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	[HA536 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 403 722 India
Active Pharmaceutical Ingredient(s) (API)	Lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, nucleoside reverse transcriptase inhibitors; lamivudine, J05AF05).
Therapeutic indication	[HA536 trade name] is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in infants and children aged 4 weeks and weighing 3 to 24.9 kg.

1. Introduction

[HA536 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in infants and children aged 4 weeks and weighing 3 to 24.9 kg.

[HA536 trade name] should be prescribed by a health care 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 Ingredient (API)

Based on scientific principles the WHO Prequalification of Medicines Programme has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. Lamivudine is thus highly soluble according to the BCS.

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

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

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

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 magnesium stearate, microcrystalline cellulose and sodium starch glycolate. Magnesium stearate is of vegetable origin. The film coating contains hypromellose, macrogol, polysorbate 80 and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a white, round-shaped, biconvex, film-coated tablet with plain surface on one side and scored on the other side. The break-line is intended for dividing tablets when a dose of half-a-tablet is to be administered, as supported by divisibility studies. The tablets are packaged in clear PVC/PVDC-aluminium blister cards and in opaque white HDPE bottles with polypropylene child resistant cap.

Three strengths, proportionally similar in composition, have been developed: 300 mg, 150 mg and 30 mg. The composition of the core tablets was furthermore selected to be qualitatively similar to that of the comparator product, Epivir® film-coated tablets. The wet granulation method was selected for manufacturing of the core tablets. Optimisation of the formulation and the processing parameters resulted in tablets with the desired characteristics. All three strengths of the multisource lamivudine tablets showed very rapidly dissolution properties, while the 300 mg strength was shown to be bioequivalent to Epivir® 300 mg film-coated tablets.

Specifications

The finished product specifications are regarded adequate for ensuring consistent quality and include tests for description, identification (HPLC and UV), average and uniformity of weight, disintegration time, tablet dimensions, water content, uniformity of dosage units (by weight variation), dissolution, assay (HPLC), related compounds (HPLC), residual solvents and microbial limits.

Stability testing

Stability studies on the FPP have been conducted at 30^0C/75%RH as long-term storage conditions and for six months at accelerated conditions. The product proved to be quite stable at both these storage conditions in all packaging configurations proposed for marketing of the product. 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

Two bioequivalence studies have been submitted to support this application.

The following bioequivalence study has been performed in 2009 according to internationally accepted guidelines.

A randomised, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study of Lamivudine 300 mg Tablets of Micro Labs Ltd, India with Epivir® (lamivudine tablets 300 mg) of GlaxoSmithKline Research in normal, healthy, adult, male and female human subjects under fasting condition. (study no. ARL/09/164).

The objective of the study was to compare the rate and extent of absorption of the stated Lamivudine 300 mg tablets with the same dose of Epivir® 300 mg tablets. The comparison was performed as a

randomised, two-treatment, two-period, single-dose, crossover study in healthy subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

Treatment T: Test – Lamivudine 300 mg tablets (lamivudine 300 mg) Batch no. LMBG002

Treatment R: Reference – Epivir® 300 tablets (lamivudine 300 mg) Batch no. 8C005

A 9-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 24 hours of the dose) were taken during each study period to obtain bioavailability characteristics AUCinf, AUC0-t, Cmax and tmax for bioequivalence evaluation. Drug concentrations for lamivudine in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 40 ng/mL for lamivudine.

The study was performed with 28 participants, data generated from a total of 27 subjects were utilised for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic means (± SD), geometric means (AUC, Cmax) for lamivudine as well as statistical results are summarised in the following table:

Lamivudine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	1.10 ± 0.71	1.01 ± 0.65	–	–
C_{max} ({ng}/mL)	2657 ± 915 (2515)*	2832 ± 981 (2675)*	94.0	87.6–101.0
AUC_{0-t} ({ng·h/mL)	10953 ± 3123 (10579)*	11368 ± 3087 (10957) *	96.5	91.1–102.4
AUC_{0-inf} (ng·h/mL)	11280 ± 3161 (10908)*	11698 ± 3058 (11306) *	96.5	91.3–102.0

* geom. mean

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and Cmax values regarding lamivudine. Accordingly, the test product Lamivudine 300 mg tablets (Micro Labs Ltd, India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference, Epivir® 300 mg tablets (GlaxoSmithKline Research).

A biowaiver was granted for the additional strength Lamivudine 30 mg Tablets (Micro Labs Ltd, India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence studies, the Lamivudine 30 mg Tablets strength was determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths is considered essentially the same, and the dissolution profiles between the formulations for the APIs were determined to be similar.

4. Summary of product safety and efficacy

[HA536 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. Epivir® 300 mg tablets fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

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 [HA536 trade name] is used in accordance with the SmPC.

Bioequivalence

According to the submitted data on quality [HA536 trade name] is a direct scale-down of Lamivudine 300 mg tablets. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator products Epivir® 300 mg tablets for which benefits have been proven in terms of virological, immunological and clinical efficacy.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA536 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 [HA536 trade name] was acceptable for the following indication: **"in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in infants and children aged 4 weeks and weighing 3 to 24.9 kg"**, and would allow inclusion of [HA536 trade name], manufactured at Micro Labs Limited, Plot No: S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa 403 722, India in the list of prequalified medicinal products.