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	[HA555 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	[HA555 trade name]is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infection in children.

1. Introduction

[HA555 trade name] is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in children.

[HA555 trade name] should be prescribed by a healthcare provider 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

Based on scientific principles the WHO PQT-M has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API, eligible for BCS-based biowaiver applications. The API is thus BCS highly soluble. Lamivudine is described in the Ph.Int., Ph.Eur. and the USP, and is considered well-established in the WHO PQP.

The pharmacopoeial based specifications include tests for description, solubility, melting point, identification (IR and HPLC), light absorption, water content (KF), limit of lamivudine enantiomer (chiral HPLC; ≤ 0.3%), chromatographic purity (HPLC), assay (HPLC), residual solvents, heavy

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

metals, specific optical rotation, residue on ignition, bulk density, particle size distribution, alkyl methane sulfonates (GC-MS) and alkyl p-toluene sulfonates (UFLC-MS).
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 packaging.

Zidovudine

Based on scientific principles the WHO PQT-M has identified zidovudine (up to 300 mg oral dose) as a BCS class 1 API, eligible for BCS-based biowaiver applications. The API is thus BCS highly soluble. 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, identification (IR and HPLC), melting range, specific optical rotation, water content (KF), residue on ignition, heavy metals, chromatographic purity (TLC and HPLC), assay (HPLC), bulk density, residual solvents and particle size distribution. Methyl methane sulfonate and methyl-p-toluene sulfonate content is also controlled on material received from one of the suppliers.
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 commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide. Attestations have been submitted confirming BSE/TSE-free status of the ingredients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The film-coated tablet is white, capsule shaped, bevelled edged, biconvex, with plain surface on one side and scored 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 during development. The tablets are packaged in round, white opaque HDPE bottles with polypropylene child resistant cap and clear PVDC/PVC-aluminium blister, further packed in a carton.

The strategy was to development a product similar in composition and in vitro dissolution properties to the WHO PQT-M comparator product Combivir® film-coated tablets, containing 150 mg lamivudine and 300 mg zidovudine. The excipients were selected to qualitatively match those of the comparator 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. Optimization studies were performed for establishing the concentration of diluent, disintegrant, lubricant and glidant. The critical steps of the manufacturing process were optimized 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.

[HA555 trade name] and Combivir® tablets showed similar dissolution profiles in the three main BCS media – in fact very rapidly dissolving properties were observed for both APIs of both test and comparator batches.

Specifications

The finished product specifications include appropriate tests for description, identification of the APIs (HPLC and UV) and titanium dioxide, average weight, uniformity of weight, disintegration time,

tablet dimensions, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC) and microbial limits.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed little change and were well within the agreed specifications at both storage conditions in all pack types. 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 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® tablet (GlaxoSmithKline) and a higher strength test tablet lamivudine and zidovudine 150/300 mg tablets (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 lamivudine and zidovudine 150/300 mg tablets (Micro Labs Limited, India) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the reference Combivir® 150/300 mg tablet (GlaxoSmithKline). In addition, additional dissolution data have been provided showing comparable in vitro dissolution at a pH 1, 4.5 and 6.8 for the dose proportional lamivudine and zidovudine tablets 30/60 mg. Accordingly, the biowaiver for the test tablet [HA555 trade name] (Micro Labs Limited, India) is considered acceptable.

4. Summary of product safety and efficacy

[HA555 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [HA555 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. The clinical safety of [HA555 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 [HA555 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA555 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA555 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 [HA555 trade name] was acceptable for the following indication: 'in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infection in children', and would allow inclusion of [HA555 trade name], manufactured at Micro Labs Limited, Plot No: S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa- 403722, India in the list of prequalified medicinal products.