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	[TB168 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
Active Pharmaceutical Ingredients (API)	Rifampicin/Isoniazid/ Pyrazinamide/Ethambutol
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM06)
Therapeutic indication	[TB168 trade name] is indicated for the initial treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB168 trade name] is indicated for the initial treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis.*

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 SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

Isoniazid and pyrazinamide are class 3/1 APIs, 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 four 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.

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.

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

Other ingredients

Other ingredients used in the tablet core formulation include calcium stearate, colloidal silicon dioxide, croscarmellose sodium, crospovidone, disodium edetate, maize starch, povidone, purified talc and shellac, which are all compendial. The first film-coat contains copovidone and purified talc, while the outer film-coat contains castor oil, colour sunset yellow, diethyl phthalate, hypromellose, magnesium stearate, purified talc and titanium dioxide. Magnesium stearate and calcium stearate are of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development

[TB168 trade name] are described in the Ph.Int. and USP. The Ph.Int. monograph includes a test for rifampicin related substances.

[TB168 trade name] are light buff coloured biconvex capsule shaped, film-coated tablets, plain on both sides. The tablets (500 or 1,000) are packed in a transparent LDPE bag, packed in a triple laminated aluminium sachet which is further packed in an HDPE container along with a leaflet. Each container is sealed with an aluminium tagger and closed with a screw cap.

The design strategy focussed on overcoming the inherent stability problems encountered with this 4-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, isoniazid, pyrazinamide 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 and pyrazinamide. 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. The tablets are seal-coated and then 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 pharmacopoeial based 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.

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, randomised, two treatment, two sequence, two period, two way, crossover bioequivalence study of four fixed combination tablets, each containing rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400mg, ethambutol 275 mg manufactured by Macleods Pharmaceutical Ltd, India comparing with separate formulation of 4 capsules of Rimactane (150 mg rifanmpicin) of Novartis South Africa (Pty) Ltd, 3 tablets of Isozid 100 mg (isoniazid 100 mg) of Fatol Arzneimittel GmbH,

Schiffweiler, Germany, 3 tablets of Rolab-Pyrazinamide 500 (pyrazinamide 500 mg) of Rolab Pvt Ltd. (Novartis South Africa), 2 tablets of Myambutol 400 mg (ethambutol hydrochloride 100 mg) of Patheon Inc Toronto, Ontario in healthy adult male human subjects under fasting conditions (study no. BEQ-005-RIPE(F)-2005).

The objective of the study was to compare the bioavailability of the stated [TB168 trade name] manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with a comparable dose of the individual reference formulations (Rimactane, Novartis; Isozid, Fatol Arzneimittel GmbH; Pyrazinamide 500, Rolab Pvt Ltd/Novartis, 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 [TB168 trade name] (rifampicin 150mg/isoniazid 75mg/pyrazinamide 400mg/ethambutol 275mg) Batch no. RF501.
Treatment R:	Reference – 4 x Rimactane® capsule (rifampicin 150 mg) Batch no. 501459. Reference – 3 x Isozid® tablet (isoniazid 100 mg) Batch no. 004114. Reference – 3 x Pyrazinamide 500® tablet (pyrazinamide 500 mg) Batch no. 135097. 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 72 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, isoniazid and pyrazinamide were analyzed using a validated HPLC method with UV detection, 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, 0.79 µg/ml for pyrazinamide and 0.050 µg/ml for ethambutol.

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, isoniazid, pyrazinamide 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)	1.92 ± 0.62	2.31 ± 0.98	-	-
C_{max} (µg/ml)	9.83 ± 1.70 (9.69)	10.58 ± 2.70 (10.23)	94.7	87.1 – 102.9
AUC_{0-t} (µg.h/ml)	65.07 ± 13.35 (63.89)	71.63 ± 20.44 (69.19)	92.3	87.2 – 97.8
AUC_{0-inf} (µg.h/ml)	78.17 ± 12.77 (77.23)	81.90 ± 18.73 (80.09)	96.4	92.5 – 100.5

* 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)	1.37 ± 0.62	1.54 ± 0.61	-	-
C_{max} (µg/ml)	5.69 ± 1.56 (5.48)	5.43 ± 1.31 (5.28)	103.8	97.8 – 110.2
AUC_{0-t} (µg.h/ml)	32.26 ± 15.19 (28.08)	32.25 ± 15.22 (28.07)	100.0	96.8 – 103.4
AUC_{0-inf} (µg.h/ml)	33.21 ± 15.53 (28.98)	33.34 ± 15.61 (29.06)	99.7	96.9 – 102.6

* Geometric mean

Pyrazinamide

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)	1.98 ± 0.63	2.10 ± 0.79	-	-
C_{max} (µg/ml)	31.40 ± 2.55 (31.31)	31.17 ± 3.53 (30.9)	101.0	98.4 – 103.8
AUC_{0-t} (µg.h/ml)	515.4 ± 61.8 (511.9)	516.2 ± 83.5 (510.0)	100.4	97.8 – 103.3
AUC_{0-inf} (µg.h/ml)	541.9 ± 68.9 (537.8)	542.0 ± 93.9 (534.8)	100.6	98.0 – 103.2

* Geometric mean; # values are corrected for the difference in the administered dose

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)	3.02 ± 0.58	2.65 ± 0.68	-	-
C_{max} (µg/ml)	3.27 ± 1.09 (3.12)	2.99 ± 0.71 (2.92)	106.9	94.5 – 121.0
AUC_{0-t} (µg.h/ml)	19.34 ± 3.35 (19.05)	18.67 ± 3.55 (18.35)	103.8	98.5 – 109.3
AUC_{0-inf} (µg.h/ml)	20.20 ± 3.45 (19.89)	19.59 ± 3.59 (19.28)	103.2	98.0 – 108.7

* 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, isoniazid, pyrazinamide and ethambutol. Accordingly, the test product [TB168 trade name] 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), Pyrazinamide 500 (Rolab Pvt. Ltd/Novartis) and Myambutol (Patheon Inc./Riemser Arzneimittel).

4. Summary of product safety and efficacy

[TB168 trade name] 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), Pyrazinamide 500 (Rolab Pvt. Ltd/Novartis) 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 acceptable when used in accordance with the conditions defined in the SmPC. 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 [TB168 trade name] 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), 3 x Pyrazinamide 500® (pyrazinamide 500 mg tablets, Rolab Pvt. Ltd/Novartis), 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, [TB168 trade name] 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 [TB168 trade name] was acceptable for the following indication: **"initial treatment phase of tuberculosis caused by *Mycobacterium tuberculosis*"** and has advised to include [TB168 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.