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	[TB174 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited–[Unit-3] 92, Sipcot Industrial Complex Hosur 635 126 Tamil Nadu India
Active Pharmaceutical Ingredient (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, hydrazides (J04AC01)
Therapeutic indication	[TB174 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB174 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.*
It is recommended that therapy is given only on the advice of a physician 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)

Isoniazid 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*). Isoniazid is thus highly soluble according to the BCS.

Isoniazid is described in the Ph.Int., Ph.Eur. and USP and is considered well-established in the Prequalification Programme. The APIMF of isoniazid has been accepted through WHO's APIMF procedure. Isoniazid is manufactured from 4-cyanopyridine.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification, appearance of solution, pH, hydrazine and related substances (TLC), heavy metals, loss on drying, sulphated ash, assay, related substances (HPLC), and residual solvents.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the isoniazid is stored in the original packing material.

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 silicon dioxide, hydrogenated castor oil, lactose monohydrate and microcrystalline cellulose, which are all compendial.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
Isoniazid tablets are described in the Ph.Int., BP and USP and are considered well- established.

[TB174 trade name] tablets are white to off white, flat, circular, bevel edged, uncoated tablets with break-line on one surface. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets (1 000) are packed in a semi-transparent polyethylene bag which is heat-sealed and packed together with a silica gel sachet in a white round HDPE jar. The jar is sealed with aluminium tagger and closed with a white HDPE screw cap.

The development of the final composition of [TB174 trade name] has been described. The manufacturing process entails direct compression. Appropriate in-process controls have been set to ensure batch-to-batch reproducibility. Validation data presented on three production batches and batch analysis data demonstrate the consistency of the process and the quality of the product.

Product specification
The pharmacopoeial based FPP release specifications include tests for appearance, identification (IR and colour test), average weight, uniformity of weight, tablet dimensions, hardness, friability, disintegration time, dissolution, assay, related substances (HPLC), microbial limits and tablet divisibility.

Stability testing
Stability studies have been performed at 30°C/65%RH as long-term storage conditions and at accelerated conditions. The data showed a slight increase in one of the related substances, though all attributes were well within the agreed specifications at both storage conditions. The data provided support the proposed shelf life and storage conditions as defined in the SPC.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2010 according to internationally accepted guidelines.

A randomized, open label, balanced, single center, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of [TB174 trade name] manufactured by Micro Labs Limited., India and Isoniazid tablets USP (Isoniazid) 300 mg manufactured by Sandoz Inc. Princeton, NJ 08540 in healthy human adult subjects, under fasting conditions (study no. S-10-007).

The objective of the study was to compare the bioavailability of the stated [TB174 trade name] manufactured by Micro Labs. Limited., India (test drug) with the same dose of the reference formulation (Isoniazid 300 mg, Sandoz) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy human adult 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 of [TB174 trade name] (isoniazid 300 mg) Batch no. IZABH0004.
Treatment R:	Reference – 1 tablet Isoniazid Sandoz 300 mg (isoniazid 300 mg)

Batch no. ME080580.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 24 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 isoniazid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.4 µg/ml for isoniazid.

The study was performed with 36 participants; data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference I arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.72 ± 0.42	0.86 ± 0.55	-	-
C_{max} (µg/ml)	7.90 ± 2.42 (7.65)	7.46 ± 2.76 (7.01)	109.1	101.3 – 117.5
AUC_{0-t} (µg.h/ml)	32.1 ± 13.2 (29.4)	31.4 ± 13.9 (28.1)	104.6	100.9 – 108.4
AUC_{0-inf} (µg.h/ml)	36.3 ± 15.0 (33.2)	35.6 ± 15.9 (31.9)	104.2	100.9 – 107.5

* 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 isoniazid. Accordingly, the test [TB174 trade name] tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Isoniazid 300 mg (Sandoz).

4. Summary of Product Safety and Efficacy

[TB174 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability [TB174 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Isoniazid 300 mg (Sandoz) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this produIt is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. Reference is made 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 Isoniazid 300 mg Tablets is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

[TB174 trade name] has been shown to be bioequivalent with Isoniazid 300 mg (Sandoz Inc. Princeton, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB174 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

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 [TB174 trade name] was acceptable for the following indication: **"treatment of tuberculosis caused by Mycobacterium tuberculosis"** and has advised that the quality, efficacy and safety of Isoniazid 300 mg Tablets are acceptable to allow inclusion of [TB174 trade name], manufactured at Micro Labs Limited [Unit-3], 92 Sipcot Industrial Complex Hosur 635 126 Tamil Nadu, India in the list of prequalified medicinal products.