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:	[TB360trade name][*]
Manufacturer of Prequalified Product:	Lupin Limited A-28/1, MIDC Area, Chikalthana Aurangabad 431210 India
Active Pharmaceutical Ingredient (API):	Isoniazid and Rifampicin
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials, combinations of drugs for treatment of tuberculosis (rifampicin and isoniazid: J04AM02)
Therapeutic indication:	[TB360 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by *Mycobacterium tuberculosis.* It is also indicated in combination with other anti-tuberculosis agents for the prevention of tuberculosis caused by *Mycobacterium tuberculosis*. Isoniazid/Rifampicin 50 mg/75 mg Dispersible Tablets is indicated for the continuation phase of treatment of tuberculosis, caused by Mycobacterium tuberculosis in children weighing less than 25 kg

1. Introduction

[TB360 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by *Mycobacterium tuberculosis.*

It is also indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis*.

[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[TB360 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 Ingredients (APIs)

Isoniazid 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

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

pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [TB360 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, colloidal silicon dioxide, pregelatinized starch, ascorbic acid, magnesium stearate, colour ponceau 4R (cochineal red A), saccharin sodium, raspberry flavour, strawberry flavour and aspartame. The commercially sourced proprietary colour ponceau 4R (cochineal red A), raspberry flavour and strawberry flavour are controlled by acceptable specifications. None of the excipients are of animal or human origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a brick red coloured, flat faced beveled edged, mottled, circular uncoated tablet, plain on both sides and with a characteristic flavour. The tablets are packaged in either plain aluminium-aluminium strips or plain aluminium/cold forming aluminium-aluminium blister cards, selected to protect the product from moisture and light.

The development of the final composition of the tablets has been described. The objective was to obtain a stable and robust dispersible tablet, bioequivalent to the individual WHO recommended comparator products, Rifampicine 150mg capsules and Isozid 100mg tablets. The selection of the excipients was based on prior knowledge of TB fixed-dose combination tablets, literature information and compatibility studies. The flavouring agents and sweeteners were used to improve the taste of the dispersible tablets. In the selected process, the APIs are protected from API-API interactions by means of separate wet granulation steps. The moisture content of the blend for compression has been identified as an intermediate CQA for stability reasons. Formulation trials were performed to optimise the concentration of excipients and process parameters. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), average weight, friability, uniformity of dosage units (by content uniformity), water content (KF), disintegration time (not more than 3 minutes), fineness of dispersion, dissolution, assay (HPLC), related substances (HPLC), limit of nitrosamine (GC/MS) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging intended for marketing of the product. The data showed with time a slight decrease in rifampicin assay value with a concomitant slight increase in rifampicin related degradation products, though remaining within agreed limits, at both storage conditions. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2018 according to internationally accepted guidelines.

Study title: A randomized, open label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study comparing fixed dose combination of Rifampicin 75 mg and Isoniazid 50 mg dispersible tablets (2 tablets) of Lupin Limited, India with Rifampicine capsules 150 mg (1 capsule) of Sandoz BV Veluwezoom 22, 1327 AH Almere The Netherlands and Isozid (isoniazid) tablets 100 mg (1 tablet) of RlEMSER Pharma GmbH, Ander Wiek 7 17493 Greifswald-Insel Riems in healthy, adult, human male subjects under fasting conditions (study no. NCS-585-17-CS).

The objective of the study was to compare the bioavailability of the stated Isoniazid/Rifampicin 50/75 mg FDC dispersible tablet manufactured for/by Lupin Ltd., India (test drug) with the reference formulations Isozid® 100 mg (Riemser Pharma GmbH) and Rifampicine 150 mg capsule (Sandoz BV) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: Test – 2 tablets Isoniazid/Rifampicin 50/75 mg
(isoniazid 100 mg + rifampicin 150 mg)
Batch no. : A890002

Treatment R: References
– 1 tablet Isozid® 100 mg
(isoniazid 100 mg)
Batch no. 002114
– 1 capsule Rifampicine 150 mg
(rifampicin 150 mg)
Batch no. HE1983

The test formulation was administered with 240 mL of water. A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 17 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 isoniazid and rifampicin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 30 ng/ml for isoniazid and about 26 ng/ml for rifampicin.

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 isoniazid and rifampicin as well as statistical results are summarised in the following tables:

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)	0.56 ± 0.21	0.84 ± 0.43	-	-
C_{max} (ng/mL)	2175 ± 604 (2097)	2145 ± 715 (2052)	102.2	93.6 – 111.6
AUC_{0-t} (ng.h/mL)	8007 ± 3813 (7129)	7833 ± 3727 (7001)	101.8	99.9 – 103.8
AUC_{0-inf} (ng.h/mL)	8825 ± 4393 --	8643 ± 4312 --	-	-

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)	1.19 ± 0.53	1.84 ± 0.88	-	-
C_{max} (µg/mL)	2.16 ± 0.54 (2.10)	2.35 ± 0.49 (2.32)	90.5	84.7 – 96.7
AUC_{0-t} (µg.h/mL)	11.60 ± 3.09 (11.15)	12.34 ± 3.04 (12.05)	92.5	88.8 – 96.4
AUC_{0-inf} (µg.h/mL)	11.87 ± 3.16 --	12.62 ± 3.09 --	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding isoniazid and rifampicin. Accordingly, the test Isoniazid/Rifampicin 50/75 mg FDC dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the references Isozid® 100 mg (Riemser Pharma GmbH) and Rifampicine 150 mg capsule (Sandoz BV).

4. Summary of Product Safety and Efficacy

[TB360 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator products. [TB360 trade name] fulfilled all criteria demonstrating bioequivalence with the reference products used namely, Isozid® 100 mg (Riemser Pharma GmbH) and Rifampicine 150 mg capsule (Sandoz BV).

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. 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 [TB360 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB360 trade name] is bioequivalent to Isozid® 100 mg (Riemser Pharma GmbH) and Rifampicine 150 mg capsule (Sandoz BV).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB360 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 [TB360 trade name] was acceptable for the following indication: "for the treatment and prevention of tuberculosis", and has advised that the quality, efficacy and safety of [TB360 trade name] allow inclusion of [TB360 trade name], manufactured at Lupin Limited, A-28/1, MIDC Area, Chikalthana, Aurangabad 431210, India in the list of prequalified medicinal products.