

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:	[HA717 trade name]*
Manufacturer of Prequalified Product:	Laurus Labs Limited, (Unit-II) Plot No. 19, 20 & 21 Western Sector, APSEZ Atchutapuram Mandal Visakhapatnam-District-531011 Andhra Pradesh India
Active Pharmaceutical Ingredient (API):	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations (emtricitabine and tenofovir disoproxil: J05AR03)
Therapeutic indication	<p>HA717 trade name] is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents from 10 years of age and weighing ≥ 30 kg.</p> <p>[HA717 trade name] may be used for pre-exposure prophylaxis in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.</p>

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

1. Introduction

[HA717 trade name] is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing ≥ 30 kg.

[HA717 trade name] may be used for pre-exposure prophylaxis in certain high-risk populations.

[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA717 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 Ingredient (API)

Emtricitabine and tenofovir disoproxil fumarate have 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 APIs, used in the manufacture of [HA717 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 anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains hypromellose, lactose monohydrate, titanium dioxide, triacetin and FD&C Blue #2/Indigo carmine aluminium lake. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

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

The multisource product is a blue-coloured, capsule-shaped, biconvex, film-coated tablet, debossed with 'LA49' on one side and plain on the other side. The tablets are presented in a white HDPE bottle, with a silica gel canister and closed with a polypropylene child-resistant closure, with induction sealing wad.

The aim of the development was to formulate an immediate release FDC dosage form, which is stable, and bioequivalent to the WHO comparator product, Truvada® film-coated tablets emtricitabine / tenofovir disoproxil fumarate 200 mg/300 mg). The selection of excipients was based on the qualitative composition of the comparator product, supported by API-excipient compatibility studies. Wet granulation method was not considered to be suitable for the manufacture of the product due to the instability of TDF in aqueous environment; therefore, the manufacturing process was finalized with the dry granulation technique. 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, TLC) and colorants, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) 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 some degradation for the water sensitive tenofovir disoproxil fumarate at the long-term storage condition, though the degradation products 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 2018 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study of Emtricitabine and Tenofovir disoproxil fumarate tablets 200 mg/300 mg of Laurus Labs Limited, India and Truvada® (emtricitabine and tenofovir disoproxil fumarate) tablets 200 mg/300 mg of Gilead Sciences Inc, Foster City, CA 94404, USA in normal, healthy, adult, human subjects under fed condition (study no. 17-VIN-0762).

The objective of the study was to compare the bioavailability of the stated emtricitabine/tenofovir disoproxil fumarate 200 mg/300 mg FDC tablet manufactured by/for Laurus Labs Limited, 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 fed 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)
Batch no. AETT100517

Treatment R: Reference – 1 tablet Truvada®
(emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 5535005A

A 13-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 24 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 4 ng/mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 33 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 \pm SD (*)	Reference (R) arithmetic mean \pm SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t _{max} (h)	1.7 \pm 0.6	1.8 \pm 0.9	-	-
C _{max} (ng/ml)	2313 \pm 517 (2263)	2390 \pm 586 (2317)	97.7	93.3 – 102.2
AUC _{0-t} (ng.h/ml)	10660 \pm 1081 (10595)	10963 \pm 1449 (10806)	98.1	96.0 – 100.1
AUC _{0-inf} (ng.h/ml)	10944 \pm 1085 (10880)	11265 \pm 1442 (11110)	97.9	96.0 – 99.9

* geometric mean

Tenofovir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean \pm SD (*)	Reference (R) arithmetic mean \pm SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t _{max} (h) [#]	1.7 \pm 0.7	1.8 \pm 0.9	-	-
C _{max} (ng/ml)	389 \pm 91 (377)	397 \pm 100 (384)	98.4	93.9 – 103.0
AUC _{0-t} (ng.h/ml)	3193 \pm 529 (3145)	3190 \pm 611 (3117)	100.9	97.0 – 105.0
AUC _{0-inf} (ng.h/ml)	3382 \pm 570 (3328)	3399 \pm 672 (3318)	100.3	96.7 – 104.0

* geometric mean

The results of the study show that present 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 200 mg/300 mg FDC tablet 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

[HA717 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, [HA717 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 [HA717 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 [HA717 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA717 trade name] has been shown to be bioequivalent with Truvada[®] (Gilead Sciences, Inc.) Foster City, CA 94404, USA.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA717 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 [HA717 trade name] was acceptable for the following indication: **“treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents (from 10 years of age and weighing \geq 30 kg), and pre-exposure prophylaxis in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection”**, and would allow inclusion of [HA717 trade name], manufactured at Laurus Labs Limited, Unit-II, Plot No. 19, 20 & 21, Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam-District-531011, Andhra Pradesh, India in the list of prequalified medicinal products.