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	[HA498 trade name][*]
Manufacturer of Prequalified Product	Hetero labs Limited, Unit – III, # 22-110, IDA, Jeedimetla, Hyderabad, Zip Code - 500 055, Telangana, India
Active Pharmaceutical Ingredient(s) (API)	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR03)
Therapeutic indication	[HA498 trade name] is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults and adolescents over 10 years of age and weighing at least 30 kg. [HA498 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

[HA498 trade name] is indicated in combination with other antiretroviral products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 30 kg. [HA498 trade name] may be used for pre-exposure prophylaxis in certain high-risk populations.

[HA498 trade name] should be prescribed by 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 Ingredient (API)

Emtricitabine

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified emtricitabine (up to 200 mg oral dose) as a BCS class 1 API. Emtricitabine is thus highly soluble according to the BCS.

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

Emtricitabine, 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone, has two chiral centres. The desired stereochemistry is built into the key intermediate in the multi-step synthesis process of emtricitabine, with L-menthol as the starting material for synthesis. Emtricitabine is known to exhibit polymorphism. Form I is consistently produced.

The API specifications are Ph.Int. based and include tests for description, solubility, identification (IR and SOR), polymorphic identity (XPRD), loss on drying, sulfated ash, heavy metals, enantiomeric content (chiral HPLC; ≤ 0.3%), related substances (HPLC), assay (potentiometry), residual solvents, particle size, microbiological examination and content of mesylates (GC-MS; each individual ≤ 7.5 ppm).

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 packing material.

Tenofovir disoproxil fumarate (TDF)

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.

The specifications for TDF include tests for description, solubility, identification, clarity of solution, water content, heavy metals, XRPD, melting point (DSC), related compounds (HPLC), enantiomeric impurity (≤ 0.40%; chiral HPLC), assay and fumaric acid content (HPLC), residual solvents, particle size and microbiological examination. The mutagenic 9-propenyladenine, which is a synthesis related substance, is controlled at ≤ 5.0 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int.

TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114°C) and a high melting form (m.p. 114-118°C). The high melting form, controlled by XRPD and melting point, is consistently produced.

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, lactose monohydrate, croscarmellose sodium, pregelatinized starch and magnesium stearate. Assurance by means of certificates was provided that the excipients are BSE/TSE free. The commercially sourced product film-coating mixture contains hypromellose, FD&C Blue #2 / Indigo carmine aluminium lake, triacetin, titanium dioxide and lactose monohydrate.

Finished pharmaceutical product (FPP)

Each tablet contains 200 mg of emtricitabine and 300 mg TDF equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

[HA498 trade name] tablets are blue, capsule shaped, film- coated tablets debossed with ‘H’ on one side and ‘124’ on the other side. The tablets are presented in an HDPE bottle also containing 1g silica

gel canister.

Pharmaceutical development and manufacture

The development of the final composition of the multisource product has been described. The objective was to develop a stable fixed-dose combination tablet bioequivalent to the comparator product, Truvada® film-coated tablets. The excipients selected for the core tablets are commonly used in tablets and qualitatively similar to that of the comparator product. The selection was furthermore supported by API-excipient compatibility studies. The APIs showed poor flow and compressibility properties. The applicant decided on the wet granulation method rather than direct compression in order to get better blend characteristics.

The process parameters were optimised to obtain tablets of desired characteristics, with dissolution profiles similar to that of the comparator product. Validation data presented for three batches demonstrated the consistency of the process and the quality of the product. Satisfactory in-process controls have been established.

Specifications
The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), average weight, water content, uniformity of dosage units (by content), dissolution (HPLC detection), related compounds and assay (HPLC) and microbiological examination. The test methods have been satisfactorily validated.

Stability testing
Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Slight degradation was observed, though the related substances content remained within acceptable limits. 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 2009 according to internationally accepted guidelines:

An open label, balanced, randomized, single-dose, two-treatment, two sequence, two-period, crossover bioequivalence study of [HA498 trade name] of Hetero Drugs Ltd, India and Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) tablets, 200 mg/300 mg of Gilead Sciences, Inc., Foster City, CA 94404, USA in healthy, adult, human subjects under fasting conditions. (study no. 08-VIN-029).

The objective of the study was to compare the bioavailability of the stated fixed dose [HA498 trade name] tablet manufactured by Hetero Drugs Ltd., India (test drug) with the same dose of the reference formulation (Truvada®, Gilead Sciences) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male 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 [HA498 trade name] (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. E8101.

Treatment R: Reference – 1 tablet Truvada®
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. C8A0045A.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 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 emtricitabine and tenofovir were analyzed using a validated LC-MS/MS method.
The limit of quantification was stated to be about 30 ng/ml for emtricitabine and 8 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 tenofovir as well as statistical results are summarised in the following tables:

Emtricitabine

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)	1.59 ± 0.68	1.51 ± 0.66	-	-
C_{max} (ng/ml)	2182 ± 595 (2103)	2166 ± 587 (2096)	100.1	93.9 – 106.8
AUC_{0-t} (ng.h/ml)	11040 ± 1840 (10880)	10877 ± 1901 (10735)	101.1	97.1 – 105.3
AUC_{0-inf} (ng.h/ml)	11384 ± 1817 (11236)	11237 ± 1939 (11096)	101.0	97.3 – 104.9

* geometric mean

Tenofovir

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)	1.11 ± 0.50	1.02 ± 0.44	-	-
C_{max} (ng/ml)	324 ± 90 (312)	340 ± 104 (325)	96.6	87.9 – 106.2
AUC_{0-t} (ng.h/ml)	2216 ± 615 (2129)	2199 ± 697 (2097)	101.5	93.5 – 110.3
AUC_{0-inf} (ng.h/ml)	2518 ± 630 (2439)	2550 ± 701 (2461)	99.2	92.6 – 106.3

* 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 emtricitabine and tenofovir. Accordingly, the fixed dose test tablet [HA498 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Truvada® (Gilead Sciences Inc.).

4. Summary of product safety and efficacy

[HA498 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and

bioavailability [HA498 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Truvada® (Gilead Sciences) for which benefits have been proven in terms of virological and immunological 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 [HA498 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA498 trade name] has shown to be bioequivalent with Truvada® (Gilead Sciences, Inc. USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA498 trade name] 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk-profile of [HA498 trade name] was acceptable for the following indications: **"in combination with other antiretroviral products for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 30 kg and for pre-exposure prophylaxis in certain high-risk populations"**, and has advised that the quality, efficacy and safety of [HA498 trade name] allow inclusion of [HA498 trade name], manufactured at Hetero labs Limited, Unit – III, # 22 – 110, IDA, Jeedimetla, Hyderabad, Zip Code - 500 055, Telangana, India, in the list of prequalified medicinal products.