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.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[HA490 trade name]* Lamivudine and Zidovudine 150 mg/300 mg tablets
Manufacturer of Prequalified Product:	Universal Corporation Ltd Club Road Plot Number 13777 P.O. Box 1748 – 00902 Kikuyu Kenya
Active Pharmaceutical Ingredients (APIs):	Lamivudine + Zidovudine
International Nonproprietary Name:	Lamivudine + Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (J05AR01)
Therapeutic indication:	[HA490 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

[HA490 trade name] are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. [HA490 trade name] should not be used for patients with clinically significant hypersensitivity to lamivudine, zidovudine or to any of the components in the formulation. It is recommended that therapy is given only on the advice of a physician experienced in the management of HIV infection.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification Programme.

Zidovudine and lamivudine tablets are described in the Ph.Int.

Active Pharmaceutical Ingredient (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 and zidovudine are thus highly soluble according to the BCS.

Lamivudine API and zidovudine API are described in the Ph.Int., Ph.Eur. and USP, and are considered well-established in the Prequalification Programme. The APIs are adequately controlled by their respective quality specifications which are pharmacopoeial based, with additional in-house specifications including particle size and tap/bulk density ratio for both APIs.

Stability testing was conducted according to the requirements of WHO. The proposed re-test periods are justified based on the stability results when the APIs are stored in the original packing material.

Other ingredients

Other ingredients used in the core tablet formulation include colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. Magnesium stearate is obtained from vegetable origin. The film coating contains hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide.

Finished pharmaceutical product (FPP)

Zidovudine and lamivudine tablets are described in the Ph.Int., BP and USP.

[HA490 trade name] are white to off-white, capsule-shaped, film-coated tablets without embossment and scored on one side. The score line is intended for subdivision of tablets when the tablet is to be administered as half a dose, as supported by a divisibility test in the product release specifications. The tablets are packaged in an HDPE bottle with a child-resistant polypropylene screw cap.

Pharmaceutical development and manufacture

The development of the final composition of [HA490 trade name] has been described. The objective was to develop a stable product, bioequivalent to the comparator product Combivir®. The excipients were selected to match the comparator product qualitatively with respect to the composition of both the core tablet and the coating. The coating serves to mask the taste of the core, to facilitate swallowing and to increase the photostability of the product, in particular with respect to zidovudine.

The tablets are manufactured by direct compression. The steps include milling of the raw materials, blending, lubrication, compression, coating and packaging. All manufacturing methods are standard for the manufacture of immediate-release tablets. The critical steps were identified and appropriate in-process controls set. Validation data presented for primary batches demonstrated the consistency of the process and the quality of the product.

Comparative dissolution studies were conducted between [HA490 trade name] and Combivir® tablets in the three BCS media according to the requirements of WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*

(WHO Technical Report Series 937, Annex 7). Based on the similarity of the dissolution profiles, a biowaiver was allowed for [HA490 trade name].

Product specification

The finished product specifications are pharmacopoeial based and include tests for description, identification of the APIs (HPLC and UV) and of titanium dioxide, uniformity of content of the tablets and the tablet halves, dissolution, related substances (HPLC), assay (HPLC) and microbiological quality.

Stability testing

Stability studies have been performed at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions. The data showed little change with time and were well within the agreed specifications at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

No bioequivalence study has been performed. As lamivudine and zidovudine are selected by the WHO as being eligible for a BCS-based biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for biowaivers, supporting data have been provided regarding formulation comparability and in vitro dissolution data.

Comparability between the reference Combivir® 150/300 mg tablet (GlaxoSmithKline) and the test tablet [HA490 trade name] (Universal Corporation Ltd., Kenya) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1, 4.5 and 6.8 have been shown.

Accordingly, the test tablet [HA490 trade name] (Universal Corporation Ltd., Kenya) meets the criteria for a BCS-based biowaiver and is therefore considered bioequivalent to the reference Combivir® 150/300 mg tablet (GlaxoSmithKline).

4. Summary of Product Safety and Efficacy

[HA490 trade name] 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 to the reference, Combivir® tablets.

The clinical safety of this product is considered acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (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 SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

Comparability between the reference Combivir® 150/300 mg tablet (GlaxoSmithKline) and the test tablet [HA490 trade name] (Universal Corporation Ltd., Kenya) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA490 trade name] are considered effective and safe when the guidance and restrictions presented in the SmPC are taken into consideration.

Benefit–risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit–risk profile of [HA490 trade name] was acceptable for the following indication: treatment of HIV-1 infection in combination with one more other antiretroviral agents and has advised to include [HA490 trade name], manufactured at Universal Corporation Ltd, Kikuyu, Kenya, in the list of prequalified medicinal products.