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:	[TB231 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 Ingredients (APIs):	rifampicin and isoniazid
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02).
Therapeutic indication:	[TB231 trade name] is indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis* in adults weighing more than 50 kg.

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

1. Introduction

[TB231 trade name] is indicated for the continuation treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis* in adults weighing more than 50 kg.

[TB231 trade name] should be initiated by a healthcare provider experienced in the managemnet 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 Ingredients (APIs)

Rifampicin

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 pharmacopoeia 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.

Isoniazid

Based on scientific principles the WHO Prequalification Team – Medicines (PQTm) has identified isoniazid up to 300 mg oral dose as a BCS class 3 API. The API is thus regarded highly soluble in terms of the BCS.

Isoniazid is described in the Ph.Int, Ph.Eur and USP and is considered well-established in the WHO PQTm. The APIMF of isoniazid has been accepted through WHO's APIMF procedure. Isoniazid is manufactured from 4-cyanopyridine.

The API specifications, which are pharmacopoeia based, include tests for description, solubility, identification (m.p., IR), appearance and pH of solution, hydrazine and related substances (TLC), heavy metals, loss on drying, sulfated ash, assay (titrimetric/HPLC), related substances (HPLC), residual solvents, manganese and particle size (by sieve analysis).

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

Other ingredients used in the core tablet formulation include povidone, shellac (bleached), microcrystalline cellulose, sodium lauryl sulphate, croscarmellose sodium, crospovidone and calcium stearate, all being pharmacopoeial controlled. The film coat contains hypromellose, propylene glycol, diethyl phthalate, titanium dioxide, purified talc and colour Ponceau 4R Lake (cochineal Red A). BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a brown to reddish brown coloured, circular, biconvex, film coated tablet, having a break-line on one side and plain on the other side. The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablets are packed in amber-coloured PVC/PVDC-Al blisters or in a PET/Alu/LDPE triple laminated sachet contained in an HDPE bottle.

The pharmaceutical development was based on previous experience in this area and focused 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 through 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 manufacturing process takes into account the incompatibility of the APIs. It involves the preparation of isoniazid granules through a wet process. The granules are blended with rifampicin, which is introduced extra-granularly, and compressed. Finally the tablets are film-coated. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The product specifications include tests for description; identification of the APIs (HPLC, TLC) and colourants; average weight; disintegration time; loss on drying; dissolution (HPLC detection); uniformity of dosage units (by weight variation); related substances (HPLC); assay (HPLC); residual solvents; and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (blister packs) and at 30°C/75%RH (bottle packs) as long-term storage conditions and for 6 months at accelerated conditions The data showed little change and were well within the agreed specifications at long-term 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 2010 according to internationally accepted guidelines.

Study title: Bioequivalence study of two tablets as single dose fixed dose combination of Rifampicin 300 mg and Isoniazid 150 mg tablets (each tablet containing rifampicin 300 mg and isoniazid 150 mg) manufactured by Macleods Pharmaceuticals Ltd., India comparing with separate formulations of two capsules of Rifadin® 300 mg capsules (each capsule contains 300 mg of rifampicin) manufactured by Gruppo Lepetit SpA, Italy and marketed by Sanofi-Aventis, UK and three tablets of Isozid® 100 mg tablets (each tablet contains 100 mg of isoniazid) manufactured by Fatol Arzneimittel GmbH, Germany, in healthy, adult, human subjects under fasting condition. (study no. BEQ-488-RI(F)-2009).

The objective of the study was to compare the bioavailability of the stated Rifampicin/Isoniazid 300mg/150 mg FDC tablet manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the individual reference formulations Rifadin® (Sanofi-Aventis) and Isozid® (Fatol Arzneimittel GmbH) 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*
2 Rifampicin/Isoniazid 300mg/150 mg FDC tablets
(rifampicin 600 mg + isoniazid 300 mg)
Batch no. ERA6001A

Treatment R: *References*
2 capsules Rifadin® 300 mg
(rifampicin 600 mg)
Batch no. A9129
3 tablets Isozid® 100 mg
(isoniazid 300 mg)
Batch no. 002079

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 16 samples within 24 hours post dose) were taken during each study periodto 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. The limit of quantification was stated to be about 250 ng/mL for rifampicin and about 99 ng/mL for isoniazid.

The study was performed with 40 participants. Data generated from a total of 39 subjects were utilizedfor 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 tables:

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)	2.18 ± 0.84	1.96 ± 0.65	-	-
C_{max} (µg/mL)	13.7 ± 3.7 (13.2)	15.2 ± 2.5 (15.0)	88.3	81.3 – 95.9
AUC_{0-t} (µg.h/mL)	94.1 ± 23.1 (91.3)	103.2 ± 17.9 (101.4)	90.0	84.4 – 96.0
AUC_{0-inf} (µg.h/mL)	96.4 ± 23.3 (93.6)	105.6 ± 18.2 (103.8)	90.2	84.8 – 96.0

* 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)	0.48 ± 0.33	0.64 ± 0.29	-	-
C_{max} (µg/mL)	10.0 ± 3.2 (9.5)	9.0 ± 2.6 (8.6)	110.7	100.1 – 122.5
AUC_{0-t} (µg.h/mL)	36.1 ± 12.2 (33.3)	35.4 ± 12.0 (32.7)	101.8	98.9 – 104.8
AUC_{0-inf} (µg.h/mL)	37.0 ± 12.5 (34.1)	36.3 ± 12.2 (33.5)	101.8	99.0 – 104.7

* geometric mean

Conclusion

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 Rifampicin/Isoniazid 300mg/150 mg FDCtablet met the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore, bioequivalent to the individual references Rifadin® (Sanofi-Aventis) and Isozid® (Fatol Arzneimittel GmbH).

4. Summary of Product Safety and Efficacy

[TB231 trade name] has been shown to conform to the samerelevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability, [TB231 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference products Rifadin® (Sanofi-Aventis) and Isozid® (Fatol Arzneimittel GmbH) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into account. Reference is made 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 clinical performance of the product 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 [TB231 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB231 trade name] has shown to be bioequivalent with Rifadin®(Sanofi-Aventis) and Isozid® (Fatol Arzneimittel GmbH)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB231 trade name] are considered effective and safe to use when the guidance and restrictions 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 that the benefit risk profile of [TB231 trade name] was acceptable for the following indication: **"treatment of tuberculosis caused by Mycobacterium tuberculosis in adults weighing more than 50kg"** and has advised that quality, efficacy and safety of [TB231 trade name] allow inclusion of [TB231 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.