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	[TB015 trade name][*]
Manufacturer of Prequalified Product	Cadila Pharmaceuticals Limited, 1389 Trasad Road, Dholka – 382 225, Ahmedabad Gujarat, India
Active Pharmaceutical Ingredient(s) (API)	Pyrazinamide
Pharmaco-therapeutic group (ATC Code)	Other drugs for treatment of tuberculosis (J04AK01)
Therapeutic indication	[TB015 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

[TB015 trade name] is indicated in the treatment of HIV, as detailed in the summary of product characteristics.

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)

Pyrazinamide 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 [TB015 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.

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

Other ingredients

Other ingredients used in the tablet formulation include starch, gum acacia, methyl paraben, purified talc and stearic acid all being pharmacopoeial controlled. None of the excipients used in the manufacture of the tablets are of human or animal origin. BSE/TSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, smooth, round, biconvex uncoated tablet, plain on both sides. The tablets are packaged in HDPE bottles with caps, PVC-aluminium and PVC/PVDC-aluminium blister cards.

The objective of the development programme was to obtain a stable, immediate- release tablet that is bioequivalent to the WHO recommended comparator product Pyrazinamid Lederle® 500mg tablets. The excipients used in the formulation are well known and widely used as pharmaceutical excipients in oral solid formulations and comply with the relevant pharmacopoeial monographs.

The manufacturing process involves wet granulation of the API with intra-granular ingredients, drying, addition of extra-granular ingredients, lubrication and compression. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (IR), average weight, uniformity of weight (by mass variation), hardness, friability, disintegration time, dissolution (HPLC detection), related substances (TLC), assay (UV), loss on drying and microbial limits. The test procedures have been adequately validated.

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 packages 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

A randomized, two-treatment, two-period, single dose crossover study has been performed in 2001. The objective of the study was to compare the bioavailability of Pyrazinamide 1000 mg tablet manufactured by/for Cadila Pharmaceutical Ltd., India (test drug) with the reference formulation PZA-CIBA 1000 mg tablet (Novartis, India) and to assess bioequivalence. The study was performed in 12 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 pyrazinamide 1000 mg (pyrazinamide 1000 mg) Batch no. 1011.
Treatment R:	Reference – 1 tablet PZA-Ciba 1000 mg (pyrazinamide 1000 mg) Batch no. 1X007L.

A 3-day wash-out period was observed between administration of test and reference. Serial blood samples were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for pyrazinamide were analyzed using a validated LC-MS method. The limit of quantification was stated to be about 0.5 µg/mL for pyrazinamide.

The study was performed with 12 participants. Data generated from a total of 12 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for pyrazinamide as well as statistical results are summarised in the following table:

Pyrazinamide

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)	1.92 ± 0.79	1.62 ± 0.93	-	-
C_{max} (µg/mL)	13.8 ± 3.9 (13.1)	13.7 ± 3.8 (13.2)	101.0	93.3 – 109.3
AUC_{0-t} (µg.h/mL)	99 ± 34 (91)	102 ± 38 (93)	98.4	88.1 – 110.0
AUC_{0-inf} (µg.h/mL)	145 ± 82 (124)	161 ± 89 (133)	93.1	75.6 – 114.8

*geometric mean

The results of the study show that the pre-set acceptance limits of 80 -125 % are met by both AUC_{0-t} and C_{max} values regarding pyrazinamide. Accordingly, the test pyrazinamide 1000 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference product, PZA-Ciba 1000 mg (Novartis, India).
The results obtained for the 1000 mg strength were extrapolated to the requested 400 mg tablet, based upon comparable dissolution data.

4. Summary of product safety and efficacy

[TB015 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. The clinical safety of [TB015 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 [TB015 trade name] is used in accordance with the SmPC.

Bioequivalence

Pyrazinamide 1000 mg tablets (Cadila Pharmaceuticals) has been shown to be bioequivalent with PZA-CIBA 1000 mg (Novartis, India). The results obtained for the 1000 mg strength were extrapolated to the requested [TB015 trade name], based upon comparable dissolution data.

Efficacy and Safety
Regarding clinical efficacy and safety, [TB015 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 [TB015 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 [TB015 trade name], manufactured at Cadila Pharmaceuticals Limited, 1389 Trasad Road, Dholka – 382 225, Ahmedabad, Gujarat, India, in the list of prequalified medicinal products.