**This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.**

## SCIENTIFIC DISCUSSION

| | |
|---|---|
| **Name of the Finished Pharmaceutical Product:** | Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets* |
| **Manufacturer of Prequalified Product:** | Shanghai Desano Bio-pharmaceutical Co., Ltd.<br>1479 Zhangheng Road<br>China (Shanghai) Pilot Free Trade Zone<br>Shanghai 201203<br>China |
| **Active Pharmaceutical Ingredient (API):** | Lamivudine/Nevirapine/Zidovudine |
| **Pharmaco-therapeutic group (ATC Code):** | Antivirals for systemic use, combinations, J05AR05 |
| **Therapeutic indication:** | Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25 kg. |

* 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/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25kg. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets 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 Ingredients (APIs)

Lamivudine, nevirapine 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 three APIs, used in the manufacture of Lamivudine/Nevirapine/Zidovudine 150mg/200mg/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 300 mg oral dose) as a BCS class 1 API. According to the data provided nevirapine is of BCS low solubility, hence particle size distribution forms part of the FPP manufacturer's specifications

### Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, polyvinyl pyrrolidone, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol / polyethylene glycol and polysorbate 80. BSE/TSE compliance declarations were providedFinished pharmaceutical product (FPP)

### Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

The multisource product is a white coloured, oval shaped, film coated, biconvex tablet with "D" and "06" debossed on one side of the tablet with break line separating "D" and "06"and having a break line on the other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablets are packaged in a white opaque HDPE bottle with child resistant polypropylene closure with induction sealing liner.

The generic Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets, a fixed-dose combination, was developed to have similar in-vitro dissolution, stability and in-vivo performance as the WHO recommended comparator products, Combivir® Tablets and Viramune® Tablets. The quality target product profile was defined based on the physicochemical properties of the APIs and characterization of the WHO recommended comparator products.

Since nevirapine API in fine particle size exhibits poor flow properties, a wet granulation process was selected to improve its granule flowability, while lamivudine and zidovudine, which have good flow properties, are added as extra-granular parts. The excipients used in Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets were selected based on the composition of the WHO recommended comparator products, Combivir® Tablets and Viramune® Tablets, results of excipient compatibility studies and prior knowledge on tablet formulation development. 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 TLC), assay (HPLC), dissolution (HPLC detection), uniformity of dosage units, related substances (HPLC), loss on drying and microbial limits.

*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, with no significant change or negative trend 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 Bio-Equivalence

The following bioequivalence study has been performed in 2015/2016 according to internationally accepted guidelines.

An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study fixed dose combination of Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg tablets of Shanghai Desano Bio-Pharmaceutical Co., Ltd., China with that of Combivir® (lamivudine and zidovudine) 150 mg/300 mg tablets of GlaxoSmithKline, Research Triangle Park, NC 27709 and Viramune® (nevirapine) 200 mg tablets of Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877 USA in healthy, adult, human subjects under fasting conditions (study no. LAMI-2733-15).

The objective of the study was to compare the bioavailability of the stated Lamivudine/Nevirapine/Zidovudine 150 mg/200mg/300 mg FDC tablet manufactured by/for Shanghai Desano Bio-Pharmaceutical Co., Ltd., China (test drug) with the reference formulations Combivir®

(GlaxoSmithKline) and Viramune® (Boehringer Ingelheim Pharmaceuticals Inc.) 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/Nevirapine/Zidovudine 150 mg/200 mg/300mg (lamivudine 150 mg + nevirapine 200 mg + zidovudine 300 mg) Batch no. BME14001.

Treatment R: References
– 1 tablet Combivir®
(lamivudine 150 mg + zidovudine 300 mg)
Batch no. 4ZP3257.
– 1 tablet Viramune®
(nevirapine 200 mg)
Batch no. 359522M.

A 21 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 27 samples within 168 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, nevirapine and zidovudine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 25 ng/ml for lamivudine, 38 ng/ml for nevirapine and 25 ng/ml for zidovudine.

The study was performed with 60 participants; data generated from a total of 54 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine, nevirapine 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) | 1.58 ± 1.07 | 1.40 ± 0.83 | - | - |
| $C_{max}$ (ng/ml) | 1598 ± 578 (1496) | 1501 ± 480 (1428) | 104.8 | 98.3 – 111.6 |
| $AUC_{0-t}$ (ng.h/ml) | 6697 ± 1823 (6460) | 6521 ± 1564 (6334) | 102.0 | 97.6 – 106.6 |
| $AUC_{0-inf}$ (ng.h/ml) | 6974 ± 1813 (6748) | 6789 ± 1572 (6606) | 102.2 | 98.0 – 106.5 |

* geometric mean

**Nevirapine**

| 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) | 2.04 ± 1.20 | 2.03 ± 1.19 | - | - |
| $C_{max}$ (ng/ml) | 4201 ± 827 (4124) | 3864 ± 646 (3807) | 108.3 | 104.7 – 112.1 |
| $AUC_{0-t}$ (ng.h/ml) | 245120 ± 40214 (241629) | 244203 ± 38739 (241159) | 100.2 | 97.8 – 102.7 |
| $AUC_{0-inf}$ (ng.h/ml) | 329011 ± 87246 (317639) | 327028 ± 101657 (313956) | 101.2 | 96.8 – 105.7 |

* 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) | 0.74 ± 0.61 | 0.66 ± 0.41 | - | - |
| $C_{max}$ (ng/ml) | 3109 ± 1757 (2674) | 3009 ± 1552 (2646) | 101.1 | 88.0 – 116.1 |
| $AUC_{0-t}$ (ng.h/ml) | 3240 ± 852 (3137) | 3162 ± 867 (3058) | 102.6 | 97.6 – 107.8 |
| $AUC_{0-inf}$ (ng.h/ml) | 3321 ± 853 (3220) | 3247 ± 871 (3144) | 102.4 | 97.5 – 107.6 |

* 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, nevirapine and zidovudine. Accordingly, the test Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Combivir® (GlaxoSmithKline) and Viramune® (Boehringer Ingelheim Pharmaceuticals Inc.).

## 4. Summary of Product Safety and Efficacy

Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator products. According to the submitted data on quality and bioavailability, Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator products Combivir® and Viramune® 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 Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets is used in accordance with the SmPC.

Bioequivalence

Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets has shown to be bioequivalent with Combivir® [(lamivudine/zidovudine 150mg/300mg tablets), GlaxoSmithKline] and Viramune® [(nevirapine 200 mg tablets), Boehringer Ingelheim Pharmaceuticals Inc.].

Efficacy and Safety

Regarding clinical efficacy and safety, Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 Lamivudine/ Nevirapine/Zidovudine 150mg/200mg/300 mg Tablets was acceptable for the following indication**: "the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, and for children that weigh at least 25 kg",** and has advised that the quality, efficacy and safety of Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets allow inclusion of Lamivudine/Nevirapine/Zidovudine 150mg/200mg/300mg Tablets, manufactured at Shanghai Desano Bio-Pharmaceutical Co., Ltd, 1479 Zhangheng Road, China (Shanghai) Pilot Free Trade Zone, Shanghai 201203, China, in the list of prequalified medicinal products.