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:	[TB332 trade name][*]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Unit II, Phase II Plot No 25-27, Survey No 366 Premier Industrial Estate Kachigam, Daman, 369 210 India
Active Pharmaceutical Ingredient (API):	Rifampicin
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials, antibiotics (J04AB02)
Therapeutic indication:	[TB332 trade name] is indicated in combination with other antituberculosis agents, for the treatment of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis.*

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

1. Introduction

[TB332 trade name] is indicated, in combination with other antituberculosis agents, for the treatment of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis.*

[TB332 trade name] should be initiated by a health care provider experienced in the management of 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)

Rifampicin API is described in the Ph.Int, Ph.Eur and the USP, and is considered well-established in the WHO Prequalification Programme.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification of the API and of its crystal form (XRPD), pH, loss on drying, heavy metals, sulfated ash, related substances (HPLC), assay (UV/HPLC), crystallinity, bulk density residual solvents and particle size distribution.

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

The capsule fill powder contains microcrystalline cellulose, povidone, maize starch, sodium lauryl sulfate, purified talc and magnesium stearate. The capsule shells contain gelatin, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, sodium lauryl sulfate, carmoisine (azorubine), sunset yellow (FD&C yellow #6), ponceau 4R (cochineal red A) and titanium dioxide. A CEP was submitted for gelatin used in the manufacture of the capsule shells. It meets the EU criteria for products with risk of transmitting animal spongiform encephalopathies. Attestation that all of the other excipients are free from TSE/BSE has been provided by the suppliers of the raw materials.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a scarlet/scarlet coloured hard gelatin, size "0" capsule filled with brick red powder. The capsules are presented in PVC-Alu blisters, in Alu-Alu strips or in a self-sealing LDPE bag, contained within a plain triple laminated LDPE/PET-Alu sachet packed in an HDPE bottle.

The objective of the developmental activities was to obtain a stable and robust formulation of [TB332 trade name] that would be bioequivalent to the WHO recommended comparator product Rifadin®. Rifampicin is classified as not highly soluble according to the BCS, thus both polymorphism and particle size distribution have been identified as critical quality attributes that may have an effect on the performance of the product. Control of these CQAs are included in the API user requirements, based on data obtained for the API batch used in the FPP biobatch. Due to poor flow characteristics of rifampicin, granules are produced – using non-aqueous wet granulation – to achieve a uniform blend with good flow properties for capsule filling. Various experiments were performed to optimize the concentration of excipients and the process parameters to obtain a product of desired characteristics.

Specifications

The product specifications are pharmacopoeial based and include tests for description, identification of the API (IR, UV) and colorants, average net content, disintegration time, dissolution (UV detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (UV), residual solvent (GC), loss on drying and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 30°C/75%RH as accelerated condition. The data showed degradation of the API at both storage conditions in all packaging configuration, though no significant change was observed. The data provided support the proposed shelf life and storage conditions as defined in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

Single dose fasting in-vivo bioequivalence study of Rifampicin capsules 300 mg (Macleods Pharmaceuticals Ltd., India) to Rifadin® (rifampicin) capsules 300 mg (Sanofi-Aventis U.S. LLC., USA) in healthy, adult, human subjects (study no. BEQ-1949-RIFA-2016).

The objective of the study was to compare the bioavailability of the stated Rifampicin 300 mg Capsules manufactured by/for Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Rifadin® (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 fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 capsule Rifampicin 300 mg
(rifampicin 300 mg)
Batch no. ERE4601A.

Treatment R: Reference – 1 capsule Rifadin®
(rifampicin 300 mg)
Batch no. 3130697

A 14 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 24 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 rifampicin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for rifampicin.

The study was performed with 24 participants; data generated from a total of 21 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for rifampicin as well as statistical results are summarised in the following table:

Rifampicin

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)	1.46 ± 0.44	1.30 ± 0.38	-	-
C_{max} (ng/mL)	6557 ± 1675 (6347)	7115 ± 1477 (6979)	90.9	84.2 – 98.2
AUC_{0-t} (ng.h/mL)	36795 ± 10688 (35144)	38124 ± 8957 (37052)	94.9	91.7 – 98.1
AUC_{0-inf} (ng.h/mL)	37434 ± 11182 (--)	38706 ± 9237 (--)	--	--

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding rifampicin. Accordingly, the test [TB332 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Rifadin® (Sanofi-Aventis U.S. LLC.).

4. Summary of product safety and efficacy

[TB332 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, [TB332 trade name] is pharmaceutically and therapeutically equivalent and thus, interchangeable with the comparator product Rifadin® (rifampin) capsules 300 mg (Sanofi-Aventis U.S. LLC) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB332 trade name] is considered acceptable when guidance and restrictions as 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 [TB332 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB332 trade name] has shown to be bioequivalent with Rifadin® (rifampicin) capsules 300 mg (Sanofi-Aventis U.S. LLC., USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB332 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB332 trade name] was acceptable for the following indication: "**in combination with other antituberculosis agents, in the treatment of tuberculosis caused by drug-susceptible Mycobacterium tuberculosis**" and would allow inclusion of [TB332 trade name], manufactured at Macleods Pharmaceuticals Limited, Unit II, Phase II, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman, 369 210, India in the list of prequalified medicinal products.