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

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| **Name of the Finished Pharmaceutical Product** | [HP030 trade name][*] |
| **Manufacturer of Prequalified Product** | Shijiazhuang Lonzeal Pharmaceuticals Co., Ltd.<br>201 Workshop<br>No.16, West Ring Road,<br>Shenze, Shijiazhuang, Hebei,<br>P.R. China 052560 |
| **Active Pharmaceutical Ingredient (API)** | Tenofovir disoproxil fumarate |
| **Pharmaco-therapeutic group (ATC Code)** | Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors (J05AF07). |
| **Therapeutic indication** | [HP030 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infection in adults and adolescents weighing at least 30 kg.<br>[HP030 trade name] is indicated for pre-exposure prophylaxis (PrEP) for adults and adolescents weighing at least 30 kg who are at substantial risk of HIV infection.<br>[HP030 trade name] is indicated, in combination with other antiretroviral medicines, for post-exposure prophylaxis (PEP) in adults and adolescents weighing at least 30 kg who have been exposed to HIV.<br>[HP030 trade name] is indicated for the treatment of chronic hepatitis B in adults and adolescents from 12 years of age.<br>[HP030 trade name] is indicated for preventing mother-to-child transmission of hepatitis B in HBV-positive pregnant women at high risk of transmitting the virus to their baby (those with HBV DNA ≥ 200 000 IU/mL or positive HBeAg). It may also be considered in all HBV-positive pregnant women when tests for HBV DNA or HBeAg are not available. |

## 1. Introduction

[HP030 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infection and chronic hepatitis B (see part 4 for full indications).

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

[HP030 trade name] should be prescribed by a healthcare provider experienced in the management of HIV infection or hepatitis B.

## 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)

Tenofovir disoproxil fumarate has 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 the API, used in the manufacture of [HP030 trade name], is 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 inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

### Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, lactose monohydrate, titanium dioxide, triacetin and FD&C blue #2/indigo carmine aluminium lake.

The excipients are supported by appropriate declarations and controlled by acceptable specifications. TSE/BSE free certificates from the suppliers have been provided with regard to the excipients.

### Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

The multisource product is a blue, almond-shaped, film coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'LZ30' debossed (stamped into) one side and '300' debossed (stamped into) the other side.

The tablets are packaged in a white opaque, round HDPE bottle with a 3g silica gel desiccant and fitted with white opaque, polypropylene child resistant cap closure and foil laminated closure liner.

The goal of the formulation development strategy was to develop an immediate-release solid oral dosage form with a similar quality profile and bioequivalent to the WHO recommended comparator product, Viread ® (tenofovir disoproxil fumarate 300mg) tablets. The excipients used in the formulation are consistent with those used in the comparator product, including the coating composition. The selection of the excipients was furthermore supported by API-excipient compatibility studies. With reference to the information on the comparator product published on the EMA's website, wet granulation was chosen for the finished pharmaceutical product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

*Specifications*

The finished product specifications include tests for appearance, identification of the API (UV and HPLC), water content (KF), dissolution (HPLC detection), weight variation, related substances

(HPLC), assay (HPLC) and microbial limits. The test methods have been satisfactorily described and validated.

*Stability testing*

Stability studies have been conducted at 30°C/75%RH 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 data showed all the parameters met their acceptance criteria at both long-term and accelerated storage conditions, with a slight increase in degradation products, in the proposed packaging configuration. 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 2020 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of tenofovir disoproxil fumarate tablets 300 mg of Shijiazhuang Lonzeal Pharmaceuticals Co., Ltd., China with Viread® (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc. Foster City, CA 94404, in healthy adult human subjects under fasting conditions (study no. C20105).

The objective of the study was to compare the bioavailability of the stated tenofovir 300 mg tablet manufactured by Shijiazhuang Lonzeal Pharmaceuticals Co., Ltd., China (test drug) with the reference formulation Viread® (Gilead Sciences Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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 Tenofovir disoproxil fumarate tablets 300 mg (Tenofovir disoproxil fumarate 300 mg) Batch no. 1900016061.

Treatment R: Reference – 1 tablet Viread® 300 mg (Tenofovir disoproxil fumarate 300 mg) Batch no. 013186.

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 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, $C_{max}$ and $t_{max}$ for bioequivalence evaluation. Drug concentrations for tenofovir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 3 ng/mL for tenofovir.

The study was performed with 26 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for tenofovir as well as statistical results are summarised in the following table:

**Tenofovir**

| **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) |

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| $t_{max}$ (h) | 1.12 ± 0.57 | 1.09 ± 0.68 | – | – |
| $C_{max}$ (ng/mL) | 293 ± 76<br>(284) | 303 ± 78<br>(293) | 97.0 | 88.6 – 106.2 |
| $AUC_{0-t}$ (ng·h/mL) | 2403 ± 502<br>(2349) | 2502 ± 542<br>(2443) | 96.2 | 89.1 – 103.8 |
| $AUC_{0-inf}$ (ng·h/mL) | 2620 ± 583<br>(2556) | 2725 ± 613<br>(2657) | 96.2 | 89.3 – 103.7 |

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and $C_{max}$ values regarding tenofovir. Accordingly, the test Tenofovir 300 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Viread® (Gilead Sciences Inc.).

## 4. Summary of product safety and efficacy

[HP030 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, [HP030 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Viread® (Gilead Sciences Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HP030 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 [HP030 trade name] is used in accordance with the SmPC.

### Bioequivalence

[HP030 trade name] has been shown to be bioequivalent with Viread® (Gilead Sciences Inc.).

### Efficacy and Safety

Regarding clinical efficacy and safety, [HP030 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 [HP030 trade name] was acceptable for the following indication: 'treatment of HIV infection and treatment of chronic hepatitis B', and would allow inclusion of [HP030 trade name], manufactured at Shijiazhuang Lonzeal Pharmaceuticals Co., Ltd., 201 Workshop, No.16, West Ring Road, Shenze, Shijiazhuang, Hebei,P.R. China 052560 in the list of prequalified medicinal products.