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	[TB171 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited (Unit-3) 92 Sipcot Industrial Complex Hosur-635 126 Tamil-Nadu India
Active Pharmaceutical Ingredients (APIs)	Pyrazinamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK01)
Therapeutic indication	[TB171 trade name] is Tablets is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

1. Introduction

[TB171 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.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

[TB171 trade name] should be initiated by a health care provider experienced in the management of tuberculosis.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

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.

Other ingredients

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

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.

Pyrazinamide 400mg Tablets are 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. Pyrazinamide 400 mg Tablets are a direct scale down of Micro Labs' Pyrazinamide 500 mg Tablets, of which 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. Evaluation criteria were tablet hardness, friability, disintegration and dissolution. Compaction force studies were conducted on the final formulation and resulted in suitable tablet characteristics.

The dissolution profiles of Micro Labs' Pyrazinamide 400mg Tablets and Pyrazinamide 500mg Tablets (the latter being the reference product, used in bioequivalence studies) in all three BCS media were demonstrated to be similar, and this was also the basis of the biowaiver allowed for Pyrazinamide 400mg Tablets. The two strengths, which are proportionally similar with respect to composition, showed "very rapid 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 (400,000 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.

A 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 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 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 preset 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).

A biowaiver was granted for the additional strength Pyrazinamide 400 mg tablet (Micro Labs Ltd, India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Pyrazinamide 400 mg tablet strength was determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths is considered essentially the same, and the dissolution profiles between the formulations for the API were determined to be similar.

4. Summary of Product Safety and Efficacy

[TB171 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference product, Sandoz Pyrazinamide®.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SPC (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 [TB171 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB171 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, it is concluded on bioequivalence between [TB171 trade name] and Sandoz Pyrazinamide® (Sandoz (Pty) Ltd., SA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB171 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [TB171 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 has advised to include [TB171 trade name], manufactured at Micro Labs Limited (Unit-3), 92 Sipcot Hosur-635 126 Tamil-Nadu, India in the list of prequalified medicinal products.