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	[TB177 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited, A-28/1, M.I.D.C Industrial Area, Chikalthana, 431 210 Aurangabad, India
Active Pharmaceutical Ingredient(s) (API)	Ethambutol
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK02)
Therapeutic indication	[TB177 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* [TB177 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex.*

1. Introduction

[TB177 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB177 trade name] is also used in the treatment of infections caused by atypical mycobacteria, such as *Mycobacterium avium complex.*

It is recommended that therapy is given only on the advice of a physician experienced in the treatment 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 is a class 3 API according to the Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*). The API is thus BCS highly soluble.

Ethambutol hydrochloride is described in the Ph.Int., Ph.Eur. and the USP and is considered well-established.

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing

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

control and applicability of the Ph.Eur. monograph to control quality of the API. Additional tests on the CEP include 1,2-dichloroethane, limited at 5 ppm, which is a synthesis starting material. The CEP allows a retest period of 5 years when ethambutol hydrochloride is stored in double polyethylene bags within a fibre drum.

Other ingredients

Other ingredients used in the tablet core formulation include colloidal silicon dioxide, magnesium stearate, maize starch, povidone k-30 and purified talc, which are all compendial. Magnesium stearate is of vegetable origin. The film-coat contains ethylcellulose, hypromellose, Lake of Sunset Yellow, polyethylene glycol 4000, propylene glycol, purified talc and titanium dioxide. The only non-compendial excipient is the colorant Lake of Sunset Yellow, included in the US List of Certified Colorants, for which in-house specifications were provided

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Ethambutol tablets are described in the Ph.Int and the BP, and Ethambutol hydrochloride tablets in the USP.

[TB177 trade name] are light orange coloured, circular, biconvex film coated tablets, plain on both sides. The tablets are packaged in a PVC-PVDC/Al blister card (10 tablets per card, 10 cards per carton) and in a sealed LDPE bag, placed inside a round white HDPE bottle with plain screw cap and aluminium tagger (packs of 100, 500 and 1000 tablets).

The submitted pharmaceutical development report justified the choice of excipients and demonstrated compatible with the excipients. The manufacturing process consists of wet granulation, lubrication with talc and magnesium stearate, compression and coating. The process was adequately validated. The validation report summarized the results for three consecutive commercial scale batches. Validation parameters included mixing times, drying conditions and compression/coating. Blend uniformity results were provided at two stages: after blending with extra-granular excipients, and after lubrication. The batches met the in-process specifications. Batch analysis data were provided for the three validation batches.

Specifications

The specifications are pharmacopoeial based and ensure consistent quality for this finished

pharmaceutical product.

Stability testing

Stability studies have been performed on the three production batches used in the process validation studies at 30°C/65%RH as long-term conditions and for six months at accelerated conditions. The tablets proved to be chemically and physically stable in all packaging configurations, under the long-term and accelerated storage conditions. Stability results supported a shelf-life of 60 months for [TB177 trade name], when stored not above 30°C, protected from moisture, in its proposed packaging.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2009 according to internationally accepted guidelines:

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two-way crossover, pivotal bioequivalence study of Ethambutol Tablets BP 400 mg of Lupin Limited, India

with Myambutol® (ethambutol hydrochloride 400 mg) tablets of Patheon Inc. Toronto, Ontario for Stat-Trade Inc.) in 26 healthy human adult male subjects, under fasting conditions (study no. 028-09).

The objective of the study was to compare the bioavailability of the stated ethambutol 400 mg tablet manufactured by Lupin Ltd., India (test drug) with the same dose of the reference formulation (Myambutol 400 mg, Patheon Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male 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 400 mg
(ethambutol 400 mg dose)
Batch no. BM88003.

Treatment R: Reference – 1 tablet Myambutol® 400 mg
(ethambutol 400 mg dose)
Batch no. JP31.

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 24 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 30 ng/ml for ethambutol.

The study was performed with 26 participants; data generated from a total of 24 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 tables:

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)	3.10 ± 0.90	3.13 ± 0.93	–	–
C_{max} (µg/mL)	1.37 ± 0.38 (1.32)	1.37 ± 0.42 (1.32)	100.4	88.6 – 113.7
AUC_{0-t} (µg·h/mL)	6.68 ± 1.00 (6.60)	6.58 ± 0.84 (6.53)	101.2	96.5 – 106.0
AUC_{0-inf} (µg·h/mL)	7.73 ± 1.46 (7.60)	7.62 ± 0.89 (7.57)	100.4	95.5 – 105.4

Conclusion

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 tablet [TB177 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Myambutol® (Patheon).

4. Summary of product safety and efficacy

[TB177 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, [TB177 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Myambutol® (Patheon) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB177 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 [TB177 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB177 trade name] has been shown to be bioequivalent with Myambutol® (Patheon).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB177 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 [TB177 trade name] was acceptable for the following indication: '**indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis***', and would allow inclusion of [TB177 trade name], manufactured at Lupin Limited, A-28/1, M.I.D.C Industrial Area, Chikalthana, 431 210 Aurangabad, India,in the list of prequalified medicinal products.