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, on April 2016.

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 HA621.

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-sequence, two-period, cross-over, single dose, oral bioequivalence study of ritonavir 100 mg tablets (Test) of Mylan Laboratories Limited, India and Norvir® (ritonavir) tablets 100 mg of AbbVie Inc, USA in healthy, adult, human subjects under fed conditions (study no. 186-16).

The objective of the study was to compare the bioavailability of the stated ritonavir 100 mg tablet manufactured by/for Mylan Laboratories Limited, India (test drug) with the reference formulation Norvir® 100 mg tablet (AbbVie Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Ritonavir 100 mg (ritonavir 100 mg) Batch no. 3053510
Treatment R:	Reference – 1 tablet Norvir® 100 mg (ritonavir 100 mg)

Batch no. 1056746

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 36 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for ritonavir.

The study was performed with 80 participants; data generated from a total of 70 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for ritonavir as well as statistical results are summarised in the following table:

Ritonavir

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)[#]	4.50 (2.00 – 7.00)	4.50 (2.00 – 6.00)	-	-
C_{max} (ng/mL)	859 ± 382 (787)	816 ± 316 (757)	104.0	97.3 – 111.0
AUC_{0-t} (ng.h/mL)	7067 ± 3406 (6438)	6824 ± 2925 (6248)	103.0	98.1 – 108.2
AUC_{0-inf} (ng.h/mL)	7367 ± 3614 --	7108 ± 3082 --	-	-

*geometric mean; # median (range)

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ritonavir. Accordingly, the test ritonavir 100 mg tablet (now [HA467 trade name]) meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Norvir® 100 mg tablet (AbbVie Inc.).

A biowaiver was granted for the additional 25 mg tablet strength (Mylan Laboratories Ltd, India, [HA621 trade name]) in accordance with WHO guideline. In comparison with the strength of the test product used in the bioequivalence study (ritonavir 100 mg tablet, [HA467 trade name]), the ritonavir 25 mg tablet was determined to be essentially the same qualitatively, with the ratio of active ingredient and excipients between the strengths also considered essentially the same and the dissolution profiles between the formulations for the API were determined the same.

4. Summary of product safety and efficacy

[HA621 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, [HA621 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Norvir® (AbbVie Inc, USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA621 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

[HA621 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance. Hence, [HA621 trade name] and Norvir® (AbbVie Inc.) can be considered bioequivalent.