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	[HA485 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited Plot No: S-155 to S-159 & N1 Phase III & Phase IV Verna Industrial Estate Verna, Goa- 403722 India Tel: + 91 832 6686262 Fax: +91 832 6686203
Active Pharmaceutical Ingredient(s) (API)	Lamivudine/zidovudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR01)
Therapeutic indication	[HA485 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

1. Introduction

[HA485 trade name], are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. [HA485 trade name] should not be used for patients with clinically significant hypersensitivity to lamivudine or to any of the components contained 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 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.*

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 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

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

specifications including particle size distribution and bulk density (tapped and untapped), 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. A TSE/BSE free certificate was provided for magnesium stearate. The film coating (Opadry White 13B58894) contains hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA485 trade name] are white to off-white, capsule-shaped, biconvex, film-coated tablet, scored on one side, debossed with 'I' on one half and '01' on the other half, and plain on the other side. The break-line is intended for subdivision of tablets when the dose is half a tablet, as supported by a divisibility test in the product release specifications. The tablets are packaged in a round, white opaque HDPE bottle sealed with an induction seal and a white screw cap (pack sizes: 30, 60 and 90 tablets) and clear PVDC/PVC-aluminium blister cards, packed in a carton box (10 tablets per blister card, 10 cards per carton).

The strategy was the development of a product similar in composition and in vitro dissolution properties to the innovator product Combivir®. The excipients were selected to qualitatively match those of the innovator product with respect to both the core tablet and coating material.

The product has been developed as an immediate-release solid dosage form for oral administration. Since both lamivudine and zidovudine show poor flowability, a wet granulation process was selected for the manufacture of the core tablets. Optimisation studies were performed for establishing the concentration of diluent, disintegrant, lubricant and glidant. The critical steps of the manufacturing process were optimised and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three primary batches demonstrated the consistency of the process and the quality of the product.

Comparative dissolution studies were conducted between [HA485 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 [HA485 trade name].

The finished product specifications include appropriate tests for appearance, identification of the APIs (HPLC and UV) and titanium dioxide, average weight, uniformity of weight, disintegration time, tablet dimensions, moisture content (KF), tablet breaking force, uniformity of dosage units (by content uniformity), dissolution, assay (HPLC), related substances (HPLC), triphenyl methanol content, enatiomeric impurity, microbial limits and subdivision of tablets.

Stability testing

Stability studies have been performed on three primary batches at 30°C/65%RH (zone IVa) as long-term storage conditions and for six months at accelerated conditions. The data showed little change 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

Conclusion

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 for a BCS-based biowaiver, a biowaiver was requested. In accordance with the WHO guidance and criteria for biowaivers, supporting data were provided on formulation comparability and in vitro dissolution data.

Comparability between the reference Combivir® 150 mg/300 mg tablet (GlaxoSmithKline) and the test tablet [HA485 trade name] (Micro Labs Limited, India) 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 [HA485 trade name] (Micro Labs Limited, India) meets the criteria for a BCS-based biowaiver and is therefore considered bioequivalent to the reference Combivir® 150 mg/300 mg tablet (GlaxoSmithKline).

4. Summary of product safety and efficacy

[HA485 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, [HA485 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Combivir® 150 mg/300 mg tablet (GlaxoSmithKline) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA485 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 and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HA485 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA485 trade name] has been shown to be bioequivalent with Combivir® 150 mg/300 mg tablet (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA485 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA485 trade name] was acceptable for the following indication: 'treatment of HIV-1 infection in combination with one more other antiretroviral agents', and would allow inclusion of [HA485 trade name], manufactured at Micro Labs Limited, Verna, Goa - 403722, India in the list of prequalified medicinal products.