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:	[HA521 trade name] *
Manufacturer of Prequalified Product:	Hetero Labs Limited Unit III, Block B, # 22-110, I.D.A., Jeedimetla Qutubullapur Municipality Hyderabad, Zip Code: 500 055 Andhra Pradesh INDIA
Active Pharmaceutical Ingredients (APIs):	Lamivudine + Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antiviral for treatment of HIV infection, combinations (J05AR01)
Therapeutic indication:	Lamivudine/Zidovudine 150mg/300mg Tablets is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agent-

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

1. Introduction

[HA521 trade name] are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. [HA521 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.

Active pharmaceutical Ingredients (APIs)

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified lamivudine (up to 300mg oral dose) as a BCS class 3 API and zidovudine (up to 300 mg oral dose) as a BCS class 1 API. These APIs are thus BCS highly soluble.

Lamivudine
Lamivudine API is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO PQP.

The lamivudine specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification (IR and HPLC), light absorption, water content, specific optical rotation, residue on ignition, heavy metals, limit of lamivudine enantiomer (chiral HPLC, ≤ 0.3%), residual solvents, chromatographic purity (HPLC), assay (HPLC) and particle size. Toluene sulfonates (LC-MS) and methane sulfonates (GC-MS) are controlled at ≤ 5 ppm.

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

Zidovudine
Zidovudine API is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO PQP.

The zidovudine specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification, specific optical rotation, water content (KF), residue on ignition, heavy metals, chromatographic purity (TLC and HPLC), assay (HPLC), residual solvents and particle size.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is 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. The film coating contains hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide. Certificates confirming that the excipients are TSE/ BSE free were provided.

Finished pharmaceutical products (FPP)

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

The multisource tablets are white, film-coated and capsule shaped, debossed with 'H' and a score line on one side and '2' on the other side. The score line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in a round white HDPE bottle closed with a continuous thread polypropylene cap.

The development of the final composition of the multisource tablets has been described. Physico-chemical characterisation of the comparator, Combivir® 150 mg/300 mg film-coated tablets, was carried out to obtain a target profile. The excipients were selected to match the comparator product qualitatively with respect to the composition of both the tablet core and the coating. Direct compression was selected for manufacture of the tablet cores. The process was optimised to obtain tablets with the desired compressibility, disintegration and dissolution characteristics. The critical steps were identified and appropriate in-process controls set.

Comparative dissolution studies were conducted between comparator tablets and the multisource product 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). The similarity of the dissolution profiles, supported a biowaiver for [HA521 trade name].

Specifications
The finished product specifications include tests for description, identification of the APIs (HPLC and UV), water content, average weight, disintegration time, dissolution (HPLC), uniformity dosage units (by content uniformity), related compounds (HPLC), assay (HPLC), residual solvents and microbiological examination.

Stability testing
Stability studies have been performed at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed form marketing of the product. The product proved to be chemically quite stable, while a slight increase in water content and disintegration time was observed, well within the agreed limits, 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 Bio-Equivalence

No bioequivalence study has been performed. As lamivudine and zidovudine are selected by the WHO 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 [HA521 trade name] (Hetero Drugs 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 [HA521 trade name] (Hetero Drugs Limited, India) 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

[HA521 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 [HA521 trade name] (Hetero Drugs Limited, India) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA521 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 [HA521 trade name] was acceptable for the following indications: treatment of children with HIV-1 infection in combination with other antiretroviral agents and primary prophylaxis of HIV-1 infection in neonates, and has advised inclusion of [HA521 trade name], manufactured at Hetero Labs Limited, Andhra Pradesh, India, in the list of prequalified medicinal products.