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	[HA424 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Atlanta Arcade, 3rd floor, Church Road, near Leela Hotel, Andheri-Kurla Road Andheri (East) Mumbai 400 059 India Tel.: + 91 22 56 26 28 00 Fax: + 91 22 29 25 65 99 Email: rakeshchaurasia@macleodspharma.com, vijay@macleodspharma.com
Active Pharmaceutical Ingredient(s) (API)	Lamivudine
Pharmaco-therapeutic group (ATC Code)	Nucleoside and nucleotide reverse transcriptase inhibitors, ATC Code J05AF05
Therapeutic indication	[HA424 trade name]is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children weighing at least 25 kg

1. Introduction

[HA424 trade name], is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children weighing at least 25 kg.

[HA424 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*.

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

Active pharmaceutical Ingredient (API)

Lamivudine is a class 1 API 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*). It is thus highly soluble in aqueous medium over the pH range 1–6.8.

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

The API is adequately controlled by its set of quality specifications which is pharmacopoeial based, with additional in-house specifications including bulk density, particle size and residual solvents. The enantiomer of lamivudine is limited to 0.3%.

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 material.

Other ingredients

Other ingredients used in the core tablet formulation include magnesium stearate, microcrystalline cellulose and sodium starch glycolate. Magnesium stearate is from vegetable origin. The film coating contains hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[HA424 trade name] are white, capsule-shaped, biconvex, film-coated tablets having score on one side and ‘ML 1’ debossed on the other side. The score-line is non-functional. The tablets are packaged in a white, round HDPE container with pack insert and 1 g pillow pack containing adsorbent and finally induction sealed, with a white polypropylene screw cap (pack size: 60 tablets), and in clear PVC/PVdC-aluminium blister cards (10 tablets per card, 6 cards in a box).

The development of the final composition of [HA424 trade name] has been described. The objective was to develop a product similar in composition and bioequivalent to the comparator product, Epivir® 150 mg film-coated tablets. The wet granulation method was selected for manufacturing the core tablets. The multisource product showed dissolution properties similar to that of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three primary batches demonstrated the consistency of the process.

The finished product specifications are regarded adequate for ensuring consistent quality of this FPP and include tests for description, identification of the API (HPLC and UV) and of the colorants, average weight, disintegration time, water (KF), dissolution, uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC) and microbial quality. Batch analysis data confirmed consistency and uniformity of manufacture and indicate that the process is under control.

Stabilitytesting

Stability studies have been conducted on primary batches at 30ºC/70%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. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SPC are acceptable

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2007 according to internationally accepted guidelines.

An open label, randomized, two-treatment, two sequence, two period, two way crossover, single dose bioequivalence study of [HA425 trade name](each tablet contains lamivudine USP 300 mg) manufactured by Macleods Pharmaceuticals Ltd., India comparing with Epivir® (lamivudine) tablets 300 mg (each tablet contains 300 mg of lamivudine) manufactured by GlaxoSmithKline, Research Triangle Park, England in healthy, adult, male, human subjects under fasting conditions (study no. BEQ-109-LAMI-2007).

The objective of the study was to compare the bioavailability of the stated [HA425 trade name] manufactured by Macleods Pharmaceuticals Ltd. India (test drug) with the same dose of the reference formulation (Epivir® 300 mg tablet, GlaxoSmithKline) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – [HA425 trade name] (lamivudine 300 mg) Batch no. LE701.
Treatment R: Reference – Epivir® 300 mg tablet (lamivudine 300 mg) Batch no. R245148.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 16 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 25 ng/ml for lamivudine.

The study was performed with 28 participants; data generated from a total of 24 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	0.97 ± 0.43	1.17 ± 0.58	-	-
C_{max} (ng/mL)	3062 ± 849 (2941)	3016 ± 810 (2903)	101.3	92.7 – 110.8
AUC_{0-t} (ng·h/mL)	13554 ± 4237 (12896)	14004 ± 3154 (13659)	94.4	85.6 – 104.1
AUC_{0-inf} (ng·h/mL)	13791 ± 4246 (13149)	14283 ± 3198 (13937)	94.4	85.9 – 103.4

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 [HA425 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Epivir® 300 mg tablet (GlaxoSmithKline).

A biowaiver was granted for the additional strength [HA424 trade name] (Macleods Pharmaceuticals Ltd. India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the [HA424 trade name] 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

[HA424 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, [HA424 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epivir®by ViiV Healthcare Research Triangle Parkfor which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA424 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 [HA424 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA424 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per rele relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA424 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 [HA424 trade name] was acceptable for the following: **'in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children weighing at least 25 kg'**, and would allow inclusion of [HA424 trade name], manufactured at Macleods Pharmaceuticals Limited, Unit II, Plot No. 25-27, Sr. No. 366, Premier Ind. Estate, Kachigam, 396 210 Daman (U.T.), India in the list of prequalified medicinal products.