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	[TB172 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited [Unit -3] 92 Sipcot Industrial Complex Hosur-635 126 Tamil-Nadu India
Active Pharmaceutical Ingredient(s) (API)	Pyrazinamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK01)
Therapeutic indication	[TB172 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB172 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*.
[TB172 trade name] is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, severe liver impairment or acute gout.
It is recommended that therapy is given only on the advice of a tuberculosis experienced physician.

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 is a class 3/1 API according to 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*).

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

The API, which is obtained from approved API manufacturer, is adequately controlled by quality specifications which are pharmacopoeial based.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 5 years was approved for pyrazinamide.

* 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 colloidal anhydrous silica, hydrogenated castor oil, lactose monohydrate, maize starch, pregelatinised starch and purified talc.

Finished pharmaceutical product (FPP)
Pharmaceutical development and manufacture
Pyrazinamide tablets are described in the Ph.Int., BP and USP and are considered well- established.

[TB172 trade name] are 12.7mm white, flat, circular bevel-edged uncoated tablets with a break-line on one surface and plain on the reverse. The break-line is intended for subdivision of tablets when the tablet is to be administered as half a dose, as supported by divisibility studies. The tablets (1,000) are packed in a sealed polythene bag, inside an HDPE container with silica gel and aluminium tagger seal.

The manufacturing process entails a conventional wet granulation followed by drying, lubrication, compression and packaging. The formulation was developed based on the excipients in Zinamide® 500 mg tablets (Merck, Sharp & Dohme, Australia). The final composition was developed by experimental trials varying the excipients (disintegrant, binder and lubricant) and the process parameters. Substituting some of the maize starch for pregelatinised starch and replacing magnesium stearate with hydrogenated castor oil, improved the formulation. Several trial formulations were needed to reach the final formulation. Evaluation criteria were tablet hardness, friability, disintegration and dissolution. Compaction force studies were conducted on the final formulation and resulted in suitable tablet characteristics. [TB172 trade name] showed “very rapidly dissolving” dissolution properties, i.e., 85% or more of the API was dissolved within 15 minutes in all three BCS biowaiver media.

Appropriate in-process controls have been set to ensure batch-to-batch reproducibility. Validation data presented on three production batches (300,000 tablets) and batch analysis data demonstrate the consistency of the process and the quality of the product. The pharmacopoeial based specifications and analytical methods with validation are considered adequate for controlling the quality of this finished pharmaceutical product at release and during shelf life.

Stability testing
Stability studies have been performed on the same three batches used in the process validation at 30°C/65%RH as long-term conditions and at accelerated conditions according to the requirements of WHO. The product showed good chemical and physical stability and a shelf-life of 48 months has been allowed for the FPP when stored at a temperature not above 30°C.

Conclusion
The quality part of the dossier is accepted.

3. Assessment of bioequivalence
The following bioequivalence study has been performed in 2007/2008 according to internationally accepted guidelines.

A randomized, open label, two-treatment, two-sequence, two-period, single dose, crossover bioequivalence study of pyrazinamide tablet BP 500 mg manufactured by Micro Labs Limited, India with Sandoz pyrazinamide tablet 500 mg manufactured by Sandoz (Pty) Ltd., SA in normal, healthy, adult, human male subjects under fasting condition (study no. MCC/AHD/07/002).

The objective of the study was to compare the bioavailability of the stated pyrazinamide 500 mg tablet manufactured by Micro Labs Ltd, India (test drug) with the same dose of the reference formulation (Pyrazinamide tablet 500 mg, Sandoz) and to assess bioequivalence. The comparison was performed as a single centre, 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 – Pyrazinamide tablets BP 500 mg tablet (pyrazinamide 500 mg) Batch no. PZFB0004

Treatment R: Reference – Sandoz Pyrazinamide 500 mg tablet (pyrazinamide 500 mg) Batch no. 504948

An 8-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 25 samples within 48 hours 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 LS-MS/MS method. The limit of quantification was stated to be about 500 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 tables:

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)	1.26 ± 0.61	1.51 ± 0.90	-	-
C_{max} (µg/mL)	12.1 ± 1.5 (12.0)	12.2 ± 2.1 (12.1)	99.7	95.5 – 103.9
AUC_{0-t} (µg.h/mL)	120 ± 26 (118)	119 ± 26 (116)	101.5	98.4 – 104.6
AUC_{0-inf} (µg.h/mL)	137 ± 28 (134)	136 ± 32 (133)	101.1	98.1 – 104.2

* geometric mean

Conclusions:
The results of the study show that the pre-set acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding pyrazinamide. Accordingly, the test tablet Pyrazinamide 500 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Sandoz Pyrazinamide 500 mg (Sandoz).

4. Summary of product safety and efficacy

[TB172 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, [TB172 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sandoz Pyrazinamide 500 mg (Sandoz Pty Ltd), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB172 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 [TB172 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB172 trade name] has been shown to be bioequivalent with Sandoz Pyrazinamide 500 mg (Sandoz Pty Ltd).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB172 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 [TB172 trade name] was acceptable for the following indication: "**treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*, in combination with other antituberculosis agents**", and would allow inclusion of [TB172 trade name], manufactured at Micro Labs Limited, 92 Sipcot Industrial Complex, Hosur-635 126, Tamil-Nadu, India, in the list of prequalified medicinal products.