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	[HA439 trade name]*
Manufacturer of Prequalified Product	Cipla Ltd Unit VII, III, IV Plot No: L-139 to L-146 and L-147 to L147-1 Verna Industrial Estate Goa – 403722 India
Active Pharmaceutical Ingredients (APIs)	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use; Antivirals for treatment of HIV infections, combinations (J05AR03).
Therapeutic indication	[HA439 trade name] is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults over 18 years of age.

1. Introduction

[HA439 trade name] is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults over 18 years of age.Detailed information on the use of this product are described in the summary of product characteristics (SmPC).

[HA439 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*.

Active pharmaceutical Ingredient (API)

Emtricitabine

Emtricitabine or 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone has two chiral carbon atoms. 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. The enantiomer of emtricitabine is controlled at level of not more than 0.3% by chiral HPLC chromatography.

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

Emtricitabine is known to exhibit polymorphism and exists in Forms I, II and III. According to XRPD and DSC data Form I is consistently produced.

The API specifications include description, solubility, identification (IR and HPLC), loss on drying, residue on ignition, heavy metals, colour of solution, enatiomeric purity (chiral HPLC), assay (HPLC), residual solvents, particle size distribution, polymorphic identity (DSC and XPRD), specific optical rotation and chromatographic purity (HPLC).

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) is the salt of tenofovir disoproxil with fumaric acid. Tenofovir disoproxil is a diester pro-drug of the purine based nucleotide analogue, tenofovir. TDF is a BCS Class 3 API, i.e. of high solubility and low permeability.

TDF is manufactured from (R)-9-[2-(phosphonylmethoxy)propyl]adenine (R-PMPA or tenofovir), which is commercially obtained. The specifications of R-PMPA, which is in turn obtained from (R)-9- (2-hydroxypropyl)adenine, are considered adequate for the manufacturing of TDF. The structure and stereochemistry of TDF was confirmed by the route of synthesis, with retention of chirality, and spectrometric data.

The specifications for TDF include description, solubility, clarity and colour of solution, identification of TDF and fumaric acid, assay and fumaric acid content by HPLC, chromatographic purity by HPLC, heavy metals, water content, residual solvents and particle size. The limits of the related substances are in agreement with ICH Q3A requirements. The enantiomeric purity, with the limit of the S-enantiomer set at ≤ 1.0%, is controlled by chiral HPLC. The mutagenic 9-propenyladenine, which is a synthesis related substance, is controlled at ≤ 5.0 ppm. Two polymorphic forms have been identified for TDF. Polymorph I is controlled by DSC and x-ray powder diffraction. The test methods have been adequately validated.

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.

Other ingredients

Other ingredients used in the core tablet formulation include croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinised starch. The excipients are compendial. Assurance by means of certificates was provided that the excipients are BSE/TSE free. The commercially sourced proprietary film-coating mixture contains FD&C Blue #2 Aluminium lake, hypromellose, lactose monohydrate, titanium dioxide and triacetin.

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.

[HA439 trade name] tablets are blue coloured, capsule shaped, biconvex, film-coated tablets plain on both sides. The tablets are presented in an induction sealed HDPE bottle fitted with a child resistant cap, provided with four silica gel bags of 1 g each (pack size: 30 tablets).

Pharmaceutical development and manufacture

The development of the final composition of [HA439 trade name] 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 were selected based on prior experience and the qualitative composition of the comparator product. The applicant decided on the wet granulation method rather than the dry granulation method in order to get better blend characteristics.

The two APIs are susceptible to hydrolysis, thus manufacturing conditions were selected to minimise possible degradation. Degradation is furthermore limited by control of the tablet moisture content and

by protective primary packaging, which includes a silica gel desiccant. The process parameters were optimised to obtain tablets of desired characteristics, with dissolution profiles similar to that of the comparator product. Validation data were presented for primary batches, demonstrating the consistency of the process and the quality of the product. Satisfactory in-process controls have been established.

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification of the APIs (HPLC and TLC), average weight, water content, uniformity of dosage units, dissolution (HPLC detection), degradation products and assay (HPLC) and microbial examination of non-sterile products. The test methods have been satisfactorily described and 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. The data showed little change with time. 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 2010 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of the fixed dose combination of [HA439 trade name] of Cipla Ltd., India with Truvada® (fixed dose combination of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) tablet of Gilead Sciences, Inc. USA, in normal, healthy, adult, human subjects under fasting condition (study no. ARL/09/404).
The objective of the study was to compare the bioavailability of the stated [HA439 trade name] tablet manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Truvada®, Gilead Sciences Inc.) and to assess bioequivalence. The comparison was performed as a single dose, 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 – [HA439 trade name] tablet (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. X91072.
Treatment R:	References – Truvada® 200/300 mg tablet (emtricitabine/tenofovir disoproxil fumarate 200/300 mg) Batch no. C9B2245A.

An 8-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 120 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 26 ng/mL for emtricitabine and 10 ng/mL for tenofovir.

The study was performed with 44 participants. Data generated from a total of 43 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 table:

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 (ANOVA log)
t_{max} (h)	1.7 ± 0.8	1.6 ± 0.7	–	–
C_{max} (ng/mL)	2006 ± 416 (1957)	2072 ± 440 (2023)	96.7	92.1 – 101.6
AUC_{0-t} (ng.h/mL)	10479 ± 2268 (10202)	10804 ± 2138 (10579)	96.4	93.2 – 99.8
AUC_{0-inf} (ng.h/mL)	10789 ± 2287 (10518)	11106 ± 2161 (10885)	96.6	93.6 – 99.7

* 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 (ANOVA log)
tmax (h)	1.2 ± 0.7	1.2 ± 0.7	-	-
Cmax (ng/mL)	271 ± 89 (258)	274 ± 79 (263)	97.9	92.7 – 103.5
AUC0-t (ng.h/mL)	1680 ± 645 (1576)	1757 ± 622 (1652)	95.4	90.0 – 101.1
AUC0-inf (ng.h/mL)	2022 ± 663 (1924)	2111 ± 643 (2014)	95.5	90.7 – 100.5

* geometric mean

Conclusions

The results of the study show that the preset acceptance limits of 80 - 125 % are met by both AUC and C_{max} values regarding emtricitabine and tenofovir. Accordingly, the test [HA439 trade name] tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Truvada® 200/300 mg tablet (Gilead Sciences Inc.).

4. Summary of product safety and efficacy

[HA439 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, [HA439 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 [HA439 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 [HA439 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA439 trade name] has been shown to be bioequivalent with Truvada® (Gilead Sciences Inc, U.S.A).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA439 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 [HA439 trade name] was acceptable for the following indication: **"in antiretroviral combination therapy for the treatment of HIV-1 infected adults over 18 years of age",** and would allow inclusion of [HA439 trade name], manufactured at Cipla Ltd, Unit VII, III, IV, Plot No: S-103 to S-105, S-107 to S-112 and L-147 to L147-1, Verna Industrial Estate, Goa – 403722, India in the list of prequalified medicinal products.