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	[HA792 trade name][*]
Manufacturer of Prequalified Product	Shanghai Desano Bio-Pharmaceutical Co., Ltd 1479 Zhangheng Road China (Shanghai) Pilot Free Trade Zone Shanghai 201203 P.R. China
Active Pharmaceutical Ingredient(s) (API)	Emtricitabine/tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antiviral for systemic use; antivirals for treatment of HIV infection, combinations. (J05AR03)
Therapeutic indication	[HA792 trade name] is indicated in combination with another antiretroviral medicine for the treatment and prophylaxis of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg. [HA792 trade name] can be used in the treatment of chronic hepatitis B in adults and adolescents from 12 years of age.

1. Introduction

[HA792 trade name] is indicated in combination with another antiretroviral medicine for the treatment and prophylaxis of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.

[HA792 trade name] can be used in the treatment of chronic hepatitis B in adults and adolescents from 12 years of age.

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

[HA792 trade name] 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)

Emtricitabine and tenofovir disoproxil fumarate (TDF) have been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients

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

for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [HA792 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.

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, croscarmellose sodium, pregelatinized starch, microcrystalline cellulose and magnesium stearate, all being controlled by acceptable specifications. The commercially sourced proprietary film-coating mixture contains hypromellose, lactose monohydrate, triacetin, titanium dioxide and FD&C blue #2 /indigo carmine aluminium lake. Lactose and magnesium stearate are of bovine and vegetable origin respectively.

TSE / BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a light blue, capsule-shaped, film coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'D17' debossed (stamped into) one side and is plain on the other side. The tablets are packaged in a round, opaque white plastic (HDPE) bottle. It also contains a sachet of desiccant (drying material). The bottle has an aluminium/plastic foil seal and a white plastic (polypropylene) screw cap.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO recommended comparator product Truvada® (emtricitabine/tenofovir disoproxil fumarate 200 mg/300 mg) tablets. The selection of excipients was based on the qualitative composition of the core tablet of the comparator product and compatibility with the APIs and literature studies. Wet granulation process was selected based on the high content and poor flowability of the APIs. 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 description, identification of the APIs (HPLC and UV), assay (HPLC), related substances (HPLC), dissolution (HPLC detection), content uniformity, water content (KF) and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30º/75%RH as long-term storage conditions and for six months at 40ºC/75%RH as accelerated storage conditions in the packaging proposed for marketing of the product. The data showed slight degradation for TDF, though all parameters were well within the agreed limits at both storage conditions. 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 2023 according to internationally accepted guidelines:

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study of [HA792 trade name] manufactured by Shanghai Desano Bio-Pharmaceutical Co., Ltd with Truvada (emtricitabine and tenofovir disoproxil fumarate) 200 mg/300 mg tablets manufactured by Gilead Sciences Inc., Foster City, CA 94404, in normal, healthy, adult, male and female human subjects under fasting conditions (study no. ARL-23-062).

The objective of the study was to compare the bioavailability of the stated [HA792 trade name] manufactured by/for Shanghai Desano Bio-Pharmaceutical Co., Ltd, China (test drug) with the reference FDC tablet Truvada® (Gilead Sciences 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 [HA792 trade name]
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. DNE23001

Treatment R: Reference – 1 tablet Truvada®
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 035226

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 emtricitabine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 40 ng/mL for emtricitabine and 5 ng/mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Emtricitabine

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)	1.72 ± 0.75	1.61 ± 0.61	–	–
C_{max} (ng/mL)	13159 ± 2551 (2523)	13995 ± 2311 (2662)	94.8	88.4 – 101.6
AUC_{0-t} (ng·h/mL)	13667 ± 2545 (12854)	14490 ± 2297 (13784)	93.3	88.3 – 98.5
AUC_{0-inf} (ng·h/mL)	2575 ± 524 –	2715 ± 552 –	–	–

* geometric mean

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)
t_{max} (h)	1.21 ± 0.64	1.12 ± 0.43	–	–
C_{max} (ng/mL)	335 ± 77 (325)	332 ± 95 (316)	102.7	94.7 – 111.4
AUC_{0-t} (ng·h/mL)	2664 ± 748 (2556)	2731 ± 662 (2639)	96.8	89.4 – 104.9
AUC_{0-inf} (ng·h/mL)	2906 ± 770 –	2974 ± 650 –	–	–

* geometric mean

The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and Cmax values regarding emtricitabine and tenofovir. Accordingly, the test [HA792 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Truvada® (Gilead Sciences Inc.).

4. Summary of product safety and efficacy

[HA792 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, [HA792 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Truvada® (Gilead Sciences Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA792 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 [HA792 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA792 trade name] has been shown to be bioequivalent with Truvada® (Gilead Sciences Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA792 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 [HA792 trade name] was acceptable for the

following indication: 'in combination with another antiretroviral medicine for the treatment and prophylaxis of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg and can be used in the treatment of chronic hepatitis B in adults and adolescents from 12 years of age', and would allow inclusion of [HA792 trade name], 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.