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	[HA655 trade name]*
Manufacturer of Prequalified Product	Shanghai Desano Bio-Pharmaceutical Co., Ltd. 1479 Zhangheng Road Pilot Free Trade Zone Shanghai 201203 China
Active Pharmaceutical Ingredients (APIs)	Lamivudine and Zidovudine
Pharmaco-therapeutic group (ATC Code)	Antiviral for treatment of HIV infection, combinations (J05AR01)
Therapeutic indication	Lamivudine and Zidovudine Tablets 150 mg/300 mg is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agent-

1. Introduction

[HA655 trade name] are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. [HA655 trade name] should not be used for patients with clinically significant hypersensitivity to lamivudine, zidovudine or to any of the components in the formulation. It is recommended that therapy is given only on the advice of 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)

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 two APIs, used in the manufacture of [HA655 trade name], are of good quality and manufactured in accordance with WHO Good Manufacturing Practices. 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.

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

Based on scientific principles WHO PQTm has identified lamivudine (up to 300mg oral dose) as a BCS class 3 API and zidovudine (up to 300mg oral dose) as a BCS class 1 API. The APIs are thus regarded highly soluble over the pH range 1 to 6.8.

Other ingredients

Other ingredients used in the core tablet formulation include colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The film coating contains hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide. Certificates confirming that the excipients are TSE/ BSE free were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, film-coated, modified capsule-shaped tablet with a breakline on both sides of the tablet. "D" is debossed on one side of the breakline and "02" is debossed on the other side of the break-line on both tablet faces such that when broken in half, "D" and "02" are present on each half tablet. The break-lines are intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in an HDPE bottle with child resistant cap. The FPP is a generic version of the WHO recommended comparator product, Combivir® tablets. The comparator product has been characterized with respect physicochemical properties to define a quality target product profile, including dissolution profiles. The excipients were selected based on the excipients used in the comparator tablets and API/API-excipient compatibility study results. A direct compression manufacturing process – involving blending, compression and film coating – has been developed. Optimization studies were performed to meet the desired tablet characteristics. The multisource tablets showed, similar to the comparator product, very rapidly dissolution properties. 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 of the APIs (HPLC and TLC), assay (HPLC), loss on drying, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), organic impurities (HPLC), residual solvents (GC) and microbial limits.

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 product proved to be quite stable at these storage conditions, with no negative trends observed. Data presented for stability studies conducted for three months at zone IVa storage condition on half tablets, placed back in the original container, also showed little change. 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 2013 according to internationally accepted guidelines.

Study title: A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of [HA655 trade name] of Shanghai Desano Bio-Pharmaceutical Co., Ltd., China with Combivir® (lamivudine and zidovudine tablets 150 mg/300 mg) of GlaxoSmithKline Research Triangle Park, NC 27709, in normal, healthy, adult, human subjects under fasting condition (study no. ARL/12/399).

The objective of the study was to compare the bioavailability of the stated [HA655 trade name] manufactured by Shanghai Desano Bio-Pharmaceutical Co., Ltd., China (test drug) with the reference formulation Combivir® (GlaxoSmithKline Research) 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 treatments in a randomized fashion:

Treatment T:	Test – 1 tablet [HA655 trade name] (lamivudine 150 mg + zidovudine 300 mg) Batch no. BF12001
Treatment R:	Reference – 1 tablet Combivir® (lamivudine 150 mg + zidovudine 300 mg) Batch no. 2ZP8707

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 36 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 and zidovudine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 15 ng/ mL for lamivudine as well as for zidovudine.

The study was performed with 60 participants; data generated from a total of 58 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
tmax (h)	1.35 ± 0.62	1.31 ± 0.58	-	-
Cmax (ng/mL)	1702 ± 547 (1616)	1733 ± 436 (1678)	96.3	90.9 – 102.1
AUC0-t (ng. h/mL)	7450 ± 1792 (7229)	7586 ± 1640 (7410)	97.6	94.0 – 101.3
AUC0-inf (ng.h/mL)	7620 ± 1792 (7405)	7762 ± 1649 (7587)	97.6	94.1 – 101.2

* geometric mean

Zidovudine

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
tmax (h)	0.71 ± 0.42	0.65 ± 0.37	-	-
Cmax (ng/mL)	1898 ± 920 (1674)	2053 ± 1004 (1851)	90.5	82.2 – 99.5
AUC0-t (ng.h/mL)	2583 ± 833 (2448)	2551 ± 760 (2444)	100.1	96.8 – 103.4
AUC0-inf (ng. h/mL)	2624 ± 835 (2490)	2590 ± 763 (2485)	100.2	96.9 – 103.5

* 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 and zidovudine. Accordingly, the test [HA655 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Combivir® (GlaxoSmithKline Research).

4. Summary of product safety and efficacy

[HA655 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, [HA655 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Combivir® (GlaxoSmithKline Research) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA655 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 [HA655 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA655 trade name] has been shown to be bioequivalent with Combivir® (GlaxoSmithKline Research).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA655 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 [HA655 trade name] was acceptable for the following indication: ' treatment of HIV-1 infection in combination with one more other antiretroviral agents", and would allow inclusion of [HA655 trade name], manufactured at Shanghai Desano Bio-Pharmaceutical Co., Ltd., 1479 Zhangheng Road Pilot Free Trade Zone Shanghai 201203 China , in the list of prequalified medicinal products.