SCIENTIFIC DISCUSSION SUPPLEMENT

Assessment of additional Bioequivalence study

Study performed where test formulation was taken with 50 mL of water (intended maximum volume for patient use)

The following bioequivalence study has been performed in 2022 according to internationally accepted guidelines.

Study title: An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover, oral bioequivalence study comparing fixed dose combination of Rifampicin/Isoniazid dispersible tablets 75 mg/50 mg (2 tablets) manufactured by Lupin Limited, India with Rifampicine Sandoz® 150 (rifampicin capsules 150 mg) [1 capsule] manufactured by Sandoz B. V., Veluwezoom 22, Almere, The Netherlands and Isoniazid tablets USP 100 mg (1 tablet) manufactured by Teva Pharmaceuticals USA, Inc., North Wales, PA 19454 in healthy, adult, human male subjects under fasting conditions (study no. 068-22).

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 Isoniazid 100 mg USP (Teva Pharmaceuticals USA, Inc.) 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.: A202142
Treatment R:	References – 1 tablet Isoniazid 100 mg USP (isoniazid 100 mg) Batch no. CDZYY – 1 capsule Rifampicine Sandoz 150 mg (rifampicin 150 mg) Batch no. KJ4395

The Test formulation was taken with 50 mL of water (40 mL for dispersion and 10 mL for rinsing). A 14-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 60 ng/mL for isoniazid and about 100 ng/mL for rifampicin.

The study was performed with 38 participants; data generated from a total of 36 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)	0.67 ± 0.57	0.61 ± 0.30	-	-
C_{max} (ng/mL)	3070 ± 1154 (2821)	2966 ± 1208 (2658)	106.1	93.9 – 120.0
AUC_{0-t} (ng.h/mL)	7866 ± 4119 (6437)	8231 ± 4347 (6451)	99.8	95.5 – 104.2
AUC_{0-inf} (ng.h/mL)	8289 ± 4299 --	8618 ± 4222 --	-	-

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)	1.52 ± 1.01	1.70 ± 0.74	-	-
C_{max} (ng/mL)	3139 ± 1210 (2929)	3318 ± 1038 (3161)	92.7	84.5 – 101.6
AUC_{0-t} (ng.h/mL)	13697 ± 5366 (12650)	14946 ± 5007 (14095)	89.8	84.1 – 95.7
AUC_{0-inf} (ng.h/mL)	14835 ± 5285 --	15772 ± 5037 --	-	-

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 Isoniazid 100 mg USP (Teva Pharmaceuticals USA, Inc.) and Rifampicine Sandoz 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, Isoniazid 100 mg USP (Teva Pharmaceuticals USA, Inc.) and Rifampicine Sandoz 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 Isoniazid 100 mg USP (Teva Pharmaceuticals USA, Inc.) and Rifampicine Sandoz 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.