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	[TB335 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited 15/A, 2nd Phase Kumbalgodu Industrial Area Bangalore - 560 074 Karnataka India Micro Labs Limited (Unit-3) 92, Sipcot industrial Complex Hosur – 635126, Tamil Nadu, India
Active Pharmaceutical Ingredient(s) (API)	Pyrazinamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK01)
Therapeutic indication	[TB335 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in children

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

1. Introduction

[TB335 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in children.

[TB335 trade name] is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, severe liver impairment or acute gout.

[TB335 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 PQTm has identified pyrazinamide up to 500 mg oral dose as a BCS class 3 API. The API is thus BCS highly soluble.

Pyrazinamide used in the manufacturer of [TB335 trade name] 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 pyrazinamide, used in the manufacture of [TB335 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 assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal silicon dioxide, sucralose, peppermint flavour, talc and magnesium stearate. TSE/BSE risk free declarations have been provided for all the excipients from their respective manufacturers

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, circular, flat faced, bevelled edge, uncoated tablet, debossed with"150" on one face and plain on the other face. The tablets are presented in aluminium strip packs and in HDPE bottles.

The aim of the development was to formulate a dispersible tablet containing 150 mg of pyrazinamide that would be therapeutically similar to the WHO recommended comparator product, Pyrafat®
500 mg film coated tablets. The selection of excipients was based on their suitability to achieve the desired characteristics of the formulation and was supported by API-excipient compatibility studies. Sucralose, as sweetener, and peppermint flavour are included for acceptability of the reconstituted dispersion. The tablets are manufactured using direct compression. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for appearance, identification (IR, HPLC), average and uniformity of mass, tablet dimensions, disintegration time (≤ 3 min), resistance to crushing, friability, water content (KF), uniformity of dosage units (by mass variation), fineness of dispersion, dissolution (UV detection), assay (HPLC), related substances (HPLC) 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 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions with no negative trend detected. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The product should be protected from light. The reconstituted preparation (tablets dispersed in water) should be used immediately after preparation.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

Study title: An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Pyrazinamide 150 mg Dispersible Tablets at a dose of 450 mg (03 tablets of 150 mg) of Micro Labs Limited, India and Pyrafat® 500 mg tablets of Riemser Pharma GmbH-An der Wiek 7-17493 Greifswald-Insel Riems in healthy, adult, human subjects under fasting condition (study no. 16-VIN-0082).

The objective of the study was to compare the bioavailability of the stated Pyrazinamide 150 mg Dispersible Tablets manufactured for/by Micro Labs Ltd., India (test drug) with the reference formulation Pyrafat® (Riemser Pharma GmbH) 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 – 3 tablets Pyrazinamide 150 mg Dispersible Tablets (Pyrazinamide 450 mg) Batch no. PDAHK0002
Treatment R:	Reference – 1 tablet Pyrafat® (Pyrazinamide 500 mg) Batch no. 032114

A 9 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 48 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 pyrazinamide were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 200 ng/ml for pyrazinamide.

The study was performed with 36 participants; data generated from a total of 36 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)	0.77 ± 0.28	0.92 ± 0.42	–	–
C_{max} (µg/mL)	12.9 ± 1.69 (12.8)	14.0 ± 1.88 (13.9)	102.5	99.8 – 105.2
AUC_{0-t} (µg ·h/mL)	145 ± 27 (142)	163 ± 25 (161)	98.0	94.6 – 101.6
AUC_{0-inf} (µg ·h/mL)	152 ± 27 (149)	171 ± 25 (169)	98.1	94.8 – 101.5

*geometric mean

Conclusion
The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and C_{max} values regarding pyrazinamide. Accordingly, the test Pyrazinamide 150 mg Dispersible Tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Pyrafat® (Riemser Pharma GmbH).

4. Summary of product safety and efficacy

[TB335 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, [TB335 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Pyrafat® 500 mg (Riemser Pharma GmbH) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB335 trade name] is considered to be acceptable when guidance and restrictions presented 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 [TB335 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB335 trade name] has been shown to be bioequivalent with Pyrafat® 500 mg (Riemser Pharma GmbH).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB335 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 [TB335 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* in children"**, and would allow inclusion of [TB335 trade name], manufactured at Micro Labs Limited, 15/A, 2nd Phase, Kumbalgodu Industrial Area, Bangalore - 560 074, Karnataka, India in the list of prequalified medicinal products.