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	[TB412 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Oxalis Labs, Village Theda P.O. Lodhimajra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174101, India
Active Pharmaceutical Ingredient(s) (API)	Rifapentine
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, (ATC Code: J04AB05)
Therapeutic indication	[TB412 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

[TB412 trade name] is indicated in combination with other tuberculosis medicines for the initial treatment of tuberculosis due to Mycobacterium tuberculosis.

[TB412 trade name] is indicated together with other medicines for the prevention of tuberculosis in persons at risk.

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)

Rifapentine is a red to brown crystalline hygroscopic powder. The API shows polymorphism and has poor water solubility (critically insoluble).

Rifapentine 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 [TB412 trade name] is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP).

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

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

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, pregelatinised starch, sodium starch glycolate, sodium lauryl sulfate, disodium edetate, sodium ascorbate, hydroxypropyl cellulose, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, aspartame, strawberry cream flavour and calcium stearate, all being controlled by acceptable specifications. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a red, mottled, capsule- shaped, uncoated 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 strip packs.

The objective of the product development was to obtain a stable and robust formulation of rifapentine dispersible 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 anti-oxidant based on its presence in the comparator product. Additionally, aspartame and strawberry cream flavour were included to make the dispersible tablets palatable. Rifapentine is a low soluble API; hence, micronized API was selected for the development. Based on prior experience of development on rifapentine-containing formulations, 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 HPLC with PDA detector), identification of sodium ascorbate (HPLC), uniformity of dosage units (by content uniformity), hardness, disintegration time, dissolution (HPLC detection), related substances (HPLC), assay (HPLC), water content (KF), antioxidant content (HPLC), subdivision of tablets, fineness of dispersion, 1-cyclopentyl-4-nitrosopiperazine content (LC-MS/MS $\leq$ 20ppm), 1-amino-4-cyclopentylpiperazine content (GC $\leq$ 0.2%) 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, though there was a slight increase of oxidative degradation products, 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 2024 according to internationally accepted guidelines.

Two tablets as single dose fed in-vivo bioequivalence study of Rifapentine dispersible tablets 150 mg (Macleods Pharmaceuticals Ltd., India) to two tablets as single dose of Priftin® (rifapentine) tablets 150 mg (Sanofi-aventis U.S. LLC, USA) in healthy, adult, human subjects (study no. BEQ-3643-RIFP-2023).

The objective of the study was to compare the bioavailability of the stated Rifapentine 150 mg dispersible tablet manufactured by/for Macleods Pharmaceuticals 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 – 2 tablets Rifapentine 150 mg (rifapentine 300 mg) Batch no. NRB32302A.

Treatment R: Reference – 2 tablets Priftin® 150 mg (rifapentine 300 mg) Batch no. 2J4572.

The test dispersible tablets were dispersed in 20 ml water (+ 30 ml of rinsing water) and administered. The reference was administered with 240 ml water. 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 72h 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 200 ng/ml for rifapentine.

The study was performed with 28 participants; data generated from a total of 28 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)	5.45 ± 0.61	5.48 ± 0.58	-	-
C_{max} (µg/mL)	9.70 ± 2.19 (9.48)	9.26 ± 1.42 (9.16)	103.6	98.6 – 108.8
AUC_{0-t} (µg.h/mL)	222 ± 51 (217)	228 ± 42 (224)	96.7	93.1 – 100.4

$AUC_{0\text{-}inf}$ (µg.h/mLl)	236 ± 54 --	242 ± 45 --	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding rifapentine. Accordingly, the test Rifapentine 150 mg dispersible 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

[TB412 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, [TB412 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB412 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 [TB412 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB412 trade name] has been shown to be bioequivalent with Priftin® (Sanofi-Aventis U.S. LLC).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB412 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 [TB412 trade name] was acceptable for the following indication: 'treatment and prevention of tuberculosis', and would allow inclusion of [TB412 trade name], manufactured at Macleods Pharmaceuticals Limited , Oxalis Labs Village Theda P.O. Lodhimajra , Tehsil Baddi, Dist. Solan Himachal Pradesh , 174101, India in the list of prequalified medicinal products.