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	[TB394 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited, A-28/1, MIDC Area, Chikalthana Aurangabad 431 210 Maharashtra State India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid and rifapentine
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02)
Therapeutic indication	[TB394 trade name] is indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis* in patients above 2 years of age and weighing more than 10 kg.

1. Introduction

[TB394 trade name] is indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis* in patients above 2 years of age and weighing more than 10 kg.

Consideration should be given to current official treatment guidelines for tuberculosis including those of WHO.

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

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 [TB394 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.

Rifapentine

Data provided in the dossier show that rifapentine is a red to brown crystalline powder. Rifapentine is of BCS low solubility, hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications.

The API specifications include tests for description, solubility, identification (IR and HPLC), polymorphic form (p-XRD), water content, residue on ignition, assay (HPLC), organic impurities (HPLC), residual solvents (GC), bulk density, tapped density, microbial limits, potential genotoxic impurities (limits are in line with ICH M7) and particle size distribution (PSD). The PSD limits are based on the results obtained for the API batch used in the manufacture of the FPP biobatch.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, sodium starch glycolate, pregelatinised starch, sodium lauryl sulfate, disodium edetate, sodium ascorbate, dewaxed shellac and calcium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, soya lecithin, xanthum gum, titanium dioxide, talc and iron oxide red. 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 brown, capsule-shaped, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a break line on one side and is 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 data. The tablets are packaged in aluminium strips.

The objective of the product development was to obtain a stable and robust, immediate-release FDC tablet that is bioequivalent to the WHO recommended comparator products: Isozid® (isoniazid) 100 mg tablets and Priftin® (rifapentine) 150 mg tablets. The quality target product profile was defined based on the physicochemical properties of the API and characteristics of the comparator products. The selection of excipients was based on the excipients used in the comparator products and API-API and API-excipient compatibility data. Since rifapentine is prone to oxidation, sodium ascorbate was included as antioxidant based on its presence in the comparator product. Separate granulation of isoniazid and rifapentine parts was adopted to minimise interactions between the APIs. Due to the poor flow properties of the rifapentine API, a wet granulation was selected to obtain readily compressible granules and achieve content uniformity and reproducible drug release. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

A risk assessment has been performed and a risk for nitrosamine impurities has been identified within the FPP manufacture. Confirmatory testing has been performed and 1-cyclopentyl-4-nitrosopiperazine (CPNP) impurity was identified. A test for this impurity has been included in the FPP specifications.

Specifications

The finished product specifications include tests for description, identification of APIs (HPLC and HPLC-PDA/DAD detector), water content (KF), assay (HPLC), uniformity of dosage units (by mass variation), dissolution (UV detection for rifapentine; HPLC detection for isoniazid), degradation products (HPLC), residual solvent (GC), sodium ascorbate content (HPLC), subdivision of tablets, 1-cyclopentyl-4-nitrosopiperazine content (GCMS; ≤ 20ppm) 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 indicates that all the tested parameters remained within acceptable limits 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 2021 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two -sequence, two-period crossover oral bioequivalence study comparing Rifapentine and Isoniazid tablet 300 mg/300 mg (1 tablet) manufactured by Lupin Limited, India with Priftin® (rifapentine tablets 150 mg × 2 tablets) manufactured by Sanofi-Aventis U.S. LLC, Bridgewater, NJ 08807 and Isozid® 100 mg (isoniazid tablets 100 mg × 3 tablets) manufactured by Riemser Pharma GmbH, Ander Wiek 7 17493 Greifswald-Insel Riems in healthy, adult, human subjects under fed conditions (study no. 037-21).

The objective of the study was to compare the bioavailability of the stated Rifapentine/Isoniazid 300 mg/300 mg FDC tablet manufactured by/for Lupin Ltd., India (test drug) with the reference formulations Priftin® 150 mg tablets (Sanofi-Aventis U.S. LLC) and Isozid® 100 mg tablet (Riemser Pharma GmbH) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Rifapentine/Isoniazid 300 mg/300 mg (rifapentine 300 mg + isoniazid 300 mg) Batch no. A190005.
Treatment R:	Reference – 2 tablets Priftin® 150 mg (rifapentine 300 mg) Batch no. A8D21. - 3 tablets Isozid® 100 mg (isoniazid 300 mg) Batch no. 002017

A 7-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 25 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for rifapentine and isoniazid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for rifapentine and 50 ng/mL for isoniazid.

The study was performed with 48 participants; data generated from a total of 48 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for rifapentine and isoniazid as well as statistical results are summarised in the following tables:

Rifapentine

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)	5.21 ± 1.00	5.35 ± 0.95	-	-
C_{max} (µg/mL)	9.4 ± 2.2 (9.1)	10.4 ± 2.6 (10.1)	90.1	86.7 – 93.7
AUC_{0-t} (µg.h/mL)	214 ± 48 (209)	240 ± 62 (232)	90.0	86.6 – 93.5
AUC_{0-inf} (µg.h/mL)	221 ± 51 --	249 ± 67 --	-	-

*geometric mean

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)	2.04 ± 0.73	2.01 ± 0.82	-	-
C_{max} (ng/mL)	4948 ± 2280 (4534)	4357 ± 1475 (4086)	111.0	103.8 – 118.7
AUC_{0-t} (ng.h/mL)	23928 ± 13100 (19726)	23238 ± 12568 (19222)	102.6	100.2 – 105.2
AUC_{0-inf} (ng.h/mL)	24847 ± 13653 --	24139 ± 13229 --	-	-

*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 rifapentine and isoniazid. Accordingly, the test Rifapentine/Isoniazid 300 mg/300 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC) and Isozid® 100 mg tablet (Riemser Pharma GmbH).

4. Summary of product safety and efficacy

[TB394 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, [TB394 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Priftin® 150 mg (Sanofi-Aventis U.S. LLC,) and Isozid® 100 mg tablet (Riemser Pharma GmbH) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB394 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 [TB394 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB394 trade name] has been shown to be bioequivalent with Priftin® 150 mg (Sanofi-Aventis U.S. LLC,) and Isozid® 100 mg tablet (Riemser Pharma GmbH).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB394 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 [TB394 trade name] was acceptable for the following indication: 'prevention of tuberculosis caused by *Mycobacterium tuberculosis* in patients above 2 years of age and weighing more than 10 kg', and would allow inclusion of [TB394 trade name], manufactured at Lupin Limited, A-28/1, MIDC Area, Chikalthana, Aurangabad 431 210, Maharashtra State, India in the list of prequalified medicinal products.