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	[HA656 trade name]
Manufacturer of Prequalified Product	Anhui Biochem Bio-Pharmaceutical Co., Ltd OSD workshop, 2nd floor of the Building 2, No. 30 Hongfeng Road, Hi-Tech Development Zone, Hefei City, Anhui Province, 230088 People's Republic of China
Active Pharmaceutical Ingredient(s) (API)	Lamivudine + zidovudine
Pharmaco-therapeutic group (ATC Code)	Antiviral for treatment of HIV infection, combinations (J05AR01)
Therapeutic indication	Lamivudine/zidovudine 150 mg/300 mg tablets is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing over 25 kg in combination with other antiretroviral agents

1. Introduction

Lamivudine/zidovudine 150 mg/300 mg tablets is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing over 25 kg.

Lamivudine/zidovudine 150 mg/300 mg Tablets should be initiated by a health care provider experienced in the management of HIV.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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)

Lamivudine and zidovudine have been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that these APIs, used in the manufacture of lamivudine/zidovudine

150 mg/300 mg tablets, are of good quality and manufactured in accordance with WHO good manufacturing practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance

with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide and povidone all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium pigment, talc and polyethylene glycol. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of them are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white or off-white, capsule-shaped, film-coated tablet debossed with "BC" on one side and scoreline on opposite side. The tablets are presented in white opaque, round HDPE bottles with white opaque child-resistant HDPE caps.

The product has been developed as fixed-dose combination film-coated tablets with similar bioavailability as the WHO recommended comparator product, combivir tablets. All the excipients used in the formulation are commonly used in the manufacture of solid oral dosage forms. Wet granulation was chosen in order to improve the flow properties of the granules. Trial formulas were developed and optimized to meet the quality specifications of the product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (HPLC and UV), water content (KF), assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), splittability (by weight variation), related substances (HPLC), residual solvent and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 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 results for all parameters at these storage conditions were within agreed acceptance criteria and no negative or atypical trends were observed. 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 2015/2016 according to internationally accepted guidelines.

A randomized, single dose, open label, two-period, cross-over bioequivalence study comparing the test product, zidovudine and lamivudine 300 mg/ 150 mg tablet (Anhui Biochem Bio-Pharmaceutical Co., Ltd., China) with the reference product, combivir® 150 mg/300 mg film-coated tablet (ViiV Healthcare UK Ltd, UK), in healthy adult human subjects under fasting conditions (study no. 15-10-180).

The objective of the study was to compare the bioavailability of the stated Lamivudine/zidovudine 150 mg/300 mg FDC tablet manufactured by/for Anhui Biochem Bio-Pharmaceutical Co., Ltd., China (test drug) with the reference formulation combivir® (ViiV Healthcare UK Ltd.) 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 two treatments in a randomized fashion:

Treatment T: Test – 1 tablet lamivudine/ zidovudine 150 mg/300 mg
(lamivudine 150 mg + zidovudine 300 mg)
Batch no. 1410033.

Treatment R: Reference – 1 tablet combivir®
(lamivudine 150 mg + zidovudine 300 mg)
Batch no. ZA0916.

A 12-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 19 samples within 36 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 and zidovudine were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 20 ng/mL for lamivudine and 40 ng/mL for zidovudine.

The study was performed with 60 participants; data generated from a total of 57 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.11 ± 0.61	1.08 ± 0.69	–	–
C_{max} (ng /mL)	1948 ± 691 (1819)	1962 ± 647 (1849)	98	92.6 – 104.4
AUC_{0-t} (ng.h/mL)	7189 ± 1606 (6999)	7164 ± 1477 (7007)	100.0	92.6 – 104.4
AUC_{0-inf} (ng.h /mL)	7360 ± 1601 (7177)	7324 ± 1468 (7175)	100.1	92.6 – 104.4

* geometric mean

Zidovudine

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)	0.42 ± 0.16	0.53 ± 0.25	–	–
C_{max} (ng/mL)	3633 ± 1527 (3298)	3459 ± 1492 (3147)	104.9	93.4 – 117.8
AUC_{0-t} (ng h/mL)	2996 ± 797 (2892)	2927 ± 802 (2834)	102.2	98.4 – 106.1

$AUC_{0\text{-}inf}$ (ng ·h/mL)	3125 ± 778 (3030)	3065 ± 798 (2975)	102.0	98.4 – 105.6

* geometric mean

Conclusion
The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding lamivudine and zidovudine. Accordingly, the test lamivudine/zidovudine 150 mg/300 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation combivir® (ViiV Healthcare UK Ltd.).

4. Summary of product safety and efficacy

[HA656 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, [HA656 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product combivir® for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [HA656 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA656 trade name] has shown to be bioequivalent with combivir® (ViiV Healthcare UK Ltd.)

Efficacy and Safety

Regarding clinical efficacy and safety, [HA656 trade name] is considered effective and safe to use when the guidance and restrictions presented in the summary of product characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA656 trade name] was acceptable for the following indication: **in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing over 25 kg** and has advised that the quality, efficacy and safety of [HA656 trade name] manufactured at Anhui Biochem Bio-Pharmaceutical Co., Ltd, OSD workshop, 2nd floor of the Building 2, No. 30 Hongfeng road, Hi-Tech Development Zone, Hefei city, Anhui province, 230088, China in the list of prequalified medicinal products.