

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:	[TB199 trade name]*
Manufacturer of Prequalified Product:	Lupin Limited A-28/1, MIDC Industrial area Chikalthana 431210 Aurangabad India
Active Pharmaceutical Ingredients (APIs):	Ethambutol hydrochloride/ Isoniazid/ Rifampicin
Pharmaco-therapeutic group (ATC Code):	Combinations of drugs for treatment of tuberculosis: rifampicin, ethambutol and isoniazid (J04AM07)
Therapeutic indication:	[TB199 trade name] is indicated for the initial treatment phase of tuberculosis, caused by <i>Mycobacterium tuberculosis</i> .

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

Introduction

[TB199 trade name] is indicated for the initial treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis*, as detailed in the summary of product characteristics (SmPC).

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredients (APIs)

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified ethambutol (up to 400 mg oral dose) and isoniazid (up to 300 mg oral dose) as BCS class 3 APIs. These two APIs are thus BCS highly soluble.

Ethambutol hydrochloride

Ethambutol hydrochloride API is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO Prequalification Programme.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification, assay, heavy metals, related substances (HPLC and TLC), specific optical rotation, loss on drying, residual solvents, colour, sulfated ash, pH and microbiological examination. 1,2-Dichloroethane is controlled at a limit of 5 ppm.

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

Isoniazid (reference number WHOAPI-086) has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that isoniazid, used in the manufacture of Ethambutol Hydrochloride/Isoniazid/Rifampicin 275mg/75mg/150mg Tablets, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Rifampicin

Rifampicin is described in the Ph.Int., Ph.Eur. and the USP and is considered well-established in the WHO Prequalification Programme. The API, accepted through WHO's APIMF procedure, is in non-compacted form.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification, crystallinity, pH, loss on drying, related substances (HPLC), assay, heavy metals, sulfated ash, residual solvents, tapped density, particle size distribution and microbiological examination.

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 in the core tablet formulation include ascorbic acid, colloidal silicon dioxide, crospovidone, gelatin, magnesium stearate, microcrystalline cellulose and pregelatinised starch. BSE/TSE-free certification has been provided for magnesium stearate and gelatin. The film coating contains iron oxide red, lecithin, polyvinyl alcohol, talc, titanium oxide and xanthan gum.

Finished Pharmaceutical Product (FPP)

A monograph for Rifampicin, isoniazid and ethambutol hydrochloride tablets has been included in the Ph.Int.

Pharmaceutical development

The pharmaceutical product is a brown-coloured, capsule-shaped, biconvex, film-coated tablet, plain on both sides. The tablets are packed in PVC/PVDC-aluminium blister cards and in polypropylene bag, which is placed in an HDPE container along with silica gel bag and polyurethane foam, the container being sealed with an aluminium tagger seal.

The development of the final composition of the tablets has been described. The selection of the excipients was based on prior knowledge of TB fixed-dose combination tablets. Ascorbic acid has been included to protect rifampicin from oxidation. According to the literature, the degradation of rifampicin is enhanced by the presence of isoniazid, and ethambutol HCl provides the acidic environment. In the selected process the APIs are partially protected from API-API interactions by means of separate granulation steps. Moisture pick-up studies showed that the product should be protected from high humidity.

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.

Specifications

The product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorants, average and uniformity of weight, tablet dimensions, loss on drying, uniformity of dosage units (by content uniformity), dissolution, related substances (HPLC and TLC), assay (HPLC) and microbiological examination.

Stability testing

Stability studies have been performed at 25°C/60%RH and 30°C/65%RH as long-term conditions and for six months at accelerated conditions in both packaging configurations intended for marketing of the product. The data showed a decrease in rifampicin assay value with a concomitant increase in rifampicin related degradation products, though remaining within agreed limits. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

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.

A randomized, open label, balanced, single center, two treatment, two period, two sequence, single dose, crossover oral bioequivalence study of test product (four tablets of fixed dose combination of rifampin 150 mg, isoniazid 75 mg and ethambutol hydrochloride 275 mg) manufactured by Lupin Limited, India with that of reference product (two capsules of Rifamate® [containing rifampin 300 mg and isoniazid 150 mg] of Sanofi Aventis), USA and three tablets of Myambutol® (ethambutol hydrochloride 400 mg of Riemser Arzneimittel, Germany) in healthy human adult male subjects, under fasting conditions (study no. S-10-103).

