This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[HA644 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 (API):	Lamivudine
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, nucleoside reverse transcriptase inhibitors (J05AF05).
Therapeutic indication:	[HA644 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection.

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

1. Introduction

[HA644 trade name], is indicated for the treatment of HIV-1 infection in adults and adolescents (aged over 12 years), in combination with other antiretroviral agents. [HA644 trade name] is not indicated for use in 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 by 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 Ingredient (API)

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

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

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

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, sodium starch glycolate and magnesium stearate. Magnesium stearate is of vegetable origin. The commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol, polysorbate and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, round shaped, biconvex, film coated tablet with bevelled edge, scored on one side and debossed with 'I08' on the other side. The score-line is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses. The tablets are packaged in clear PVC/PVDC-aluminium blister cards and in opaque white HDPE bottles with polypropylene child resistant caps.

Three strengths, proportionally similar in composition and using a similar manufacturing process, 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 pharmacopoeial based, regarded adequate for ensuring consistent quality and include tests for description, identification (HPLC and TLC), average and uniformity of weight, disintegration time, tablet dimensions, water content, uniformity of dosage units (by weight variation), dissolution (HPLC detection), assay (HPLC), related compounds (HPLC), enantiomeric purity (chiral HPLC), residual solvents and microbial limits.

Stability testing

Stability studies on the FPP have been conducted at 30°C/75%RH (zone IVb) 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 Bio-Equivalence

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

Study title: A randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Lamivudine tablets 300mg 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 bioavailability of the stated Lamivudine 300 mg tablet manufactured for/by Micro Labs Ltd., India (test drug) with the reference formulation Epivir® (GlaxoSmithKline Research) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Lamivudine 300mg (lamivudine 300mg) Batch no. LMBG002
Treatment R:	Reference – 1 tablet Epivir® (lamivudine 300mg) 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 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for lamivudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 40 ng/ml for lamivudine.

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

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine as well as statistical results are summarised in the following table:

Lamivudine

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

* geometric mean

The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and C_{max} values regarding lamivudine. Accordingly, the test Lamivudine 300mg Tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Epivir® (GlaxoSmithKline Research).

A biowaiver was granted for the additional 150 mg tablet strength (Micro Labs Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, [HA644 trade name] was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths is considered essential the same and the dissolution profiles between the formulations for the API was determined the same.

4. Summary of Product Safety and Efficacy

[HA644 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. [HA644 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

The clinical safety of this product is considered to be acceptable when guidance and restrictions in the summary of product characteristics are taken into account. Reference is made to the Summary of Product Characteristics (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 [HA644 trade name] is used in accordance with the summary of product characteristics (SmPC).

Bioequivalence

[HA644 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, [HA644 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [HA644 trade name] was acceptable for for the treatment of HIV-1 infection as detailed in the summary of product characteristics and has advised to include [HA644 trade name], manufactured at Micro Labs Ltd, Verna Industrial Estate, Goa, Indiain the list of prequalified medicinal products.