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	[HA668 trade name]*
Manufacturer of Prequalified Product	Beximco Pharmaceuticals Limited OSD Unit, Track II 126 Kathadia Auchpara Tongi 1711 Gazipur Bangladesh
Active Pharmaceutical Ingredient (API)	Lamivudine
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, nucleoside reverse transcriptase inhibitors (J05AF05).
Therapeutic indication	[HA668 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

[HA668 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.

The therapy should be initiated 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 WHO 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 are pharmacopoeial based and include tests for appearance, solubility, identification (IR and HPLC), light absorption, melting point, water content (KF), specific optical rotation, residue on ignition, heavy metals, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.30%), chromatographic purity (HPLC), residual solvents (GC), assay (HPLC), particle size, toluene sulfonates (UFLC-MS; each ≤ 5 ppm), methane sulfonates (GC-MS; each ≤ 5 ppm) and microbial limits.

* 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 microcrystalline cellulose, sodium starch glycolate, povidone and magnesium stearate all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG, polysorbate and iron oxide black. BSE/TSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a grey coloured, modified diamond shaped, biconvex, bevelled edge film coated tablet, debossed with 'A' on one side and '101' on the other side. The tablets are packaged in a white, opaque HDPE bottle with a white polypropylene child-resistant cap and an induction sealer.

The aim of the formulation development was to develop a robust and stable formulation of [HA668 trade name] which is comparable to the WHO recommended comparator product Epivir® (lamivudine) tablets 300 mg in terms of stability and bioavailability. The excipients used in the formulation are well established with almost similar function as that of the excipients in the WHO recommended comparator product. Since wet granulation provides a robust process for large scale manufacturing, it was selected as to manufacture [HA668 trade name]. Several trials were conducted to optimize the formulation as well as the manufacturing process. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification (IR and HPLC), average weight, uniformity of dosage units (by weight variation), hardness, water content (KF), dissolution (UV detection), organic impurities (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. 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 SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

An open-label, balanced, randomized, two-treatment, two-period, two-sequence, two-way crossover, single oral dose bioequivalence study of [HA668 trade name] of Beximco Pharmaceuticals Ltd., Bangladesh with Epivir® (lamivudine) tablets 300 mg of ViiV Healthcare Research Triangle Park, NC 27709 in normal healthy, adult, human subjects under fasting condition (study no. BE/16/275).

The objective of the study was to compare the bioavailability of the stated [HA668 trade name] manufactured by/for Beximco Pharmaceuticals Ltd., Bangladesh (test drug) with the reference formulation Epivir® (ViiV Healthcare Research Triangle Park) and to assess bioequivalence. The comparison was performed as a single center, open label, randomized, crossover study in healthy

subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet [HA668 trade name] (lamivudine 300 mg) Batch no. 10233
Treatment R:	Reference – 1 tablet Epivir® (lamivudine 300 mg) Batch no. 5ZP1465

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 48 hours 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 60 ng/ml for lamivudine.

The study was performed with 28 participants. Data generated from a total of 26 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 summarized 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)	1.28 ± 0.74	1.35 ± 0.64	–	–
C_{max} (ng/mL)	3225 ± 798 (3129)	3210 ± 855 (3097)	101.0	92.4 – 110.5
AUC_{0-t} (ng·h/mL)	14006 ± 2364 (13816)	13929 ± 3064 (13603)	101.6	95.8 – 107.7
AUC_{0-inf} (ng·h/mL)	14430 ± 2472 -	14296 ± 3070 -	-	-

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 [HA668 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Epivir® (ViiV Healthcare Research Triangle Park).

4. Summary of product safety and efficacy

[HA668 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, [HA668 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epivir® by ViiV Healthcare Research Triangle Park for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA668 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 [HA668 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA668 trade name] has been shown to be bioequivalent with Epivir® 300 mg tablets (ViiV Healthcare Research Triangle Park).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA668 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 [HA668 trade name] was acceptable for the following indication: '**the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescent and for children weighing at least 25 kg'**, and would allow inclusion of [HA668 trade name], manufactured at Beximco Pharmaceuticals Limited, OSD Unit, Track II, 126 Kathadia, Auchpara Tongi 1711, Gazipur, Bangladesh in the list of prequalified medicinal products.