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	[TB070 name][*]
Manufacturer of Prequalified Product	Lupin Limited A-28/1, MIDC Industrial Area Chikalthana Aurangabad 431 210 India Lupin Limited EPIP, SIDCO Industrial Complex Kartholi, Bari Brahmana Jammu & Kashmir 181133 India Tel: +91-1923 220046/220672/22076 Fax: +91-1795 661452
Active Pharmaceutical Ingredients (APIs)	Ethambutol hydrochloride, isoniazid, pyrazinamide and rifampicin
Pharmaco-therapeutic group (ATC Code)	J04AM06; Rifampicin, pyrazinamide, ethambutol and isoniazid
Therapeutic indication	Initial treatment of tuberculosis due to Mycobacterium tuberculosis.

1. Introduction

[TB070 trade name] is indicated for the initial treatment of tuberculosis due to *Mycobacterium tuberculosis.*

[TB070 trade name] should be prescribed by a health care provider experienced in the management 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)

Ethambutol hydrochloride, isoniazid, pyrazinamide and rifampicin have been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [TB070 trade name] are of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). 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 inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, crospovidone, pregelatinized starch, ascorbic acid, gelatin, colloidal silicon dioxide and magnesium stearate. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol- part hydrolyzed,

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

talc, titanium dioxide, iron oxide red, lecithin (soya) and xanthan gum. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a brown coloured, capsule shaped, film-coated tablet with a scoreline on one side and plain on the other side. The score-line is not intended to be functional (for ease of swallowing). The tablets are packaged in either Alu/PVC/PVDC blisters, Alu/Alu blisters or HDPE bottles.

The objective of the product development was to obtain a stable and robust formulation, bioequivalent to the individual WHO recommended comparator products; Rifamate® (rifampin 300 mg and isoniazid 150 mg) capsules, Pyrafat® (pyrazinamide 500 mg) tablets, Myambutol® (ethambutol hydrochloride 400 mg) tablets. Data on development pharmaceutics have been provided to justify the excipients and concentrations used for the finished pharmaceutical product. Wet granulation manufacturing process was selected to manufacture the finished pharmaceutical product There are two granulation steps: The rifampicin part and rest of the formulation are blended and granulated separately. They are then charged together, lubricated then compressed. Coating is then applied. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification of APIs (HPLC) and colourants, average weight, loss on drying, dissolution (HPLC detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC), residual solvents (GC), limit of 1-methyl-4-nitrosopiperazine (LC-MS/MS ≤ 2.5ppm) and microbial limits.

Stability testing

Stability studies have been performed at 25°C/60%RH as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the Alu/PVC/PVDC blister and HDPE bottle packaging proposed for marketing of the product. Additional stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition in the Alu/Alu blister packaging proposed for marketing of the product. The data provided indicates that the product is stable at both storage conditions. 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 2017 according to internationally accepted guidelines:

An open label, balanced, randomized, single dose, two-treatment, two-sequence, two-period crossover bioequivalence study comparing Akurit 4 (rifampin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol hydrochloride 275 mg) tablets (1 x 04 tablets) of Lupin Limited, India with Reference product as separate formulations of Rifamate® (rifampin 300 mg and isoniazid 150 mg) capsules (1 x 02 capsules) of Sanofi Aventis, USA, Pyrafat® (pyrazinamide 500 mg) tablets (1 x 03 tablets) of Riemser Arzneimittel AG, Germany, Myambutol® (ethambutol hydrochloride 400 mg) tablets (1 x 03 tablets) of Riemser Arzneimittel, Germany, in healthy, adult, human male subjects under fasting conditions (study no. 650-17).

The objective of the study was to compare the bioavailability of the stated Ethambutol/Isoniazid/Pyrazinamide/Rifampin 275mg/75mg/400mg/150mg FDC tablet manufactured by/for Lupin Limited, India (test drug) with the reference formulations Myambutol® (Riemser Arzneimittel AG), Rifamate® (Sanofi Aventis) and Pyrafat® (Riemser Arzneimittel AG) 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 Ethambutol/Isoniazid/Pyrazinamide/Rifampin 275mg/75mg/400mg/150mg
(ethambutol 1100 mg + isoniazid 300 mg + pyrazinamide 1600mg + rifampin 600 mg)
Batch no. A702319.

