

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	[TB392 trade name]*
Manufacturer of Prequalified Product	Svizera Labs Private Limited Plot No. D16/6, TTC Industrial Area MIDC, Turbhe Navi Mumbai – 400703 India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, hydrazides (J04AC01)
Therapeutic indication	[TB392 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to <i>Mycobacterium tuberculosis</i> , 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

1. Introduction

[TB392 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.

[TB392 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 pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB392 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 dibasic calcium phosphate, maize starch, polyvinyl pyrrolidone, sodium starch glycolate, talc and magnesium stearate. 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, round, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a break-line on one side and plain on the other side. 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 are packaged in either plastic (PVC/PVDC) or aluminium foil blister cards or in plastic bags within HDPE jars.

The objective of the product development was to obtain an immediate release, stable and robust formulation, bioequivalent to the WHO recommended comparator product; Isozid® (isoniazid 100 mg) tablets. The quality target product profile was defined based on the properties of the active pharmaceutical ingredient, characterization of the comparator product and literature review of the comparator product. The critical quality attributes were satisfactorily identified. The excipients used were based on their similarity to the comparator product and API-excipient compatibility studies. To achieve the target tablet characteristics a wet granulation process was selected to manufacture the finished pharmaceutical product. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics. 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 colour development), average weight, uniformity of tablet weight, disintegration time, loss on drying, dissolution (UV detection), uniformity of dosage units (by mass variation), assay (HPLC), related substances (HPLC) 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 in both pack types. 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 2023 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study of [TB392 trade name] of Svizera Labs Private Limited, Plot D 16/6, MIDC,

TTC Industrial Area, Turbhe, Navi Mumbai – 400 703, India with Isozid (Isoniazid) 100 mg tablets (100 mg × 3 tablets) of Riemser Pharma GmbH, in normal, healthy, adult, human subjects under fasting conditions (study no. ARL/23/015).

The objective of the study was to compare the bioavailability of the stated [TB392 trade name] manufactured by/for Svizera Labs Private 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 [TB392 trade name]
(isoniazid 300 mg)
Batch no. SL 138
Treatment R: Reference – 3 tablets Isozid® 100 mg
(isoniazid 300 mg)
Batch no. 003118

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 24 hours 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 100 ng/mL for isoniazid.

The study was performed with 28 participants; data generated from a total of 27 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) [#]	0.50 (0.33 – 1.50)	0.75 (0.25 – 1.75)	–	–
C _{max} (ng/mL)	9042 ± 2115 (8790)	8143 ± 1974 (7869)	111.7	102.4 – 121.8
AUC _{0-t} (ng.h/mL)	32495 ± 15250 (28675)	32521 ± 15488 (28417)	100.9	98.5 – 103.4
AUC _{0-inf} (ng.h/mL)	33330 ± 15576 (29431)	33316 ± 15788 (29141)	101.0	98.6 – 103.4

median (min – max)

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 [TB392 trade name] 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).

4. Summary of product safety and efficacy

[TB392 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, [TB392 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 [TB392 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 [TB392 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB392 trade name] has been shown to be bioequivalent with Isozid® (Riemser Pharma GmbH).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB392 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 [TB392 trade name] was acceptable for the following indication: 'in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis*, including in regimens for drug-resistant tuberculosis and also as monotherapy or with other medicines for the prevention of tuberculosis in persons at risk', and would allow inclusion of [TB392 trade name], manufactured at Svizera Labs Private Limited, Plot No. D16/6, TTC Industrial Area, MIDC, Turbhe, Navi Mumbai – 400703, India in the list of prequalified medicinal products.