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	[TB259 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Phase II, Unit II, Plot No. 25 – 27 Survey No. 366 Premier Industrial Estate Kachigam Daman – 396210 India
Active Pharmaceutical Ingredient(s) (API)	Rifampicin
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, antibiotics (J04AB02).
Therapeutic indication	[TB259 trade name] is indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB259 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis.* It is also indicated together with other medicines for the prevention of tuberculosis in persons at risk.

[TB259 trade name] is also indicated in combination with other medicines for the treatment of leprosy.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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.

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

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 sulphate, purified talc and magnesium stearate. The capsule shells contain gelatin, sodium methylparaben, sodium propylparaben, sodium lauryl sulfate, titanium dioxide, FD&C Yellow #6 / Sunset yellow, carmoisine and ponceau 4R. The suppliers of gelatin provided EDQM-CEPs demonstrating TSE/BSE-compliance of this excipient. The other excipients are not of animal or human origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a scarlet / scarlet hard gelatin size "2" capsule filled with brick red powder. The capsules are packaged in Al-Al strips or in a self-sealing LDPE bag, inside a plain triple laminated (LDPE/AL/PET) sachet and then in an HDPE container with HDPE screw cap.

The objective of developmental activities was to develop a stable and robust formulation of Rifampicin 150 mg Capsules that would be bioequivalent to the WHO 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, including dissolution rate and bioavailability. Control of these CQAs are included in the user requirements, based on data obtained for the API batch used in the capsule 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 other process parameters to obtain a product of desired characteristics.

Specifications

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

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and at accelerated conditions in the packaging proposed for marketing of the product. The data showed degradation of the rifampicin at both storage conditions, though no significant change were observed at accelerated storage conditions. 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 2015 according to internationally accepted guidelines.

Study title: Bioequivalence study of single dose of Rifampicin capsules BP 150 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Rifadin® (rifampicin) capsules 150 mg marketed by Aventis Pharma Ltd., UK in healthy, adult, human subjects under fasting condition (study no. BEQ-1518-RIFA-2015).

The objective of the study was to compare the bioavailability of the stated Rifampicin BP 150 mg capsule manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Rifadin® (Aventis Pharma Ltd.) 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 treatments in a randomized fashion:

Treatment T:	Test – 1 capsule Rifampicin BP 150 mg (rifampicin 150 mg) Batch no. ERE3304
Treatment R:	Reference – 1 capsule Rifadin® (rifampicin 150 mg) Batch no. A3024

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 24 h 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 100 ng/ml for rifampicin.

The study was performed with 30 participants; data generated from a total of 29 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 tables:

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)	1.50 ± 0.57	1.66 ± 0.62	_	_
C_{max} (ng/mL)	2656 ± 819 (2546)	2865 ± 723 (2795)	91.1	85.3 – 97.3
AUC_{0-t} (ng·h/mL)	12203 ± 3899 (11488)	13221 ± 3929 (12685)	90.6	86.2 – 95.1
AUC_{0-inf} (ng·h/mL)	12539 ± 3901 --	13594 ± 3917 --	_	_

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 Rifampicin BP 150 mg capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Rifadin® (Aventis Pharma Ltd).

4. Summary of product safety and efficacy

[TB259 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, [TB259 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Rifadin® (Aventis Pharma Ltd) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB259 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 [TB259 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB259 trade name] has been shown to be bioequivalent with Rifadin® (Aventis Pharma Ltd).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB259 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 [TB259 trade name] was acceptable for the following indication: ' treatment of tuberculosis caused by *Mycobacterium tuberculosis*', and would allow inclusion of [TB259 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase II, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India in the list of prequalified medicinal products.