablet Ethambutol hydrochloride 100 mg (ethambutol 100 mg) Batch no. EDBHK0001.
Treatment R:	Reference – 1 tablet Ethambutol hydrochloride USP 100 mg (ethambutol 100 mg) Batch no. 5160273.

A 10-day wash-out period was observed between administration of the test and reference. Serial blood samples (1 pre-dose sample and 28 samples within 72 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 1 ng/mL for ethambutol.

The study was performed with 48 participants. Data generated from a total of 46 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:

Ethambutol

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)#	3.0 (1.5 – 5.0)	2.75 (0.5 – 5.0)	-	-
C_{max} (ng/mL)	243 ± 65 (233)	237 ± 72 (226)	103.2	96.1 – 110.9
AUC_{0-t} (ng.h/mL)	1672 ± 412 (1626)	1654 ± 407 (1608)	101.1	96.7 – 105.8
AUC_{0-inf} (ng.h/mL)	1824 ± 499 --	1785 ± 450 --	-	-

*geometric mean; #median (range)

The results of the study show that the pre-set acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ethambutol. Accordingly, the test ethambutol hydrochloride 100 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference ethambutol hydrochloride USP 100 mg tablet (STI Pharma).

A biowaiver was granted for the additional 50 mg tablet strength (Micro Labs Limited, India) in accordance to WHO guidelines. In comparison with the strength of the test product used in the bioequivalence study, the ethambutol hydrochloride 50 mg dispersible tablet was determined to be qualitatively the same; the ratio of the active ingredient and excipients between the strengths was considered essentially the same; and the dissolution profiles between the formulations for the API were determined to be the same.

4. Summary of product safety and efficacy

[TB367 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, [TB367 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product ethambutol hydrochloride USP 100 mg tablet (STI Pharma). for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB367 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

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 [TB367 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB367 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, [TB367 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [TB367 trade name] was acceptable for the following indication: **"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 would allow inclusion of [TB367 trade name], manufactured at Micro Labs Limited (Unit-03), 92, Sipcot Industrial Complex, Hosur, Tamil Nadu, 635126, India in the list of prequalified medicinal products.