SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets*
Manufacturer of Prequalified Product:	Macleods Pharmaceutical Limited Plot No. 25-27, Survey No. 366 Premier Industrial Estate Kachigam, Daman – 396 210 (UT) India
Active Pharmaceutical Ingredients (APIs):	Rifampicin/Isoniazid/Ethambutol
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials, drugs for treatment of tuberculosis (J04AB02 for rifampicin, J04AC01 for isoniazid, J04AK02 for ethambutol).
Therapeutic indication:	Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is indicated for the initial treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis.*

* Trade names are not prequalified. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only

1. Introduction

Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is indicated for the initial treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis.*
Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is not indicated for use in patients with clinically significant hypersensitivity to rifampicin, isoniazid, and/or ethambutol or to any of the components contained in the formulation.
Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is not indicated for use in patients with acute liver disease, icterus or severe liver impairment, and in patients with optic neuritis. Co-administration of Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets with 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 according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredients (APIs)

Isoniazid is a class 3/1 API, ethambutol hydrochloride a class 3 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*).
All three 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 (compacted) include bulk density and particle size distribution.

Other ingredients

Other ingredients used in the tablet core formulation include colloidal anhydrous silica, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch and shellac (bleached), which are all compendial. The film-coat contains Color Ponceau 4R Lake, hypromellose, polyethylene glycol 400, purified talc and titanium dioxide. Magnesium stearate is of vegetable origin.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development
A monograph for Rifampicin, isoniazid and ethambutol hydrochloride tablets has been adopted by WHO's Expert Committee on Specifications for Pharmaceutical Preparations for addition to the Fourth edition of the Ph.Int., Second Supplement.
Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets are maroon coloured, circular, biconvex, film-coated tablets having plain surface on both the sides. The tablets (1,000) are 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 design strategy focussed on overcoming the inherent stability problems encountered with this 3-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. adopted monograph of Rifampicin, isoniazid and ethambutol hydrochloride tablets. The hydrazone formation may furthermore be enhanced by the presence of ethambutol hydrochloride, which is hygroscopic and provides a favourable acidic environment.

The manufacture involves two separate wet granulation processes, one for ethambutol hydrochloride and the other for isoniazid. The granulation of ethambutol hydrochloride in presence of shellac results in effectively coating the ethambutol hydrochloride. The dried 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 25°C/60%RH as long-term conditions and at accelerated conditions. At the time of the prequalification, a shelf-life of 24 months has been allowed for the FPP when stored at a temperature not above 25°C.

Conclusions

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 four tablets of fixed dose combination, each containing rifampicin 150 mg, isoniazid 75 mg and ethambutol 275 mg manufactured by Macleods Pharmaceuticals Ltd., India comparing with separate formulation of 4 capsules of Rimactane 150 (each containing rifampicin 150 mg) of Novartis South Africa (Pty) Ltd., 3 tablets of Isozid 100 mg (each containing isoniazid 100 mg) of Fatol Arzneimittel GmbH, Schiffweiler, Germany, 2 tablets of Myambutol 400 mg (each containing ethambutol dihydrochloride 400 mg) of RIEMSER Arzneimittel AG and 3 tablets of Myambutol 100 mg (each containing ethambutol hydrochloride 100 mg) of Patheon Inc. Toronto, Ontario in healthy, adult, male, human subjects under fasting conditions (study no. BEQ-024-RIE(F)-2005).

The objective of the study was to compare the bioavailability of the stated rifampicin/isoniazid/ethambutol 150mg/75mg/275mg fixed dose combination manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the individual reference formulations (Rimactane, Novartis; Isozid, Fatol Arzneimittel GmbH, and Myambutol, Patheon Inc./Riemser Arzneimittel) 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 – 4 x Rifampicin/isoniazid/ethambutol 150mg/75mg/275mg tablet (rifampicin 150mg/isoniazid 75mg/ethambutol 275mg)
Batch no. RN501.

