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	[TB008 trade name][*]
Manufacturer of Prequalified Product	Cadila Pharmaceuticals Limited Main Pharma Block 1389, Trasad Road Dholka – 382 225, Ahmedabad Gujarat State, India
Active Pharmaceutical Ingredient (API)	Ethambutol
Pharmaco-therapeutic group (ATC Code)	Drugs for treatment of tuberculosis (ethambutol: J04AK02)
Therapeutic indication	[TB008 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB008 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB008 trade name] should be initiated by a health care provider 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)

Based on scientific principles the WHO Prequalification Team – Medicines (PQTm) has identified ethambutol hydrochloride up to 400 mg oral dose as a BCS class 3 API. The API is thus regarded highly soluble in aqueous medium over the physiological pH range.

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. Additional user requirements include particle size distribution and bulk density.

Other ingredients

Other ingredients used in the core tablet formulation include dibasic calcium phosphate, gelatin,

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

sorbitol, maize starch and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains ethyl cellulose, hydroxypropylmethyl cellulose, polyethylene glycol and titanium dioxide. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, smooth, round, biconvex, film coated tablet plain on both the sides. The tablets are presented in PVC-Al and PVC/PVDC-Al blister packs and in HDPE bottle packs.

The manufacturing process consists of wet granulation, drying, screening, lubrication, compression and coating (organic based). Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three consecutive production scale batches demonstrated the consistency of the process and the quality of the product.

Specifications

The finished product specifications are pharmacopoeial based and include tests for tablet description, identification of API (IR and colour reaction) and colourant, average weight, uniformity of weight, disintegration time, dissolution, related substances (TLC), assay (HPLC), water content (KF), residual solvents (GC) and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 30°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions with no apparent negative trend in the proposed packaging configurations. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The tablets must be protected from light.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2012 according to internationally accepted guidelines.

Study title: A randomized, open-label, two-treatment, two-period, two-sequence, single-dose, two-way crossover bioequivalence study of Ethambutol hydrochloride 400 mg tablets (each film coated tablet contains ethambutol HCl 400 mg) of Cadila Pharmaceuticals Ltd., India compared with Ethambutol tablet 400 mg (each film coated tablet contains ethambutol HCl, USP 400 mg, NDC 61748-014-06) manufactured by West-Ward Pharmaceutical Corp. Eatontown, NJ07724 LX2 and manufactured for VersaPharm Incorporated Marietta, GA 30065-1509 in healthy, adult, human subjects under fasting condition (study no. 12-008).

The objective of the study was to compare the bioavailability of the stated Ethambutol hydrochloride 400 mg tablets manufactured for/by Cadila Pharmaceuticals Ltd., India (test drug) with the reference formulation Ethambutol HCl, USP 400 mg tablet (manufactured by West-ward and distributed by VersaPharm Incorporated Marietta) 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 treatments in a randomized fashion:

Treatment T: Test – 1 Ethambutol hydrochloride 400 mg tablet (ethambutol 400 mg)
Batch no. ET075E2001
Treatment R: Reference – 1 tablet Ethambutol HCl, USP 400 mg (ethambutol 400 mg)
Batch no. 69967B

A 10-day wash-out period was observed between administration of test and reference.

Serial blood samples (1 pre-dose sample and 25 samples within 72 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 25 ng/ml for ethambutol.

The study was performed with 32 participants; data generated from a total of 30 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)	2.90 ± 1.03	2.82 ± 0.83	-	-
C_{max} (ng /mL)	1539 ± 446 (1473)	1460 ± 397 (1405)	104.8	94.3 – 116.5
AUC_{0-t} (ng·h/mL)	8196 ± 1872 (7968)	8001 ± 1479 (7870)	101.3	96.8 – 105.9
AUC_{0-inf} (ng·h/mL)	8796 ± 1996 (8556)	8580 ± 1610 (8435)	101.4	97.1 – 106.0

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 Ethambutol hydrochloride 400 mg tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Ethambutol HCl, USP 400 mg tablet (West-ward Pharmaceutical Corp).

4. Summary of product safety and efficacy

[TB008 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, [TB008 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Ethambutol HCl, USP 400 mg tablet (West-ward Pharmaceutical Corp) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB008 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 [TB008 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB008 trade name] has been shown to be bioequivalent with Ethambutol HCl, USP 400 mg tablet (West-ward Pharmaceutical Corp).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB008 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 [TB008 trade name] was acceptable for the following indication: 'in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* ', and would allow inclusion of [TB008 trade name], manufactured at Cadila Pharmaceuticals Limited, Main Pharma Block, 1389, Trasad Road, Dholka – 382225, Ahmedabad, Gujarat State, India in the list of prequalified medicinal products.