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	[TB411 trade name]*
Manufacturer of Prequalified Product	Lupin Limited
Active Pharmaceutical Ingredient(s) (API)	Ethambutol hydrochloride 100 mg dispersible tablets
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK02)
Therapeutic indication	[TB411 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis* including in regimens for drug-resistant tuberculosis.

1. Introduction

[TB411 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis* including in regimens for drug-resistant 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*.

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 pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB411 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 core tablet formulation include microcrystalline cellulose, colloidal silicon dioxide, maize starch, crospovidone, croscarmellose sodium, aspartame, povidone, low substituted hydroxypropyl cellulose, talc, silicified microcrystalline cellulose, orange flavour and magnesium stearate, all being controlled by acceptable specifications. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for all the excipients.

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has a break line on one side and is 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 data. The tablets are packaged in aluminium foil strip packs.

The objective of the product development was to obtain a stable and robust formulation of ethambutol hydrochloride 100 mg dispersible tablets that is bioequivalent to the WHO recommended comparator product, ethambutol hydrochloride 100 mg film-coated tablets (STI Pharma, LLC, 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. Orange flavour and aspartame were used to mask the unpleasant taste characteristics and enhance palatability of the tablets. A non-aqueous wet granulation manufacturing process was selected to improve the flowability of the API in the manufacturing of the finished product. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP has no potential to contain N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitroso ethambutol on selected batches post prequalification.

Specifications

The finished product specifications include tests for description, identification of the API by HPLC (UV and PDA/DAD detection), disintegration time, fineness of dispersion, water content, dissolution (HPLC detection), uniformity of dosage unit (by mass variation and content uniformity), assay (HPLC), degradation products (TLC and HPLC), residual solvent (GC), subdivision of tablets (by mass variation) and microbial limits

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated storage condition in the packaging proposed for marketing of the product. The data provided indicates that the product is stable at both storage conditions. 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 2023 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover, oral bioequivalence study comparing ethambutol dispersible tablets 100 mg manufactured by Lupin Limited, India with ethambutol hydrochloride tablets USP 100 mg (film coated) manufactured for STI Pharma, LLC, Newtown PA 18940 distributed by STI Pharma, LLC, Newtown PA 18940 in healthy, adult, human subjects under fasting conditions (study no. LBC-23-036).

The objective of the study was to compare the bioavailability of the stated ethambutol hydrochloride 100 mg dispersible tablet manufactured by/for Lupin Ltd., India (test drug) with the reference formulation ethambutol hydrochloride tablets USP 100 mg tablet (STI Pharma, LLC) 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 tablet ethambutol hydrochloride tablet 100 mg
(ethambutol 100 mg)
Batch no. A396034.

Treatment R: Reference – 1 tablet ethambutol hydrochloride USP 100 mg
(ethambutol 100 mg)
Batch no. ET543E0001.

The test dispersible tablet was dispersed in 40 mL water (+ 10 mL of rinsing water) and administered. The reference was administered with 240 mL water. A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 36 h 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 10 ng/mL for ethambutol.

The study was performed with 36 participants; data generated from a total of 35 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	3.30 ± 1.08	3.17 ± 1.14	–	–
C_{max} (ng/mL)	201 ± 43 (196)	209 ± 73 (198)	99.3	91.5-107.9
AUC_{0-t} (ng·h/mL)	1290 ± 268 (1264)	1252 ± 267 (1225)	103.3	98.5-108.2
AUC_{0-inf} (ng·h/mL)	1456 ± 300 (1427)	1428 ± 301 (1397)	102.1	97.9-106.5

4. Summary of product safety and efficacy

[TB411 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, [TB411 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product ethambutol Hydrochloride USP 100 mg (STI Pharma, LLC) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB411 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 [TB411 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB411 trade name] has been shown to be bioequivalent with ethambutol hydrochloride USP 100 mg (STI Pharma, LLC)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB411 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 [TB411 trade name] was acceptable for the following indication: ' in combination with other tuberculosis medicines for the treatment of tuberculosis due to Mycobacterium tuberculosis including in regimens for drug-resistant tuberculosis', and would allow inclusion of [TB411 trade name], manufactured at Lupin Limited, A-28/1 MIDC Industrial Area, Chikalthana, Chhatrapati Sambhajinagar -431 210, India in the list of prequalified medicinal products.