SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Lamivudine and Zidovudine Tablets 150 mg/300 mg*
Manufacturer of Prequalified Product:	Shanghai Desano Bio-Pharmaceutical Co., Ltd. 1479 Zhangheng Road Zhangjiang High-Tech Park Shanghai 201203 China
Active Pharmaceutical Ingredients (APIs):	Lamivudine + Zidovudine
Pharmaco-therapeutic group (ATC Code):	Antiviral for treatment of HIV infection, combinations (J05AR01)
Therapeutic indication:	Lamivudine and Zidovudine Tablets 150 mg/300 mgis indicated for the treatment of HIV-1 infection in combination with other antiretroviral agent-

*Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Lamivudine and Zidovudine Tablets 150 mg/300 mg are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Lamivudine and Zidovudine Tablets 150 mg/300 mgshould 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 Ingredients (APIs)

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 SeriesNo. 953, 2009, Annex 4). This procedure provides an assurance that these two APIs, used in the manufacture of Lamivudine/Zidovudine 150mg/300mg Tablets, 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.
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 products (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 breakline on both tablet faces such that when broken in half, "D" and "02" are present on each half tablet. The breaklines 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 todefine 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 Bio-Equivalence

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 Lamivudine and Zidovudine tablets USP 150 mg/300 mg 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 Lamivudine/Zidovudine 150/300 mg FDC tablet manufactured for/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 Lamivudine/Zidovudine 150/300 mg (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 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 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)
t_{max} (h)	1.35 ± 0.62	1.31 ± 0.58	-	-
C_{max} (ng/ml)	1702 ± 547 (1616)	1733 ± 436 (1678)	96.3	90.9 – 102.1
AUC_{0-t} (ng.h/ml)	7450 ± 1792 (7229)	7586 ± 1640 (7410)	97.6	94.0 – 101.3
AUC_{0-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)
t_{max} (h)	0.71 ± 0.42	0.65 ± 0.37	-	-
C_{max} (ng/ml)	1898 ± 920 (1674)	2053 ± 1004 (1851)	90.5	82.2 – 99.5
AUC_{0-t} (ng.h/ml)	2583 ± 833 (2448)	2551 ± 760 (2444)	100.1	96.8 – 103.4
AUC_{0-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 Lamivudine/Zidovudine 150/300 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Combivir® (GlaxoSmithKline Research).

4. Summary of Product Safety and Efficacy

Lamivudine and Zidovudine 150 mg/300 mg Tablets conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference, Combivir® tablets.

The clinical safety of this product is considered acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

Comparability between the reference Combivir® 150/300 mg tablet (GlaxoSmithKline) and the test tablet Lamivudine and Zidovudine Tablets 150 mg/300 mg(Shanghai Desano Bio-pharmaceutical Co., Ltd., China) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven.

Efficacy and Safety

Regarding clinical efficacy and safety, Lamivudine and Zidovudine Tablets 150 mg/300 mgare considered effective and safe when the guidance and restrictions presented in the SmPC 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 by consensus that the benefit–risk profile of Lamivudine and Zidovudine Tablets 150 mg/300 mgwas acceptable for the following indications: treatment of children with HIV-1 infection in combination with other antiretroviral agents and primary prophylaxis of HIV-1 infection in neonates, and has advised inclusion of Lamivudine and Zidovudine Tablets 150 mg/300 mg, manufactured at Shanghai Desano Bio-Pharmaceutical Co., Ltd., Shanghai, China, in the list of prequalified medicinal products.