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 Panexcell Clinical Lab Private Limited, Navi Mumbai on October 2020.

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 HA691.

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 2022 according to internationally accepted guidelines.

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, cross over, oral bioequivalence study comparing Betrim Forte [Co-Trimoxazole Tablet BP 960mg (containing 800 mg sulfamethoxazole and 160 mg trimethoprim)] of Milan Laboratories (India) Pvt. Ltd. with Cotrim Forte-Ratiopharm® 800mg/160mg tablet [containing 800 mg sulfamethoxazole and 160 mg trimethoprim (equivalent to 960 mg co-trimoxazole)] of Ratiopharm GmbH, Germany in healthy, adult, human, subjects under fasting conditions (study no. 064-21).

The objective of the study was to compare the bioavailability of the stated Sulfamethoxazole/ Trimethoprim 800mg/160mg FDC tablet manufactured by/for Milan Labs Pvt., India (test drug) with the reference formulation Cotrim Forte® Ratiopharm (Ratiopharm GmbH) 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 – 1 tablet Sulfamethoxazole/Trimethoprim 800mg/160mg (sulfamethoxazole 800 mg + trimethoprim 160mg) Batch no. MG21809.
Treatment R:	Reference

– 1 tablet Cotrim Forte® Ratiopharm

(sulfamethoxazole 800 mg + trimethoprim 160mg)

Batch no. W24599B.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for sulfamethoxazole and trimethoprim were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 201 ng/ml for sulfamethoxazole and 10 ng/ml for trimethoprim.

The study was performed with 24 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for sulfamethoxazole and trimethoprim as well as statistical results are summarised in the following tables:

Sulfamethoxazole

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)[#]	3.57 ± 0.98	2.73 ± 1.77	-	-
C_{max} (µg/ml)	46.9 ± 7.0 (46.3)	49.8 ± 7.3 (49.3)	94.1	88.2 – 100.3
AUC_{0-72h} (µg.h/ml)	705 ± 149 (687)	744 ± 115 (736)	93.4	86.0 – 101.3

* geometric mean

Trimethoprim

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)[#]	2.08 ± 1.63	1.89 ± 2.38	-	-
C_{max} (ng/ml)	1756 ± 422 (1703)	1923 ± 478 (1870)	91.1	82.0 – 101.1
AUC_{0-72h} (ng.h/ml)	20417 ± 4384 (19917)	21952 ± 5734 (21265)	93.7	88.5 – 99.1

* 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 sulfamethoxazole and trimethoprim. Accordingly, the test Sulfamethoxazole/Trimethoprim 800mg/160mg FDC tablet meets the criteria for bioequivalence with

regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Cotrim Forte® Ratiopharm (Ratiopharm GmbH).

4. Summary of product safety and efficacy

[HA691 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, [HA691 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Cotrim Forte® Ratiopharm (Ratiopharm GmbH) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA691 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

[HA691 trade name] has been shown to be bioequivalent with Cotrim Forte® Ratiopharm (Ratiopharm GmbH)