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	[TB173 trade name] *
Manufacturer of Prequalified Product	Micro Labs Limited 92, Sipcot Industrial Complex Hosur 635 126 Tamil Nadu India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, hydrazides (J04AC01)
Therapeutic indication	[TB173 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB173 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 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)

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.

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

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

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.

[TB173 trade name] tablets are white to off-white, flat, circular, bevelled 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 – a divisibility test is included in the release specifications. 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 [TB173 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.

Comparative dissolution studies were conducted between Micro Labs' isoniazid 300 mg tablets and isoniazid 100 mg tablets in the three BCS media according to the requirements of WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series 937, Annex 7). Based on the similarity of the dissolution profiles, a biowaiver was allowed for isoniazid 100 mg tablets. Both strengths showed very rapidly dissolving dissolution properties.

Product specifications

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 SmPC.

Conclusion

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 centre, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of isoniazid 300 mg tablets manufactured by Micro Labs Ltd,

India and isoniazid tablets USP [TB174 trade name] 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. Ltd, 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 24h 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.4 ng/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.

Isoniazid

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	0.72 ± 0.42	0.86 ± 0.55	–	–
C_{max} (ng/mL)	7.90 ± 2.42 (7.65)	7.46 ± 2.76 (7.01)	109.1	101.3-117.5
AUC_{0-t} (ng ·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

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 tablet isoniazid 300 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the comparator isoniazid 300 mg (Sandoz).

A biowaiver was granted for the additional strength isoniazid 100 mg tablet (Micro Labs. Limited., India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the isoniazid 100 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 APIs were determined to be similar.

4. Summary of product safety and efficacy

[TB173 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [TB173 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. According to the submitted data on quality and bioavailability [TB173 trade name] is a direct scale down of [TB174 trade name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product isoniazid tablets USP 300 mg (Sandoz) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB173 trade name] 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 [TB173 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB173 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB173 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 [TB173 trade name] was acceptable for the following indication: 'treatment of tuberculosis caused by *Mycobacterium tuberculosis*', and would allow inclusion of [TB173 trade name], manufactured at Micro Labs Limited, 92 Sipcot Industrial Complex Hosur 635 126 Tamil Nadu, India in the list of prequalified medicinal products.