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 Raptim Research Private Limited, Navi Mumbai in July 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 HA722.

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 2020 according to internationally accepted guidelines.

An open-label, balanced, randomized, two treatment, two sequence, two period, two way cross-over, single oral dose bioequivalence study of fixed dose combination of [HA722 trade name] of Emcure Pharmaceuticals Limited and Tivicay (dolutegravir) tablets 50 mg of ViiV Healthcare Research Triangle Park, NC 27709, Epivir (lamivudine) tablets 300 mg of ViiV Healthcare Research Triangle Park, NC 27709 and Viread (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc. Foster City, CA 94404 in normal, healthy, adult, human subjects under fasting conditions (study no. BE/20/271).

The objective of the study was to compare the bioavailability of the stated [HA722 trade name] manufactured by/for Emcure Pharmaceuticals Ltd., India (test drug) with the reference formulations Tivicay® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.) 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 [HA722 trade name] (dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. EM95065A.
Treatment R:	Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. GB2B.

– 1 tablet Epivir®
(lamivudine 300 mg)
Batch no. 2P5N.
– 1 tablet Viread®
(tenofovir disoproxil fumarate 300 mg)
Batch no. 012738

A 15-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 25 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 dolutegravir, lamivudine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 28 ng/mL for dolutegravir, 20 ng/mL for lamivudine and 4 ng/mL for tenofovir.

The study was performed with 48 participants; data generated from a total of 46 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for dolutegravir, lamivudine and tenofovir as well as statistical results are summarised in the following tables:

Dolutegravir

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)	2.77 ± 1.39	3.11 ± 1.19	-	-
C_{max} (ng/mL)	2646 ± 748 (2544)	2467 ± 629 (2382)	106.8	101.6 – 112.3
AUC_{0-t} (ng.h/mL)	54080 ± 21008 (50408)	51227 ± 15973 (48728)	103.5	97.2 – 110.1
AUC_{0-inf} (ng.h/mL)	56817 ± 22961 --	53692 ± 17326 --	-	-

Lamivudine

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)	2.05 ± 0.92	1.82 ± 0.80	-	-
C_{max} (ng/mL)	2386± 623 (2309)	2560 ± 587 (2496)	92.5	87.5 – 97.8
AUC_{0-t} (ng.h/mL)	12702 ± 2524 (12453)	13307 ± 2783 (13018)	95.7	92.20– 99.5
AUC_{0-inf} (ng.h/mL)	12996 ± 2524 --	13594 ± 2796 --	-	-

Tenofovir

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)	1.20 ± 0.66	1.21 ± 0.61	-	-
C_{max} (ng/mL)	369 ± 88 (357)	365 ± 93 (353)	101.2	94.2 – 108.8
AUC_{0-t} (ng.h/mL)	2678 ± 553 (2621)	2724 ± 632 (2653)	98.8	95.4 – 102.3
AUC_{0-inf} (ng.h/mL)	2874 ± 600 --	2940 ± 655 --	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding dolutegravir, lamivudine and tenofovir. Accordingly, the test [HA722 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Tivicay® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.).

4. Summary of product safety and efficacy

[HA722 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, [HA722 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Tivicay® (ViiV Healthcare Research Triangle Park), Epivir® (ViiV Healthcare Research Triangle Park) and Viread® (Gilead Sciences, Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA722 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

[HA722 trade name] has been shown to be bioequivalent with Tivicay® (ViiV Healthcare Research Triangle Park), Epivir® (ViiV Healthcare Research Triangle Park) and Viread® (Gilead Sciences, Inc.).