

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	[TB410 trade name]*
Manufacturer of Prequalified Product	Lupin Limited A-28/1, MIDC Area, Chikalthana Chhatrapati sambhajinagar Aurangabad 431210 Maharashtra State, India
Active Pharmaceutical Ingredient (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Drugs for treatment of tuberculosis, Hydrazides, Isoniazid (J04AC01)
Therapeutic indication	[TB410 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.

1. Introduction

[TB410 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.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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 [TB410 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

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

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, colloidal silicon dioxide, povidone, saccharin sodium, crospovidone, raspberry flavour and magnesium stearate; all, except raspberry flavour, being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. Raspberry flavour is controlled by acceptable specifications. Magnesium stearate is of vegetable origin. TSE/BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to yellowish, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has a break line on one side and is plain on the other side. The tablets are packaged in aluminium foil strip packs.

The development of the final composition of the tablets has been described. The objective was to obtain a stable and robust dispersible tablet, bioequivalent to the WHO recommended comparator product, Isoniazid 100mg dispersible tablets (Teva Pharmaceuticals, USA). The selection of the excipients was based on the qualitative composition of the comparator product and API-excipient compatibility studies. The flavouring and sweetening agents were used to improve the taste of the dispersible tablets. Wet granulation using isopropyl alcohol was selected as the manufacturing process for the finished pharmaceutical product. Studies showed that acceptable disintegration time and fineness of dispersion were not achieved using purified water as binder solution. Hence, the use of the organic solvent in the formulation was justified. Based on the 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.

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 include tests for description, identification (HPLC and UV), disintegration time, fineness of dispersion, water content (KF), dissolution (UV detection), uniformity of dosage units (by weight variation and content uniformity), assay (HPLC), degradation products (HPLC), residual solvent, subdivision of tablets and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated storage conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these 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 2023 according to internationally accepted guidelines:

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study comparing Isoniazid dispersible tablets 100 mg manufactured by Lupin Limited, India with Isoniazid tablets USP 100 mg manufactured for Teva Pharmaceuticals USA, Inc., North Wales, PA 19454 in healthy, adult, human subjects under fasting conditions (study no. LBC-23-043).

The objective of the study was to compare the bioavailability of the stated Isoniazid 100 mg dispersible tablet manufactured by Lupin Limited, India (test drug) with the reference Isoniazid tablet 100 mg USP (Teva Pharmaceuticals USA) 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. A396041.

Treatment R: Reference – 1 tablet Isoniazid 100 mg USP
(isoniazid 100 mg)
Batch no. CKMSW.

The dispersible tablet was dispersed in 40 mL water (+ 10 mL of rinsing water) and administered. A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 2 ng/mL for isoniazid.

The study was performed with 24 participants; data generated from a total of 24 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 (geometric mean)	Reference (R) arithmetic mean ± SD (geometric mean)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t _{max} (h)	0.50 (0.17 – 1.75)	0.50 (0.33 – 1.25)	–	–
C _{max} (ng/mL)	1979 ± 668 (1865)	1959 ± 579 (1863)	100.1	87.6 – 114.3
AUC _{0-t} (ng·h/mL)	6617 ± 4264 (5263)	6446 ± 4199 (5112)	103.0	98.6 – 107.5
AUC _{0-inf} (ng·h/mL)	6701 ± 4361 (5310)	6532 ± 4297 (5161)	102.9	98.6 – 107.4

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 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 formulation Isoniazid tablet 100 mg USP (Teva Pharmaceuticals USA).

4. Summary of product safety and efficacy

[TB410 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, [TB410 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Isoniazid tablet 100 mg USP (Teva Pharmaceuticals USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB410 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 [TB410 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB410 trade name] has been shown to be bioequivalent with Isoniazid tablet 100 mg USP (Teva Pharmaceuticals USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB410 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 [TB410 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 would allow inclusion of [TB410 trade name], manufactured at Lupin Limited, A-28/1, MIDC Area, Chikalthana, Chhatrapati sambhajnagar, Aurangabad 431210, Maharashtra State, India in the list of prequalified medicinal products.