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	[TB406 trade name][*]
Manufacturer of Prequalified Product	Cadila Pharmaceuticals Limited 1389 Trasad Road, Dholka - 382 225, District: Ahmedabad, Gujarat, India
Active Pharmaceutical Ingredient(s) (API)	Ethambutol hydrochloride
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK02)
Therapeutic indication	[TB406 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. [TB406 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium* complex.

1. Introduction

[TB368 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.

[TB368 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as Mycobacterium avium complex.
[TB368 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*.

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 [TB406 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:

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

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 silicified microcrystalline cellulose, polyvinyl pyrrolidone, crospovidone, aspartame, colloidal silicon dioxide, banana flavour and magnesium stearate, all of which are 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 light yellow, 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 a score line 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 either aluminium blisters or strips.

The objective of the product development was to obtain a stable and robust, immediate-release dispersible tablet that is bioequivalent to the WHO recommended comparator product Myambutol® (ethambutol hydrochloride) 100 mg tablets. The quality target product profile was defined based on the physicochemical properties of the API and characteristics of the comparator product. The selection of excipients was based on their wide use in the manufacture of this type of solid oral dosage form and API-excipient compatibility data. A sweetener and flavouring agent were used to improve the taste of the dispersible tablets. Due to the poor flow properties of the ethambutol hydrochloride API, a wet granulation manufacturing process was selected to obtain readily compressible granules. 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-nitrosamines on selected batches post prequalification.

Specifications

The finished product specifications include tests for description, identification of API (TLC and HPLC) and of chloride (chemical), average weight, water content (KF), uniformity of weight, disintegration time, hardness, fineness of dispersion, dissolution (HPLC detection), uniformity of dosage units (by mass variation), 2-aminobutanol content (TLC), related substances (HPLC), assay (HPLC), residual solvent (GC) 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 condition in the packaging proposed for marketing of the product. The data showed a slight increase in the degradation products, though the levels stayed well within agreed limits at the long-term storage condition. 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.

A randomized, open-label, two-treatment, two-period, two-sequence, single-dose, two-way crossover bioequivalence study of Ethambutol Hydrochloride dispersible tablet 100 mg of Cadila Pharmaceuticals Ltd., India with Myambutol® (ethambutol hydrochloride) 100 mg tablet of Labatec Pharma S. A., 1217 Meyrin (Geneve, Suisse) Switzerland in healthy, adult, human subjects under fasting condition (study no. 22-015).

The objective of the study was to compare the bioavailability of the stated Ethambutol Hydrochloride 100 mg dispersible tablet manufactured by/for Cadila Pharmaceuticals Ltd., India (test drug) with the reference formulation Myambutol® 100 mg tablet (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 tablet Ethambutol Hydrochloride tablet 100 mg (ethambutol 100 mg)
Batch no. ET935E3001.

Treatment R: Reference – 1 tablet Myambutol® 100 mg (ethambutol 100 mg)
Batch no. 3911.

The test dispersible tablet was dispersed in 50 mL water (+ 190 mL of rinsing water) and administered. The reference was administered with 240 mL water. A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 48h 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 54 participants; data generated from a total of 53 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)#	2.50 (1.00 – 5.00)	2.75 (1.00-5.00)	–	–
C_{max} (ng/mL)	314 ± 107 (296)	322 ± 99 (308)	96.0	88.0 – 104.8
AUC_{0-t} (ng·h/mL)	1676 ± 325 (1641)	1679 ± 315 (1647)	99.6	95.8 – 103.6
AUC_{0-inf} (ng·h/mL)	1865 ± 348 (1830)	1870 ± 341 (1837)	99.6	96.1 – 103.3

*geometric mean; #median (range)

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 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 Myambutol® 100 mg tablet (Labatec Pharma S. A.).

4. Summary of product safety and efficacy

[TB406 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, [TB406 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Myambutol® 100 mg tablet (Labatec Pharma S. A.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB406 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 [TB406 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB406 trade name] has been shown to be bioequivalent with Myambutol® 100 mg tablet (Labatec Pharma S. A.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB406 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 [TB406 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 [TB406 trade name], manufactured at Cadila Pharmaceuticals Limited, 1389 Trasad Road, Dholka - 382225, District: Ahmedabad, Gujarat, India in the list of prequalified medicinal products.