Treatment R: Reference – 4 x Rimactane® capsule
(rifampicin 150 mg)
Batch no. 133966.
Reference – 3 x Isozid® tablet
(isoniazid 100 mg)
Batch no. 004114.
Reference – 2 x Myambutol® 400 mg + 3 x Myambutol 100 mg tablet
(ethambutol 400 mg and 100 mg)
Batch no. 303350 (400 mg) and GZ10 (100 mg).

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 15 samples within 48 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, and isoniazid were analyzed using a validated HPLC method and ethambutol concentrations were analyzed using a validated LC-MS method. The limit of quantification was stated to be about 0.25 µg/ml for rifampicin, 0.10 µg/ml for isoniazid and 0.050 µg/ml for ethambutol.

The study was performed with 28 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, isoniazid and ethambutol 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)	2.27 ± 0.47	1.89 ± 0.66	-	-
C_{max} (µg/ml)	11.33 ± 2.54 (11.05)	12.65 ± 2.61 (12.39)	89.2	81.7 – 97.3
AUC_{0-t} (µg.h/ml)	71.15 ± 20.51 (68.75)	79.59 ± 24.84 (76.29)	90.1	84.4 – 96.3
AUC_{0-inf} (µg.h/ml)	83.63 ± 21.44 (81.20)	92.34 ± 21.76 (89.97)	90.3	84.3 – 96.7

* 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)	1.18 ± 0.67	1.33 ± 0.73	-	-
C_{max} (µg/ml)	5.57 ± 1.56 (5.31)	5.45 ± 1.54 (5.16)	103.0	95.5 – 111.1
AUC_{0-t} (µg.h/ml)	29.20 ± 16.44 (23.96)	28.84 ± 16.09 (23.66)	101.2	97.6 – 104.9
AUC_{0-inf} (µg.h/ml)	30.07 ± 16.80 (24.77)	29.96 ± 16.56 (24.65)	100.5	97.2 – 103.9

* geometric mean

Ethambutol

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)	3.06 ± 0.66	2.94 ± 0.85	-	-
C_{max} (µg/ml)	2.09 ± 0.81 (1.96)	2.27 ± 1.04 (2.07)	94.9	82.5 – 109.1
AUC_{0-t} (µg.h/ml)	13.18 ± 3.82 (12.67)	13.60 ± 3.73 (13.14)	96.4	87.9 – 105.6
AUC_{0-inf} (µg.h/ml)	14.02 ± 3.89 (13.53)	14.41 ± 3.72 (13.99)	96.7	88.8 – 105.3

* 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, isoniazid and ethambutol. Accordingly, the test product Rifampicin/isoniazid/ethambutol 150mg/75mg/275 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, administered as individual formulations, Rimactane® (Novartis), Isozid (Fatol Arzneimittel GmbH), and Myambutol (Patheon Inc./Riemser Arzneimittel).

4. Summary of Product Safety and Efficacy

Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator products , administered as individual formulations, Rimactane® (Novartis), Isozid (Fatol Arzneimittel GmbH), and Myambutol (Patheon Inc./Riemser Arzneimittel).

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 consideration. Reference is made to the SPC (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

4 x Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets have shown to be bioequivalent to, administered as individual formulations, 4 x Rimactane® (rifampicin 150 mg capsules, Novartis), 3 x Isozid® (isoniazid 100 mg tablets, Fatol Arzneimittel GmbH), 2 x Myambutol® 400 mg (ethambutol 400 mg tablets, Patheon Inc./Riemser Arzneimittel) and 3 x Myambutol® 100 mg (ethambutol 100 mg tablets, Patheon Inc./Riemser Arzneimittel).

Efficacy and Safety

Regarding clinical efficacy and safety, Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are 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 Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets was acceptable for the following indication: **"initial treatment phase of tuberculosis caused by *Mycobacterium tuberculosis*"** and has advised to include Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets, 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.