The objective of the study was to compare the rate and extent of absorption of the stated fixed dose combination tablet rifampicin/isoniazid/ethambutol Hydrochloride 150 mg /75 mg/ 275 mg with the individual reference formulations (Rifamate® [Sanofi Aventis] and Myambutol® [Riemser Arzneimittel]). The comparison was performed as a randomized, two-treatment, two-period, single-dose, crossover study in healthy male subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

Treatment T: Test – 4 tablets rifampicin/isoniazid/ethambutol hydrochloride
150 mg/ 75 mg/ 275 mg
(rifampicin 600 mg + isoniazid 300 mg + ethambutol 1100 mg)
Batch no. GC08020

Treatment R: Reference – 2 capsules Rifamate[®]
(rifampicin 600 mg + isoniazid 300 mg)
Batch no. 3081598

Reference – 3 tablets Myambutol[®]
(ethambutol 1200 mg)
Batch no. 005690

A 14-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 48 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC_{inf} , AUC_{0-t} , C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for rifampicin, isoniazid and ethambutol in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 59 ng/mL for rifampicin, 406 ng/mL for isoniazid and 51 ng/mL for ethambutol.

The study was performed with 36 participants, data generated from a total of 33 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence. The difference in the administered dose of ethambutol was taken into account in the analysis.

Arithmetic means (\pm sd), geometric means (AUC , C_{max}) for rifampicin, isoniazid and ethambutol as well as statistical results are summarised in the following table:

Rifampicin

Pharmacokinetic Parameter	Test formulation (T) Arithmetic mean (\pm SD)	Reference (R) Arithmetic mean (\pm SD)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.34 \pm 0.90	1.92 \pm 0.80	-	-
C_{max} (μ g/mL)	9.65 \pm 2.03 (9.48)*	10.04 \pm 1.88 (9.84)*	96.4	91.6 – 101.4
AUC_{0-t} (μ g.h/mL)	68.0 \pm 18.7 (66.1)*	71.3 \pm 18.1 (69.0)*	95.9	89.5 – 102.7
AUC_{0-inf} (μ g.h/mL)	70.0 \pm 20.0 (68.0)*	72.9 \pm 19.0 (70.5)*	96.4	89.9 – 103.4

* geom. mean

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) Arithmetic mean (\pm SD)	Reference (R) Arithmetic mean (\pm SD)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.27 \pm 0.78	1.03 \pm 0.76	-	-
C_{max} (μ g/mL)	7.14 \pm 1.71 (6.91)*	8.16 \pm 2.09 (7.91)*	87.4	81.9 – 93.4
AUC_{0-t} (μ g.h/mL)	34.8 \pm 11.8 (32.8)*	36.2 \pm 11.8 (34.2)*	95.8	93.4 – 98.4
AUC_{0-inf} (μ g.h/mL)	39.8 \pm 14.3 (37.4)*	41.1 \pm 13.9 (38.8)*	96.4	93.8 – 99.1

* geom. mean

Ethambutol

Pharmacokinetic Parameter	Test formulation (T) Arithmetic mean (\pm SD)	Reference (R) Arithmetic. mean (\pm SD)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	3.08 \pm 1.03	2.91 \pm 1.04	-	-
C_{max} (μ g/mL)	3.02 \pm 1.02 (2.85)*	2.98 \pm 1.01 (2.81)*	101.3	90.6 – 113.2
AUC _{0-t} (μ g.h/mL)	15.7 \pm 3.4 (15.3)*	16.3 \pm 4.1 (15.8)*	97.0	90.3 – 104.3
AUC _{0-inf} (μ g.h/mL)	17.5 \pm 3.7 (17.0)*	18.1 \pm 4.4 (17.6)*	96.7	90.4 – 103.6

* geom. mean

Conclusion

The results of the study show that the pre-set acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding rifampicin, isoniazid and ethambutol. Accordingly, the test fixed dose combination Rifampicin/Isoniazid/Ethambutol Hydrochloride 150/75/275 mg tablets meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore, bioequivalent to the individual reference formulations (Rifamate® [Sanofi Aventis] and Myambutol® [Riemser Arzneimittel]).

4. Summary of Product Safety and Efficacy

[TB199 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, (two capsules of Rifamate® (containing rifampin 300 mg and isoniazid 150 mg) of Sanofi Aventis, USA and three tablets of Myambutol® (ethambutol hydrochloride) 400 mg of Riemser Arzneimittel, Germany).

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

[TB199 trade name] was shown to be bioequivalent to, administered as individual formulations, two capsules of Rifamate® (containing rifampicin 300 mg and isoniazid 150 mg) of Sanofi Aventis, USA and three tablets of Myambutol® (ethambutol hydrochloride) 400 mg of Riemser Arzneimittel, Germany).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB199 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 [TB199 trade name] was acceptable for the following indication: **“initial treatment phase of tuberculosis caused by *Mycobacterium***

tuberculosis” and has advised to include [TB199 trade name], manufactured at Lupin Limited, A-28/1, MIDC Industrial area, Chikalthana, 431210 Aurangabad, India, in the list of prequalified medicinal products.