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	[TB398 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited At 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 (J04AB05)
Therapeutic indication	[TB398 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

[TB398 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 [TB398 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)

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 [TB398 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, low-substituted hydroxypropyl cellulose, sodium starch glycolate, sodium lauryl sulfate, hydroxypropyl cellulose, disodium edetate, sodium ascorbate, colloidal silicon dioxide and calcium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-partially hydrolysed, macrogol/ polyethylene glycol, 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 reddish-brown, round shaped, bevelled edge, biconvex, film-coated tablet debossed with "J" and "37" on either side of 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 data. The tablets are packaged in Alu/Alu strips.

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 anti-oxidant based on its presence in the comparator product. Rifapentine is a low soluble API; hence, micronized API was selected for the development. Based on prior experience of development on rifapentine-containing formulation, 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 specification

Specifications

The finished product specifications include tests for description, identification of API (HPLC with PDA detector) and colourants, uniformity of dosage units (by weight variation), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), water content (KF), antioxidant content (HPLC), subdivision of tablets, 1-cyclopentyl-4-nitrosopiperazine content (LC-MS/MS ≤ 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 6 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 2021 according to internationally accepted guidelines.

Single dose fed in-vivo bioequivalence study of Rifapentine tablets 300 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-2951-RIFP-2020).

The objective of the study was to compare the bioavailability of the stated Rifapentine 300 mg 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 – [TB398 trade name]
(rifapentine 300 mg)
Batch no. NRA32101A.

Treatment R: Reference – 2 tablets Priftin® 150 mg
(rifapentine 300 mg)
Batch no. 0J3091.

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 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 203 ng/ml for rifapentine.

The study was performed with 24 participants; data generated from a total of 23 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)	5.39 ± 0.60	5.57 ± 0.63	–	–
C_{max} (µg/mL)	10.8 ± 2.4 (10.5)	9.9 ± 2.0 (9.7)	107.6	101.6 – 114.0
AUC_{0-t} (µg·h/mL)	242 ± 65 (232)	232 ± 51 (225)	103.1	97.3 – 109.3
AUC_{0-inf} (µg·h/mL)	257 ± 68 –	249 ± 60 –	–	–

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 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

[TB398 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, [TB398 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 [TB398 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 [TB398 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB398 trade name] has been shown to be bioequivalent with Priftin® 150 mg tablet (Sanofi-aventis U.S. LLC).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB398 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 [TB398 trade name] was acceptable for the following indication: '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', and would allow inclusion of [TB398 trade name], manufactured at Macleods Pharmaceuticals Limited At Oxalis Labs, Village Theda P.O. Lodhimajra, Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174101, India, in the list of prequalified medicinal products.