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	[TB158 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceutical Limited Plot No. 25-27, Survey No. 366 Premier Industrial Estate Kachigam, Daman – 396 210 (UT) India Oxalis Labs Village Theda, P.O Lodhimajra, Baddi, Distt. Solan, Himachal Pradesh, 174101, India
Active Pharmaceutical Ingredients (APIs)	rifampicin and isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02).
Therapeutic indication	[TB158 trade name] is indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

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

1. Introduction

[TB158 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.* [TB158 trade name] is not indicated for use in patients with clinically significant hypersensitivity to rifampicin, isoniazid or to any of the components contained in the formulation, and in patients with acute liver disease, icterus or severe liver impairment. Co-administration of [TB158 trade name] with voriconazole or any HIV protease inhibitor is contraindicated. It is recommended that therapy is given only on the advice of a tuberculosis experienced physician.

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 Ingredients (APIs)

Rifampicin and isoniazid
Isoniazid is a class 3/1 API and rifampicin a class 2 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*).
Both APIs are described in the Ph.Int., Ph.Eur. and the USP and are considered well-established.
The APIs, which are obtained from approved API manufacturers, are adequately controlled by their respective quality specifications which are pharmacopoeial based, with additional in-house specifications including residual solvents. The specifications for rifampicin include crystallinity and bulk density.
Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 24 months or more was approved for each of the APIs.

Other ingredients

Other ingredients used in the tablet core formulation include colloidal anhydrous silica, crospovidone, magnesium stearate, maize starch, povidone, shellac (bleached), sodium lauryl sulphate and sodium starch glycollate, which are all compendial. The film coating contains diethyl phthalate, hypromellose, Lake of Ponceau 4R, purified talc and titanium dioxide. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development
Rifampicin and isoniazid tablets are described in the Ph.Int. and Rifampicin and isoniazid capsules in the USP. The Ph.Int. monograph includes a test for rifampicin related substances.
Rifampicin/Isoniazid 150mg/75mg Tablets are brown to reddish brown, round biconvex, film-coated tablets, plain on both the sides. The tablets (500 or 1000) are packed in an LDPE bag, which is further packed in a triple laminated aluminium sachet. The sachet is packed in a round, white opaque HDPE jar, sealed with an aluminium tagger and closed with a polypropylene screw cap.
The pharmaceutical development was based on previous experience in this area and focussed on overcoming the inherent stability problems encountered with this 2-FDC tablet dosage form. According to literature rifampicin is not only prone to hydrolysis and oxidation, but it can also react (indirectly though acid degradation or directly) with isoniazid to form a hydrazone. This hydrazone is described in the Ph.Int. monograph of Rifampicin and isoniazid tablets. The manufacture involves the preparation of isoniazid granules through a wet process. The granules are blended with rifampicin, which is introduced extragranularly, and compressed. Finally, the tablets are film-coated.
Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three production scale batches demonstrated the consistency of the process and the quality of the product.

The specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product.

Stability testing
Stability studies have been performed at 30°C/70%RH as long-term conditions and at accelerated conditions. At the time of the prequalification, a shelf-life of 36 months has been allowed for the FPP when stored at a temperature not above 30°C.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2005 according to internationally accepted guidelines.

An open label, randomized, two-treatment, two sequence, two period, two way crossover, bioequivalence study of rifampicin and isoniazid in two fixed dose combination tablets (each containing rifampicin 150 mg and isoniazid 75 mg) manufactured by Macleods Pharmaceuticals Ltd. India comparing with Rifinah® - 300 tablets (each containing rifampicin 300 mg and isoniazid 150 mg) of Aventis Pharma (Pty) Ltd., Midrand, in healthy, adult, male, human subjects under fasting conditions (study no. BEQ-004-RI(F)-2005).

The objective of the study was to compare the bioavailability of the stated rifampicin/isoniazid 150 mg/75 mg fixed dose combination manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the fixed dose reference tablet (Rifinah-300, Aventis Pharma) 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 – 2 x Rifampicin/isoniazid 150mg/75mg tablet (rifampicin 150 mg/isoniazid 75 mg) Batch no. RC502.
Treatment R:	Reference – Rifinah-300® tablet (rifampicin 300 mg/isoniazid 150 mg) Batch no. A4204.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 14 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 and isoniazid were analyzed using a validated HPLC method with UV detection. The limit of quantification was stated to be about 0.25 µg/ml for rifampicin and 0.10 µg/ml for isoniazid.

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 rifampicin and isoniazid as well as statistical results are summarised in the following table:

Rifampicin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.48 ± 0.62	2.05 ± 0.60	-	-
C_{max} (µg/mL)	5.59 ± 0.86 (5.54)	5.64 ± 1.03 (5.53)	99.7	91.6 – 108.4
AUC_{0-t} (µg.h/mL)	31.20 ± 5.68 (30.66)	31.62 ± 6.89 (30.92)	99.1	92.8 – 105.9
AUC_{0-inf} (µg.h/mL)	33.64 ± 5.32 (33.23)	34.28 ± 6.86 (33.62)	98.8	93.4 – 104.6

* geometric mean

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.75 ± 0.44	0.93 ± 0.49	-	-
C_{max} (µg/mL)	3.68 ± 0.99 (3.56)	3.48 ± 1.04 (3.34)	106.3	95.2 – 118.6
AUC_{0-t} (µg.h/mL)	14.8 ± 6.7 (12.91)	14.4 ± 6.2 (12.73)	101.4	97.3 – 105.7
AUC_{0-inf} (µg.h/mL)	15.5 ± 6.9 (13.68)	15.1 ± 6.5 (13.32)	102.7	98.8 – 106.8

* geometric mean

Conclusions

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding rifampicin and isoniazid. Accordingly, the test product Rifampicin/isoniazid 150 mg/75 mg fixed dose combination tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Rifinah-300® (Aventis Pharma).

4. Summary of Product Safety and Efficacy

Background

[TB158 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator`s product. According to the submitted data on quality and bioavailability, [TB158 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Rifinah-300® tablet (rifampicin 300 mg/isoniazid 150 mg) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB158 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

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

2 x [TB158 trade name] has shown to be bioequivalent with Rifinah-300® tablet (rifampicin 300 mg/isoniazid 150 mg, Aventis Pharma).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB158 trade name] are considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics is taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [TB158 trade name] was acceptable for the following indication: **"treatment of tuberculosis caused by Mycobacterium tuberculosis"** and would allow inclusion of [TB158 trade name], manufactured at Macleods Pharmaceutical Limited, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396 210 (UT), India in the list of prequalified medicinal products.