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	[TB347 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited (Unit-03) 92, Sipcot Industrial Complex Hosur Tamil Nadu, 635126 India.
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Drugs for treatment of tuberculosis, Hydrazides, Isoniazid (J04AC01)
Therapeutic indication	[TB347 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug-resistant tuberculosis caused by *Mycobacterium tuberculosis.* It is also indicated as monotherapy or in combination with other anti-tuberculosis agents for the prevention of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB347 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.

It is also indicated as monotherapy or with other medicines for the prevention of tuberculosis in persons at risk.

[TB347 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)

Isoniazid has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB347 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

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

(APIMF) to verify compliance with WHO norms and standards, and inspection 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, aspartame, crospovidone, colloidal silicon dioxide, iron oxide red, magnesium stearate and strawberry flavour. The commercially sourced proprietary strawberry flavour which is included in the tablet formulation is supported by appropriate declarations and controlled by acceptable specifications. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a peach coloured, circular, flat faced, bevelled edge tablet with deep break line (snap tabs) on one face and shallow convex with '50' debossing on the other face. The break line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are presented in aluminium strip packs.

Two strengths of isoniazid dispersible tablets, proportionally similar in composition and manufactured from a common blend, were developed: 100 mg and 50 mg. The development focused on the lower strength. Once the formulation for the 50 mg strength was finalized, the 100 mg strength was pursued using dose-proportionality approach. The 100 mg strength was used in the BE study against the WHO comparator product Isoniazid USP 100 mg tablets of Sandoz Inc, USA. The selection of excipients was based on previous formulation experience and knowledge about excipients that have been used successfully in prequalified products of dispersible tablets from the same manufacturer. Direct compression was opted in view of its conventional acceptability and robustness in general. Based on satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. The two strengths showed similar dissolution profiles in the main BCS media, which formed the basis of the biowaiver for the 50 mg strength.

Specifications

The finished product specifications include tests for appearance, identification (HPLC and colour reaction), average mass, uniformity of mass, tablet dimensions, disintegration time, resistance to crushing, friability, water content (by KF), uniformity of dosage units (by mass variation), fineness of dispersion, dissolution (UV detection), assay (HPLC), related substances (HPLC), subdivision of tablets and microbial limit test. The analytical methods have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the package proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with no negative trend observed. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

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.

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study of Isoniazid dispersible tablets 100 mg of Micro Labs Limited, India comparing with Isoniazid tablet USP 100 mg of Sandoz Inc. Princeton, NJ 08540 in healthy, adult, human subjects under fasting condition (study no. 072-16).

The objective of the study was to compare the bioavailability of the stated Isoniazid 100 mg dispersible tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation Isoniazid tablet USP 100 mg (Sandoz Inc.) 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 two treatments in a randomized fashion:

Treatment T: Test – 1 dispersible tablet Isoniazid 100 mg (isoniazid 100 mg) Batch no. IEBHK0001.
Treatment R: Reference – 1 tablet Isoniazid USP 100 mg (isoniazid 100 mg) Batch no. ME140742.

The Test tablet was dispersed in 50 ml water before intake and the Reference formulation was taken with 240 ml water. A 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 24h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 50 ng/ml for isoniazid.

The study was performed with 36 participants; data generated from a total of 32 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 table:

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)[#]	0.67 (0.17 – 3.0)	0.50 (0.33 – 1.50)	-	-
C_{max} (ng/mL)	1916 ± 630 (1812)	1879 ± 601 (1788)	101.3	95.3 – 107.7
AUC_{0-t} (ng·h/mL)	6945 ± 3859 (5830)	6758 ± 3616 (5701)	102.3	99.7 – 104.9
AUC_{0-inf} (ng·h/mL)	7225 ± 3982 --	7042 ± 3705 --	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding isoniazid. Accordingly, the test Isoniazid 100 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Isoniazid tablet USP 100 mg (Sandoz Inc).

A biowaiver was granted for the additional 50 mg tablet strength (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 50 mg dispersible tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the API were determined the same

4. Summary of product safety and efficacy

[TB347 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [TB347 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 [TB347 trade name] is a direct scale down of [TB348 trade name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product isoniazid tablet USP 100 mg (Sandoz Inc.). The clinical safety of [TB347 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 [TB347 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB347 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, [TB347 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 [TB347 trade name] was acceptable for the following indication: 'in combination with other antituberculosis drugs is indicated for treatment of multi-drug resistant tuberculosis, and as monotherapy or in combination for the prevention of tuberculosis caused by *Mycobacterium tuberculosis*', and would allow inclusion of [TB347 trade name], manufactured at Micro Labs Limited (Unit-03), 92, Sipcot Industrial Complex, Hosur, Tamil Nadu, 635126, India in the list of prequalified medicinal products