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	[TB068 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited A-28/1, M.I.D.C. Industrial Area Chikalthana Aurangabad 431210 India
Active Pharmaceutical Ingredients (APIs)	Rifampicin and isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (rifampicin and isoniazid: J04AM02)
Therapeutic indication	[TB068 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB068 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.*
[TB068 trade name] should be initiated by a health care provider experienced in the management of tuberculosis.

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

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 (IR), crystallinity, pH, loss on drying, related substances (HPLC), assay (HPLC), heavy metals, sulfated ash, tapped 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.

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

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

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, m.p.), appearance and pH of solution, hydrazine and related substances (TLC), loss on drying, heavy metals, sulfated ash, assay (titrimetric/HPLC), related substances (HPLC), residual solvents 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 microcrystalline cellulose, crospovidone, pregelatinized starch, ascorbic acid, colloidal silicon dioxide and magnesium stearate. The film coat contains hypromellose, polyethylene glycol, talc, titanium dioxide, colour iron oxide red and simethicone emulsion (30%). The excipients are compendial. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a brick-red coloured, capsule shaped, biconvex, film coated tablet with 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 the tablet into equal doses. The tablets are packed in PVC/PVDC-Al blisters or in a propylene bag inside an HDPE bottle, together with a bag containing 1 gram silica gel as desiccant protecting rifampicin from hydrolysis.

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. In the selected process the APIs are partially protected from interaction by means of separate granulation steps. Ascorbic acid is included to protect rifampicin from oxidation.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented demonstrated the consistency of the process and the quality of the product.

Specifications

The product specifications include tests for tablet description, identification of the APIs (HPLC) and colourants, average weight, uniformity of weight, dissolution (HPLC detection), assay (HPLC), related substances (HPLC), loss on drying and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 25°C/60%RH, 30°C/65%RH and 30°C/75%RH as long-term storage conditions and for 6 months at 40°C/75%RH as accelerated conditions. The data showed slight degradation for rifampicin though all parameters were well within the agreed limits in all pack types. 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: A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, pivotal bioequivalence study of Test Product [four tablets of fixed dose combination of Rifampin 150 mg and Isoniazid 75 mg] of Lupin Limited, India with Reference Product [two capsules of Rifamate® (containing rifampin 300 mg with isoniazid 150 mg)] of Sanofi Aventis, US, LLC in 36 healthy human adult male subjects, under fasting conditions. (study no. 130-10).

The objective of the study was to compare the bioavailability of the stated Rifampin/Isoniazid 150/75 mg FDC tablet manufactured by/for Lupin Limited, India (test drug) with the reference formulation Rifamate® (Sanofi Aventis) 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 tablets Rifampin/Isoniazid 150/75 mg (rifampicin 600 mg + isoniazid 300 mg) Batch no. GA08086
Treatment R:	Reference – 2 tablets Rifamate® (rifampicin 600 mg + isoniazid 300 mg) Batch no. 3081598

An 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 LC-MS/MS method. The limit of quantification was stated to be about 100 ng/ml for rifampicin and 112 ng/ml for isoniazid.

The study was performed with 36 participants; data generated from a total of 32 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 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)	3.60 ± 0.93	3.55 ± 0.89	-	-
C_{max} (ng/ml)	12232 ± 3129 (11866)	12515 ± 3054 (12155)	97.6	92.2 – 103.4
AUC_{0-t} (ng.h/ml)	89786 ± 22019 (87457)	89583 ± 19134 (87471)	100.0	94.7 – 105.5
AUC_{0-inf} (ng.h/ml)	91952 ± 22974 (89462)	91637 ± 19977 (89457)	100.0	94.9 – 105.4

* geometric mean

Isoniazid

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)	0.68 ± 0.55	0.91 ± 0.63	-	-
C_{max} (ng/ml)	4649 ± 1713	4422 ± 1824	105.9	92.0 – 122.0

	(4313)	(4073)		
AUC_{0-t} (ng.h/ml)	14547 ± 7408 (12523)	14331 ± 6693 (12456)	100.5	94.0 – 107.6
AUC_{0-inf} (ng.h/ml)	15719 ± 7973 (13539)	15440 ± 7223 (13425)	100.9	94.6 – 107.5

* 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 FDC tablet Rifampin/Isoniazid 150/75 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the individual reference Rifamate® (Sanofi Aventis).

4. Summary of product safety and efficacy

[TB068 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability [TB068 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Rifamate® (Sanofi Aventis) 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 as stated in the Summary of Product Characteristics are considered. 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 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 [TB068 trade name] is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

[TB068 trade name] has shown to be bioequivalent with Rifamate® (Sanofi Aventis, US, LLC).

Efficacy and Safety

Regarding clinical efficacy and safety [TB068 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [TB068 trade name] was acceptable for the following indication: **"treatment of tuberculosis caused by Mycobacterium tuberculosis"** and has advised that the quality, efficacy and safety of [TB068 trade name] are acceptable to allow inclusion of [TB068 trade name] , manufactured at Lupin Limited, A-28/1, M.I.D.C. Industrial Area, Chikalthana, Aurangabad 431210, India in the list of prequalified medicinal products.