Treatment R: Reference
– 3 tablets Myambutol®
(ethambutol 1200 mg)
Batch no. D851
– 2 capsules Rifamate®
(isoniazid 300 mg + rifampin 600 mg)
Batch no. 3145489.
– 3 tablets Pyrafat®
(pyrazinamide 1500 mg)
Batch no. 034085-A.

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 22 samples within 48h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ethambutol, isoniazid, pyrazinamide and rifampin were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 30 ng/ml for ethambutol, 60 ng/ml for isoniazid, 301 ng/ml for pyrazinamide and 26 ng/ml for rifampin.

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 ethambutol, isoniazid, pyrazinamide and rifampin as well as statistical results are summarised in the following tables:

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)	3.59 ± 1.07	3.36 ± 1.07	-	-
C_{max} (ng/ml)	3584 ± 1413 (3597)	3820 ± 1439 (3479)	103.4	94.5 – 113.2
AUC_{0-t} (ng.h/ml)	18335 ± 5006 (19156)	20046 ± 6400 (18907)	101.3	95.4 – 107.7
AUC_{0-inf} (ng.h/ml)	20499 ± 5281 --	22524 ± 6930 --	-	-

* geometric mean (dose normalised)

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)	0.96 ± 0.46	0.77 ± 0.57	-	-
C_{max} (ng/ml)	7957 ± 3571 (7176)	7784 ± 2683 (7340)	97.8	83.3 – 114.7

AUC_{0-t} (ng.h/ml)	35089 ± 16237 (29826)	34080 ± 15446 (29632)	100.7	95.6 – 106.0
AUC_{0-inf} (ng.h/ml)	36215 ± 16918 --	34962 ± 15937 --	-	-

* 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)	1.87 ± 1.31	1.42 ± 1.12	-	-
C_{max} (µg/ml)	43.2 ± 8.2 (39.9)	43.4 ± 8.6 (42.5)	94.0	88.7 – 99.5
AUC_{0-t} (µg.h/ml)	614 ± 105 (569)	558 ± 115 (548)	103.9	99.9 – 108.0
AUC_{0-inf} (µg.h/ml)	639 ± 124 --	589 ± 130 --	-	-

* geometric mean (dose normalised)

Rifampin

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)	2.35 ± 0.88	1.80 ± 0.70	-	-
C_{max} (µg/ml)	9.92 ± 2.32 (9.65)	11.4 ± 2.58 (11.1)	86.7	81.3 – 92.4
AUC_{0-t} (µg.h/ml)	71.3 ± 14.1 (69.6)	80.2 ± 15.5 (78.8)	88.4	84.8 – 92.1
AUC_{0-inf} (µg.h/ml)	72.4 ± 15.2 --	81.0 ± 15.9 --	-	-

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ethambutol, isoniazid, pyrazinamide and rifampin. Accordingly, the test Ethambutol/Isoniazid/Pyrazinamide/Rifampin 275mg/75mg/400mg/150mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Myambutol® (Riemser Arzneimittel AG), Rifamate® (Sanofi Aventis) and Pyrafat® (Riemser Arzneimittel AG).

4. Summary of Product Safety and Efficacy

[TB070 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 [TB070 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference products Myambutol® (Riemser Arzneimittel AG), Rifamate® (Sanofi Aventis) and Pyrafat® (Riemser Arzneimittel AG) 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 [TB070 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB070 trade name] has shown to be bioequivalent to the reference formulations Myambutol® (Riemser Arzneimittel AG), Rifamate® (Sanofi Aventis) and Pyrafat® (Riemser Arzneimittel AG).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB070 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 and bioequivalence the team of assessors considered that the benefit-risk profile of [TB070 trade name] was acceptable for the following indication: "the initial treatment of tuberculosis due to Mycobacterium tuberculosis" and has advised that the quality, efficacy and safety of [TB070 trade name] are acceptable to allow inclusion of [TB070 trade name], manufactured at Lupin Limited, A-28/1, MIDC Industrial Area, Chikalthana, Aurangabad-431 210, India and Lupin Limited, EPIP, SIDCO Industrial Complex, Kartholi, Bari Brahmana, Jammu & Kashmir-181133, India in the list of prequalified medicinal products.