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	[TB375 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited EPIP, SIDCO Industrial Complex Kartholi, Bari Brahmana Jammu & Kashmir 181133 India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, hydrazides (J04AC01)
Therapeutic indication	Tuberculosis

1. Introduction

[TB375 trade name] is indicated for the treatment of tuberculosis, caused by Mycobacterium tuberculosis. Isoniazid is not indicated for use in patients with clinically significant hypersensitivity to isoniazid or to any of the components contained in the formulation. 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)

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 [TB375 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 (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

[*] 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 microcrystalline cellulose, povidone, copovidone, polyethylene glycol, crospovidone, colloidal silicon dioxide and stearic acid. None of the excipients used in the manufacture of the tablets are of human or animal origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, circular, flat-faced, bevelled edge, uncoated tablet with a score line on one side and plain on the other side. The score line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in amber PVC/PVDC-Alu blisters.

The objective of the product development was to obtain a stable and robust formulation, bioequivalent to the WHO recommended comparator product; Isozid® (isoniazid 100 mg) tablets. Commonly used excipients were selected to achieve a bioequivalent product. Based on properties of the active pharmaceutical ingredient, literature search and development trials, the composition was finalized. Wet granulation process was selected to manufacture the finished pharmaceutical product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (IR and HPLC), average weight, uniformity of dosage units (by weight variation), water content (KF), uniformity of weight of tablet, dissolution (HPLC detection), assay (HPLC), related substances (HPLC), subdivision of tablet and microbial limits.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data provided indicate that the product is stable at both storage conditions. 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 2019 according to internationally accepted guidelines.

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, cross over, oral bioequivalence study comparing Isoniazid tablets 300 mg manufactured by Lupin Limited, India with Isozid® 100 mg (isoniazid) tablet (1 x 3 tablets) manufactured by Reimser Pharma GmbH, Ander Wiek 7 17493 Greifswald-Insel Riems in healthy, adult, human, male subjects under fasting conditions (study no. 843-18 / LBC-19-013).

The objective of the study was to compare the bioavailability of the stated Isoniazid 300 mg tablet manufactured by/for Lupin Limited, India (test drug) with the reference formulation Isozid® (Riemser Pharma GmbH) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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 tablet Isoniazid 300 mg

(isoniazid 300 mg)
Batch no. J890174.

Treatment R: Reference – 3 tablets Isozid® 100 mg

(isoniazid 300 mg)

Batch no. 001046.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 ng/ml for isoniazid.

The study was performed with 36 participants; data generated from a total of 33 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.90 ± 0.60	0.74 ± 0.45	-	-
C_{max} (ng/ml)	6503 ± 2455 (6077)	7094 ± 2310 (6690)	90.8	81.9 – 100.8
AUC_{0-t} (ng.h/ml)	21918 ± 10778 (18993)	21957 ± 10539 (19119)	99.3	96.8 – 102.0
AUC_{0-inf} (ng.h/ml)	22254 ± 11006--	22264 ± 10733--	-	-

*geometric mean

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 Isoniazid 300 mg tablet meets the criteria

for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Isozid® (Riemser Pharma GmbH).

Summary of product safety and efficacy

[TB375 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, [TB375 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Isozid® (Riemser Pharma GmbH) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB375 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.

4. 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 [TB375 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB375 trade name] has been shown to be bioequivalent with Isozid® (Riemser Pharma GmbH)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB375 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 [TB375 trade name] was acceptable for the following indication: 'tuberculosis', and would allow inclusion of [TB375 trade name], manufactured Lupin Limited EPIP, SIDCO Industrial Complex, Kartholi, Bari Brahmana Jammu & Kashmir, 181133, India in the list of prequalified medicinal products.