SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	[HA392 trade name][*]
Manufacturer of PreQualified Product:	Matrix Laboratories Limited F-4, F-12, Malegaon M.I.D.C, Sinnar Nashik – 422103, Maharashtra state India
Active Pharmaceutical Ingredient (API):	Lamivudine and Zidovudine
International Nonproprietary Name:	Lamivudine 150 mg/ Zidovudine 300 mg
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations J05AR01.
Therapeutic indication:	[HA392 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

1. Introduction

[HA392 trade name] is indicated for the treatment of HIV-1 infection in combination with at least one other antiretroviral agent. Lamivudine and zidovudine are not indicated for use in patients with clinically significant hypersensitivity to lamivudine, zidovudine or to any of the components contained in the formulation. It is recommended that therapy is given only on the advice of an HIV experienced physician.

2. Assessment of Quality

Active Pharmaceutical Ingredients (APIs)

Lamivudine and zidovudine are both class 1 APIs according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms).

Lamivudine API and zidovudine API are both described in the Ph.Int., Ph.Eur. and the USP.
The APIs, which are obtained from approved API manufacturers, are adequately controlled by their respective quality specifications which are pharmacopoeial based, with additional in-house specifications for residual solvents, particle size and bulk and tapped density.

Based on the results of stability testing conducted according to the requirements of WHO, a two-year retest period was approved for both lamivudine and zidovudine when stored in the proposed container at a temperature not exceeding 30°C.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycolate, magnesium stearate and a film coating mixture consisting of hypromellose, titanium dioxide and propylene glycol. Magnesium stearate is from plant origin.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development
[HA392 trade name] tablets are white to off-white, capsule shaped, biconvex film-coated tablets, debossed with "M103" on one side and plain on the other side. The primary packs are white opaque HDPE bottles with screw cap and blister packs (clear transparent PVdC coated PVC film with backing of aluminum foil)

The development of the final composition has been described. Similarity of dissolution profiles against Combivir® in the three BCS dissolution media has been demonstrated. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three production scale batches demonstrated the consistency of the process and the quality of the product.

The proposed specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product.

Stability testing
Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term conditions and at accelerated conditions. At the time of the prequalification, a provisional shelf-life of 24 months has been allowed for the FPP, packaged in both bottles and blister packs. The applicant committed to continue long-term testing on production scale batches for a period of time sufficient to cover the whole proposed shelf-life and to report any out-of-specification results immediately to WHO.

Conclusion

The quality part of both dossiers is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2007 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of lamivudine/zidovudine 150mg/300mg tablet (Matrix Laboratories Ltd, India) with Combivir® (Lamivudine/Zidovudine) 150mg/300mg tablet, (GlaxoSmithKline, Inc. USA), in 44 healthy human adult male subjects under fasting conditions (study no. 036-07).

The objective of the study was to compare the bioavailability of the stated lamivudine/zidovudine 150mg/300mg fixed dose combination manufactured by Matrix Laboratories Ltd., India (test drug) with the same dose of the fixed dose reference tablet (Combivir®, GlaxoSmithKline) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomised, 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 – [HA392 trade name] tablet (lamivudine 150 mg/zidovudine 300 mg)
Batch no. LZDA116001.

Treatment R: Reference – Combivir® tablet (lamivudine 150 mg/zidovudine 300 mg)
Batch no. 6ZP1816.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 lamivudine and zidovudine were analyzed using a validated LC-MS method. The limit of quantification was stated to be about 25 ng/ml for lamivudine as well as for zidovudine.

The study was performed with 44 participants; data generated from a total of 43 subjects were used for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Lamivudine

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} (hour)	1.23 ± 0.55	1.24 ± 0.60	-	-
C_{max} (ng/ml)	1856 ± 633 (1734)	1988 ± 636 (1895)	91.5	82.4–101.7
AUC_{0-t} (ng·hour/ml)	6801 ± 1561 (6569)	7091 ± 1283 (6951)	94.1	88.0–100.6
AUC_{0-inf} (ng·hour/ml)	7136 ± 1562 (6916)	7419 ± 1301 (7312)	94.6	88.8–100.7

* geometric mean

Zidovudine

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} (hour)	0.77 ± 0.54	0.73 ± 0.60	-	-
C_{max} (ng/ml)	1974 ± 961 (1761)	1953 ± 778 (1801)	97.8	83.8–114.1
AUC_{0-t} (ng·hour/ml)	2634 ± 692 (2549)	2525 ± 545 (2468)	103.3	97.3–109.7
AUC_{0-inf} (ng·hour/ml)	2708 ± 695 (2625)	2599 ± 558 (2541)	103.3	97.4–109.5

* geometric mean

Conclusion

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and C_{max} values regarding lamivudine and zidovudine. Accordingly, the test product [HA392 trade name] fixed dose combination tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Combivir® (GlaxoSmithKline).

4. Summary of Product Safety and Efficacy

[HA392 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Combivir® (Lamivudine/Zidovudine) 150 mg/300 mg tablet (GlaxoSmithKline).

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[HA392 trade name] has shown to be bioequivalent to Combivir® (Lamivudine/Zidovudine) 150 mg/300 mg tablet (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, lamivudine/stavudine are considered effective and safe to use when the guidance and restrictions presented in the summary of product characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality and bioequivalence the team of assessors considered by consensus that the benefit risk profile of [HA392 trade name] was acceptable for the following indication: HIV infection in combination with other antiretroviral agents and has advised to include [HA392 trade name], manufactured at Matrix Laboratories Limited, F-4, F-12, Malegaon M.I.D.C, Sinnar, Nashik – 422103, Maharashtra state, India, in the list of prequalified medicinal products.