SCIENTIFIC DISCUSSION SUPPLEMENT

1. Introduction

A new BE study was necessitated due to a Notice of Concern (NOC) issued by WHO Prequalification Unit relating to the implementation status of Good Clinical Practices standards at Semler Research Centre Private Ltd., Bangalore, India.

WHO/PQT has requested applicants of the affected products to review the impact of these findings and take actions to confirm bioequivalence of their products.

This supplement therefore includes the submission and review outcome of a new BE study for [TB196 trade name].

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*.

There have been no material changes to the quality aspects and the content remains unchanged.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

A randomized, open label, balanced, single center, two treatments, two period, two sequence, single dose, crossover, bioequivalence study comparing Isoniazid tablets 100 mg manufactured by Lupin Limited, India with lsozid® (isoniazid) 100 mg tablets manufactured by Fatol Arzneimittel Gmbh, AG an der Wiek 7, 17493 Grcifswald-Insel, Riems Germany, in healthy, adult human male subjects, under fasting condition (study no. ARL/16/177).

The objective of the study was to compare the bioavailability of the stated Isoniazid 100 mg tablet manufactured by Lupin Limited, India (test drug) with the reference formulation Isozid® (Fatol Arzneimittel Gmbh) 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 two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Isoniazid 100 mg (isoniazid 100 mg) Batch no. A601150.
Treatment R:	Reference – 1 tablet Isozid® 100 mg (isoniazid 100 mg) Batch no. 002114

A 9-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 13 samples within 12 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for isoniazid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 ng/mL for isoniazid.

The study was performed with 32 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 as well as statistical results are summarised in the following table:

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)	0.69 ± 0.45	0.82 ± 0.52	–	–
C_{max} (ng/mL)	2086 ± 816 (1902)	1899 ± 767 (1735)	109.6	97.3 – 123.6
AUC_{0-t} (ng·h/mL)	6625 ± 3028 (5719)	6799 ± 3160 (5842)	97.9	94.6 – 101.3
AUC_{0-inf} (ng·h/mL)	7075 ± 3331 --	7295 ± 3494 --	–	–

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding isoniazid. Accordingly, the test Isoniazid 100 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Isozid® (Fatol Arzneimittel Gmbh).

4. Summary of product safety and efficacy

[TB196 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [TB196 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product lsozid® (Fatol Arzneimittel Gmbh, AG an der Wiek 7, 17493 Grcifswald-Insel, Riems Germany) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB196 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment of bioequivalence study

Bioequivalence

[TB196 trade name] has been shown to be bioequivalent with lsozid® (Fatol Arzneimittel Gmbh, AG an der Wiek 7, 17493 Grcifswald-Insel, Riems Germany).