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 Isoniazid 300 mg tablet and biowaiver information for [TB173 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.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Isoniazid Tablets BP, 300 mg manufactured by Micro Labs Ltd. India compared with that of Isoniazid Tablets, USP 300 mg, manufactured for: Sandoz Inc. Princeton, NJ 08540, in healthy, adult, human subjects under fasting conditions (study no. 0554-16).

The objective of the study was to compare the bioavailability of the stated Isoniazid BP 300 mg tablet manufactured by Micro Labs Ltd. India (test drug) with the reference formulation Isoniazid tablets, USP 300 mg (Sandoz Inc.) 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 BP 300 mg (isoniazid 300 mg) Batch no. IZABH0130.
Treatment R:	Reference – 1 tablet Isoniazid USP 300 mg (isoniazid 300 mg) Batch no. ME150324.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 24h 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 were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 23 ng/mL for isoniazid.

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.

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)	0.67 (0.167 – 2.50)	0.83 (0.33 – 2.00)	–	–
C_{max} (ng/mL)	7325 ± 1688 (7146)	7021 ± 1815 (6760)	105.7	99.5 – 112.4
AUC_{0-t} (ng·h/mL)	34795 ± 14206 (31270)	33865 ± 13964 (30214)	103.5	100.5 – 106.6
AUC_{0-inf} (ng·h/mL)	35291 ± 14557 --	34410 ± 14359 --	-	-

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 BP 300 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Isoniazid USP 300 mg tablet (Sandoz).

A biowaiver was granted for the additional 100 mg tablet strength (Micro Labs Ltd. India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Isoniazid 100 mg tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the APIs were determined the same.

4. Summary of product safety and efficacy

[TB173 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. According to the submitted data on quality and bioavailability [TB173 trade name] is a direct scale down of Isoniazid 300 mg tablets. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product isoniazid USP 300 mg tablets (Sandoz) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB173 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

[TB173 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.