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	[HA726 trade name]*
Manufacturer of Prequalified Product	Emcure Pharmaceuticals Limited Plot No. P-1 & P-2, ITBT Park Phase II, MIDC, Hinjwadi, Pune Maharashtra 411057 India
Active Pharmaceutical Ingredient(s) (API)	Emtricitabine /Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections (J05AR03)
Therapeutic indication	[HA726 trade name] is indicated in combination with at least one other antiretroviral product for the treatment of HIV-1 infection in adults and adolescents over 10 years of age and weighing at least 30 kg. [HA726 trade name] may be used in combination with other measures for pre-exposure prophylaxis (PrEP) in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.

1. Introduction

[HA726 trade name] is indicated in combination with at least one other antiretroviral product for the treatment of HIV-1 infection in adults and adolescents over 10 years of age and weighing at least 30 kg.

[HA726 trade name] may be used in combination with other measures for pre-exposure prophylaxis (PrEP) in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.

[HA726 trade name] should be prescribed 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*.

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

Active pharmaceutical Ingredient (API)

Emtricitabine

Emtricitabine 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 [HA726 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 assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate (TDF) is the salt of tenofovir disoproxil with fumaric acid. Tenofovir disoproxil is a diester pro-drug of the purine-based nucleotide analogue, tenofovir. The pro-drug has increased oral bioavailability compared to tenofovir. TDF is BCS high soluble.

TDF, (R)-9-(2-phosphonomethoxypropyl) adenine disoproxil fumarate, is manufactured in several steps from adenine via (R)-9-(2-hydroxypropyl) adenine. The specifications and test methods for the isolated intermediates are considered to be satisfactory. The structure and stereochemistry of TDF were confirmed by the route of synthesis and spectrometric data. TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114^{0}C) and a high melting form (m.p. 114-118^{0}C). The high melting form, controlled by XRPD and melting point (DSC), is consistently produced.

The specifications for TDF include tests for description, solubility, identification (IR, HPLC), polymorphic identity (XRPD), clarity of solution, water content (KF), heavy metals, melting point, related substances (HPLC), 9-propenyladenine (HPLC; ≤ 5 ppm), enantiomeric purity (chiral HPLC; S-isomer ≤ 0.40%), assay (HPLC), fumaric acid content (HPLC), residual solvents (GC), particle size and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, croscarmellose sodium, pregelatinized starch and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, titanium dioxide, talc, lecithin (soya) and xanthan gum. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, modified capsule-shaped, film coated tablet, debossed with 'EM' on one side and '144' on other side. The tablets are presented in a white, opaque, wide mouth, round HDPE bottle with a 3g silica gel canister and closed with a white, opaque polypropylene child-resistant cap.

The development strategy was to formulate an immediate release FDC dosage form, which is stable, and bioequivalent to the WHO comparator product Truvada® (emtricitabine/tenofovir disoproxil fumarate 200 mg/300 mg) Tablets. The quality target product profile was defined based on the properties of the active pharmaceutical ingredients, characterization of the comparator product and intended patient population. The excipients selected for the finished pharmaceutical product have been widely used in oral pharmaceutical formulations. Most of the excipients were similar to excipients used in the comparator product. Emtricitabine and Tenofovir disoproxil fumarate have low

bulk density, very poor flow and compressibility characteristics, therefore wet granulation was selected as the manufacturing process to improve flowability and compressibility. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC with DAD), water content (KF), assay (HPLC), uniformity of dosage units (by content uniformity), related substances (HPLC), dissolution (HPLC detection), residual solvents and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30ºC/75%RH as long-term storage condition in the packaging proposed for marketing of the product. The product proved to be stable at the storage condition. 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.

Randomized, Open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Emtricitabine 200 mg and Tenofovir Disoproxil Fumarate 300 mg tablets of Emcure Pharmaceuticals Ltd., India with Truvada® (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) tablets of Gilead Sciences, Inc. Foster City, CA 94404 in normal, healthy, adult, human subjects under fasting condition (study no. ARL/13/421).

The objective of the study was to compare the bioavailability of the stated Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300 mg FDC tablet manufactured by/for Emcure Pharmaceuticals Ltd., India (test drug) with the reference formulation 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 Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300 mg (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Lot no. EM36111.
Treatment R:	Reference– 1 tablet Truvada® (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Lot no. 000101.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 72 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 emtricitabine and tenofovir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 20 ng/mL for emtricitabine and 5 ng/mL for tenofovir.

The study was performed with 48 participants; data generated from a total of 45 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)	1.8 ± 0.6	1.9 ± 0.9	–	–
C_{max} (ng/mL)	2 118 ± 520 (2 054)	2 126 ± 507 (2 063)	99.5	93.8 – 105.6
AUC_{0-t} (ng·h/mL)	11 630 ± 2 141 (11 424)	11 827 ± 1 973 (11 656)	98.0	94.5 – 101.7
AUC_{0-inf} (ng·h/mL)	11 988 ± 2 145 (11 787)	12 188 ± 2 002 (12 019)	98.1	94.7 – 101.5

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) [#]	1.1 ± 0.4	1.2 ± 0.5	–	–
C_{max} (ng/mL)	409 ± 129 (390)	381 ± 112 (367)	106.5	100.6 – 112.7
AUC_{0-t} (ng·h/mL)	2 873 ± 755 (2 781)	2 964 ± 831 (2 862)	97.2	92.4 – 102.2
AUC_{0-inf} (ng·h/mL)	3 143 ± 750 (3 062)	3 193 ± 853 (3 097)	98.9	94.6 – 103.3

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding emtricitabine and tenofovir. Accordingly, the test Emtricitabine/Tenofovir Disoproxil Fumarate 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 formulation Truvuda® (Gilead Sciences, Inc.).

4. Summary of product safety and efficacy

[HA726 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, [HA726 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 [HA726 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 [HA726 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA726 trade name] has been shown to be bioequivalent with Truvada® (Gilead Sciences, Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA726 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics re 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 [HA726 trade name] was acceptable for the following indication: '**in combination with at least one other antiretroviral product for the treatment of HIV-1 infection in adults and adolescents over 10 years of age and weighing at least 30 kg** ', and has advised that the quality, efficacy and safety of [HA726 trade name] allow inclusion of [HA726 trade name], manufactured at Emcure Pharmaceuticals Limited, Plot No. P-1 & P-2, ITBT Park, Phase II, MIDC, Hinjwadi, Pune, Maharashtra, 411057, India, in the list of prequalified medicinal products.