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	[TB393 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited A-28/1, MIDC Area, Chikalthana Chhatrapati Sambhajinagar 431 210 Maharashtra State India
Active Pharmaceutical Ingredient(s) (API)	Rifapentine
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials (J04AB05)
Therapeutic indication	[TB393 trade name] is indicated in combination with other tuberculosis medicines for the initial treatment of tuberculosis due to *Mycobacterium tuberculosis*. It is also indicated together with other medicines for the prevention of tuberculosis in persons at risk.

1. Introduction

[TB393 trade name] is indicated in combination with other tuberculosis medicines for the initial treatment of tuberculosis due to *Mycobacterium tuberculosis*.

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

Use of [TB393 trade name] should be initiated and monitored by a health care provider experienced in the management and prevention of *Mycobacterium tuberculosis* infection.

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)

Data provided in the dossier show that rifapentine is a red to brown crystalline, hygroscopic powder. Rifapentine has poor water solubility (critically insoluble), hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. The API from the manufacturer has been shown to be consistent and of identical polymorph as that used for the FPP biobatch.

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

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 including 1-cyclopentyl-4-nitrosopiperazine (CPNP) (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, hydroxypropyl cellulose, sodium ascorbate, sodium lauryl sulfate, disodium edetate, colloidal silicon dioxide and calcium stearate, all being pharmacopoeial controlled.

The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, iron oxide red, macrogol/ polyethylene glycol, propylene glycol, iron oxide yellow and FD&C yellow #6/sunset yellow FCF aluminium lake. None of the excipients are derived from human or animal sources. 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 brown, round, 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 either aluminium strips or aluminium foil on aluminium foil blister cards.

The objective of the product development was to obtain a stable and robust formulation of rifapentine tablets, bioequivalent to the WHO recommended comparator product, 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 product. Excipients were selected based on literature study and excipients present in the comparator product. Since rifapentine is prone to oxidation, sodium ascorbate was included as antioxidant based on its presence in the comparator product. The API has very poor flow properties therefore, a wet granulation process was selected for manufacturing of the rifapentine tablets. 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 API (HPLC and UV), water content (KF), assay (HPLC), uniformity of dosage units (by weight variation), dissolution (UV detection), degradation products (HPLC), subdivision of tablets, sodium ascorbate content (HPLC), 1-cyclopentyl-4-nitrosopiperazine content (GCMS ≤ 15ppm) and microbial limits. The analytical methods were adequately validated.

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 product proved to be quite stable at these storage conditions since no negative trends or significant changes were observed and all the tested parameters remained within acceptable limits.

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 tablet 300 mg (one tablet) manufactured by Lupin Limited, India with Priftin® (rifapentine tablets 150 mg x two tablets) manufactured by Sanofi-Aventis U.S. LLC, Bridgewater, NJ 08807 in healthy, adult, human subjects under fed conditions (study no. 0.38-21).

The objective of the study was to compare the bioavailability of the stated rifapentine 300 mg tablet manufactured by/for Lupin Ltd., India (test drug) with the reference formulation Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC) 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 300 mg (rifapentine 300 mg) Batch no. A190003
Treatment R:	Reference – 2 tablets Priftin® 150 mg (rifapentine 300 mg) Batch no. A8D21

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 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 rifapentine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for rifapentine.

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 rifapentine as well as statistical results are summarised in the following table:

Rifapentine

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)	4.81 ± 0.91	5.27 ± 0.61	-	-
C_{max} (µg/mL)	14.4 ± 3.7 (13.9)	14.0 ± 3.3 (13.7)	101.6	95.2 – 108.3
AUC_{0-t} (µg·h/mL)	337 ± 86 (327)	335 ± 78 (326)	100.2	95.4 – 105.2
AUC_{0-inf} (µg·h/mL)	356 ± 97 --	355 ± 99 --	-	-

The results of the study show that the pre-set acceptance limits of 80 - 125 % are met by both AUC and C_{max} values regarding rifapentine. Accordingly, the test rifapentine 300 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC).

4. Summary of product safety and efficacy

[TB393 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, [TB393 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product, Priftin® (Sanofi-Aventis), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB393 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 [TB393 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB393 trade name] has been shown to be bioequivalent with Priftin ® (Sanofi-Aventis).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB393 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 [TB393 trade name] was acceptable for the following indication: ‘is indicated in combination with other tuberculosis medicines for the initial treatment or prevention of tuberculosis due to *Mycobacterium tuberculosis*’, and would allow inclusion of [TB393 trade name], manufactured at Lupin Limited, A-28/1, MIDC Area, Chikalthana, Aurangabad 431210, Maharashtra State, India, in the list of prequalified medicinal products.